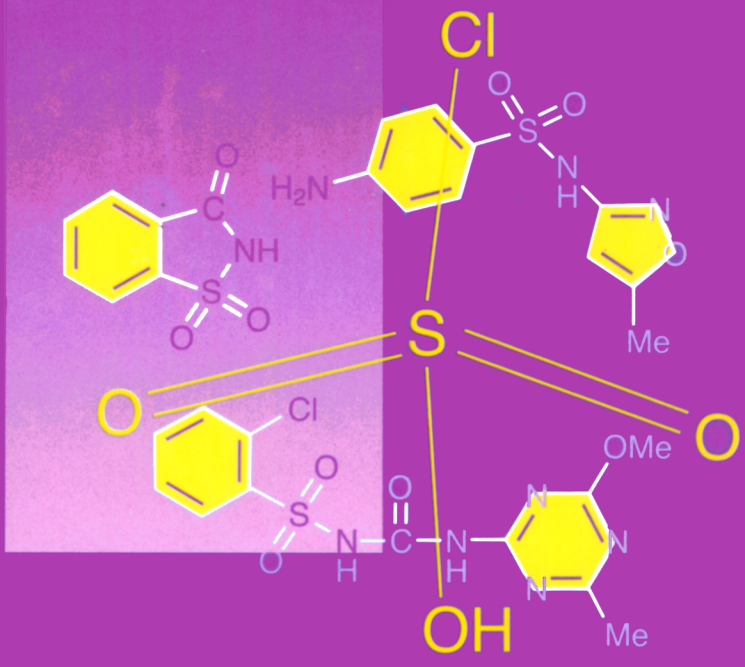
RS•C
ROYAL SOCIETY OF CHEMISTRY



chlorosulfonic acid

A VERSATILE REAGENT

R. J. CREMLYN

Chlorosulfonic Acid
A Versatile Reagent

Chlorosulfonic Acid

A Versatile Reagent

R.J. Cremlyn
University of Hertfordshire

RS•C
ROYAL SOCIETY OF CHEMISTRY

ISBN 0-85404-498-1

A catalogue record for this book is available from the British Library

Published by The Royal Society of Chemistry,
Thomas Graham House, Science Park, Milton Road,
Cambrdige CB4 0WF, UK
Registered Charity Number 207890

For further information see our web site at www.rsc.org

Typeset by Keytec Typesetting Ltd, Bridport, Dorset, DT6 3BE
Printed by Athenaeum Press Ltd, Gateshead, Tyne and Wear, UK

Preface

Chlorosulfonic acid was discovered in 1854 and has become a widely used sulfonating agent. It is of particular value when used in excess for the direct chlorosulfonation of a wide range of organic compounds. The resultant sulfonyl chlorides are important synthetic intermediates which are utilized in the preparation of many commercially significant sulfonyl derivatives such as sulfonamides and sulfonates. Chlorosulfonic acid is thus a major industrial reagent for the manufacture of detergents, pharmaceuticals, dyes, ion-exchange resins, plastics, artificial sweetners and various other chemicals.

In addition, chlorosulfonic acid is a versatile laboratory reagent which plays a key role in promoting several different types of reaction, such as alkylation, halogenation, rearrangement, cyclization and polymerization. In many of these reactions, chlorosulfonic acid functions as a powerful acid catalyst and dehydrating agent. Currently, there is no book on the market specifically dealing with chlorosulfonic acid and, in view of its considerable synthetic importance over many years, there is an urgent need to provide a coherent body of information on the reagent. The book seeks to achieve this objective and so the text appears timely. This view has been reinforced by the large number of research papers that I have published dealing with the use of chlorosulfonic acid in synthetic organic chemistry. The book should be valuable to all those in industry, universities and colleges who use, or may wish to use, chlorosulfonic acid in their work. The appendix at the end of the book includes the relevant references up to December 2001.

My thanks are due to many former staff and students of the Chemical Sciences Division of the University of Hertfordshire who assisted me in my research programme on the synthetic applications of chlorosulfonic acid. Thanks are also due to Mrs Janet Freshwater and other members of the editorial staff of the Royal Society of Chemistry for their assistance during the passage of the book through the press.

R.J. Cremlyn

Professor Cremlyn was educated at Swansea University College, Wales and Trinity Hall, Cambridge. Most of his long and distinguished career has been spent as a lecturer at the University of Hertfordshire, UK, where he is Emeritus Professor of Organic Chemistry. During that time he has published many research papers and articles on his major research interest – the chemistry and biological activity of organosulfur and organophosphorus compounds, especially as crop protection agents.

Contents

List of Abbreviations

AIBN	2,2′-azobisisobutronitrile
aq.	aqueous
Ar	aryl
CI	colour index
COD	chemical oxygen demand
conc.	concentrated
dil.	dilute
DCC	dicyclohexylcarbodiimide
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DVB	divinylbenzene
E	electromeric electronic effect
equiv.	equivalent
Et	ethyl
FTIR	Fourier transform infrared
H-acid	8-amino-1-hydroxynaphthalene-3,6-disulfonic acid
HPLC	high performance liquid chromatography
I	inductive electronic effect
k	rate constant
M	mesomeric electronic effect
m	*meta* position
Me	methyl
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
S_N	nucleophilic substitution
S_N1	nucleophilic substitution – unimolecular
S_N2	nucleophilic substitution – bimolecular
S_AN	nucleophilic substitution – addition–elimination
o	*ortho* position
p	*para* position
PABA	*p*-aminobenzoic acid
Ph	phenyl
PTFE	polytetrafluoroethylene
PVC	polyvinyl chloride
PVF	polyvinyl fluoride
R	alkyl radical, unless otherwise defined

RT	room temperature
TCNQ	7,7,8,8-tetracyanoquinodimethane
tert.	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
tosyl	*p*-toluenesulfonyl
UV	ultraviolet
X	a halogen atom, unless otherwise defined

CHAPTER 1

Introduction

Chlorosulfonic acid was first prepared by Williamson[1] in 1854 by the action of phosphorus pentachloride on concentrated sulfuric acid and later[2] by the direct action of hydrochloric acid on sulfur trioxide. Other methods of preparation include: distillation of fuming sulfuric acid (oleum) with phosphorus pentoxide in a stream of gaseous hydrogen chloride; the action of phosphorus trichloride or oxychloride, chlorine, thionyl chloride, or sulfur monochloride on concentrated or fuming sulfuric acid; passing a mixture of sulfur dioxide and chlorine into glacial acetic acid; or reaction of carbon tetrachloride with fuming sulfuric acid.[3]

Chlorosulfonic acid is also named chlorosulfuric acid in Chemical Abstracts, but chlorosulfonic acid is the commercial name by which it is more widely known. Other names are: sulfuric chlorohydrin, sulfuric acid chlorohydrin, monochlorosulfuric acid, monochlorosulfonic acid, chlorohydrated sulfuric acid and sulfuryl hydroxychloride.[4]

1 Manufacture

Modern chemical plants manufacture chlorosulfonic acid by the direct union of equimolar quantities of sulfur trioxide and dry hydrogen chloride gas.[4] The process is a continuous flow operation and, since it is highly exothermic, heat removal is essential to maintain the reaction temperature at 50–80 °C. The sulfur trioxide may be used in the form of 100% liquid or as a dilute gaseous mixture from a contact sulfuric acid plant. Likewise, the hydrogen chloride may be 100% gas or in a diluted form. The chemical reactor may be a packed column cooled by a water-cooled condenser to moderate the vigour of the reaction and hence avoid decomposition of the product. The chemical plant must be composed of non-corroding materials such as glass, glass-lined steel, enamel or steel coated with polytetraethylene (PTFE) so that the chlorosulfonic acid is not much contaminated with iron. A typical analysis of commercial chlorosulfonic acid would be as follows: $ClSO_3H$ 98–99.5%; H_2SO_4 0.2–2%; free SO_3 0–2%; HCl 0–0.5% and Fe 5–50 ppm. Chlorosulfonic acid may be stored and transported in steel containers, but in this case the iron content will be in the range 25–50 ppm. The annual production of chlorosulfonic acid increased substantially after World War

II due to expansion of the synthetic detergent industry and of dyes, drugs and pesticides. Worldwide there are approximately twenty listed manufacturers of chlorosulfonic acid: in the USA the two major ones are EI DuPont de Nemours Co Inc ($> 30\,000$ t yr^{-1}) and the Gabriel Chemical Co ($> 13\,000$ t yr^{-1}). The price of chlorosulfonic acid has risen from approximately US$ 209 t^{-1} in 1977 to US$ 389 t^{-1} in 1991. Further details of the preparation of chlorosulfonic acid are given in Chapter 10, p 272.

2 Physical Properties

Chlorosulfonic acid ($ClSO_3H$) is a colourless or straw-coloured liquid which fumes in air and decomposes slightly at its boiling point. The physical properties are shown in Table 1;[4] these vary slightly from sample to sample reflecting the different amounts of the various impurities present, *e.g.* hydrogen chloride, sulfur trioxide and related compounds. It is difficult to prepare a really pure sample of chlorosulfonic acid because of its instability at the boiling point, even under reduced pressure, which tends to degrade rather than purify the molecule. Pure chlorosulfonic acid has been obtained by fractional crystallization. Chlorosulfonic acid is a strong acid which is toxic and corrosive and behaves as a dehydrating, oxidizing and chlorinating agent. It is soluble in halocarbons containing hydrogen; for instance, chloroform, dichloromethane and 1,1,2,2-tetrachloroethane but is only sparingly soluble in carbon tetrachloride and carbon disulfide. It is soluble in liquid sulfur dioxide, sulfuryl chloride, acetic acid, acetic anhydride, trifluoroacetic acid, trifluoroacetic anhydride and nitrobenzene.

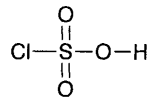
Table 1 *Physical properties of chlorosulfonic acid, $ClSO_3H$*

Property	*Value*
Mol. wt.	116.531
Mp (°C)	−81 to −80
Bp (°C) at 760 mm Hg	151–152
Bp (°C) at 19 mm Hg	74–75
Specific gravity (density), d_4^{20} (g ml^{-1})	1.753
Viscosity, mPa.s (= cP) at 15.6 °C	3.0
Viscosity, mPa.s (= cP) at 49 °C	1.7
Refractive index, n_D^{15}	1.437
Dielectric constant at 15 °C	60 ± 10
Electrical conductivity (ohm.cm) at 25 °C	$0.2–0.3 \times 10^{-3}$
Vapour density at 216 °C (kg m^{-3})[(a)]	2.4
Heat of formation, ΔH_f, 298, (kJ mol^{-1})	−597.1
Specific heat, kJ kg^{-1} K^{-1}	1.18
Heat of vapourization (J g^{-1})	452–460
Heat of solution in water (kJ mol^{-1})	168.6

[(a)]Vapour density is not precise because chlorosulfonic acid partially decomposes at the boiling point

The structure of chlorosulfonic acid **1** was proved by Dharmatti[5] who showed by magnetic susceptibility measurements that the chlorine atom was directly

attached to the sulfur atom and further supporting evidence was obtained from Raman spectral studies.[6,7]



1

3 Chemical Properties

Chlorosulfonic acid is a powerful acid with a relatively weak sulfur–chlorine bond. It fumes in moist air producing pungent clouds of hydrogen chloride and sulfuric acid (Equation 1).

$$ClSO_3H + H_2O \longrightarrow H_2SO_4 + HCl \quad (1)$$

When chlorosulfonic acid is heated it partially decomposes into sulfuryl chloride (SO_2Cl_2), sulfuric acid, sulfur trioxide, pyrosulfuric acid ($H_2S_2O_7$), hydrogen chloride, pyrosulfuryl chloride ($Cl_2S_2O_5$) and other compounds. At 170 °C, there is an equilibrium between chlorosulfonic acid, sulfuryl chloride and sulfuric acid (Equation 2). Sulfur dioxide and chlorine are not observed when chlorosulfonic acid is heated between 170 and 190 °C, but do appear at higher temperatures or when it is heated in a sealed tube (Equation 3).[3]

$$2ClSO_3H \underset{}{\overset{170\,^\circ C}{\rightleftharpoons}} SO_2Cl_2 + H_2SO_4 \quad (2)$$

$$2ClSO_3H \xrightarrow{>190\,^\circ C} Cl_2 + SO_2 + H_2SO_4 \quad (3)$$

When chlorosulfonic acid is treated with powerful dehydrating agents like phosphorus pentoxide, it is converted into its anhydride, pyrosulfuryl chloride ($Cl_2S_2O_5$). Chlorosulfonic acid, by boiling in the presence of mercury salts or other catalysts, decomposes quantitatively into sulfuryl chloride and sulfuric acid. It functions as a chlorinating agent with sulfur, arsenic, antimony and tin and yields sulfur dichloride and the tetrachlorides of the other elements.[3] With powdered tellurium or selenium, chlorosulfonic acid gives cherry-red or moss-green colours respectively and these can be used in spot tests for the acid. On heating with charcoal, it is decomposed with the evolution of sulfur dioxide, hydrogen chloride and carbon dioxide. In synthetic organic chemistry, chlorosulfonic acid can be used for sulfation of alcohols (Equation 4); sulfamation of amines (Equation 5); and the sulfonation and chlorosulfonation of aromatic compounds (Equations 6 and 7). In the latter reaction, there must be an excess (at least two equivalents) of the reagent present. All these reactions depend on the relative weakness of the sulfur–chlorine bond in chlorosulfonic acid. Chlorosulfonic acid only reacts slowly with saturated aliphatic hydrocarbons in the absence of a double bond or other reactive site, such as a tertiary hydrogen atom. Straight chain aliphatic alcohols, *e.g.* lauryl alcohol (dodecan-1-ol) can therefore be sulfated by chlorosulfonic acid without degradation or discolouration which often occurs with sulfur trioxide; this is important in the manufacture of hair shampoos,

like sodium lauryl sulfate **2** (Equation 8); the sulfation reaction is often carried out in pyridine solution.

$$ROH + ClSO_3H \longrightarrow ROSO_3H + HCl \quad (4)$$

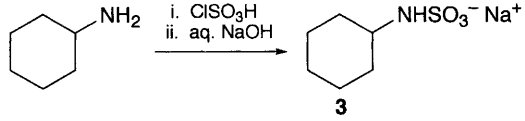
$$RNH_2 + ClSO_3H \xrightarrow{\text{pyridine}} RNHSO_3H + [HCl] \quad (5)$$

$$ArH + ClSO_3H \rightleftharpoons ArSO_3H + HCl \quad (6)$$

$$ArH + 2ClSO_3H \rightleftharpoons ArSO_2Cl + H_2SO_4 + HCl \quad (7)$$

$$n\text{-}C_{12}H_{25}OH + ClSO_3H \xrightarrow{\text{pyridine}} n\text{-}C_{12}H_{25}OSO_3H + [HCl] \xrightarrow{\text{NaOH (aq.)}} \underset{\mathbf{2}}{n\text{-}C_{12}H_{25}SO_4^-\ Na^+} \quad (8)$$

With primary or secondary amines, chlorosulfonic acid yields the corresponding sulfamic acid (Equation 5); this reaction with cyclohexylamine afforded the artificial sweetener sodium cyclamate **3** (Equation 9). In contrast to alkanes, alkenes readily react with chlorosulfonic acid to give the alkyl chlorosulfonates; thus ethylene (ethene) is absorbed by chlorosulfonic acid to give ethyl chlorosulfonate **4** (Equation 10).



3 (9)

$$CH_2{=}CH_2 + ClSO_3H \longrightarrow \underset{\mathbf{4}}{CH_3CH_2OSO_2Cl} \quad (10)$$

Aromatic hydrocarbons also react smoothly with an equimolar amount of chlorosulfonic acid or an excess of the reagent to yield either the sulfonic acid or the sulfonyl chloride (Equations 6 and 7). The direct conversion of aromatic compounds into their sulfonyl chlorides (chlorosulfonation or chlorosulfonylation) is probably the most important reaction of chlorosulfonic acid because sulfonyl chlorides are intermediates in the synthesis of a wide range of sulfonyl derivatives. The process is of wide application because many substituents on the aromatic ring, *e.g.* alkyl, alkoxy, amide, carboxy, cyano, hydroxy, nitro and multiple bonds are unaffected by the reagent.

Chlorosulfonation is essentially an electrophilic substitution reaction, consequently the reaction is facilitated by the presence of electron-donor groups, like alkyl, alkoxy and hydroxy, when it proceeds under relatively mild conditions, *e.g.* the minimum excess (approx. two equivalents) of the reagent, temperatures of −5 °C to 25 °C and an inert diluent such as chloroform. On the other hand, when electron-withdrawing groups, *e.g.* nitro, carbonyl or carboxy are present, the reaction requires more drastic conditions, *e.g.* a large excess of the reagent (five to ten equivalents) and heating to 100–150 °C.[8]

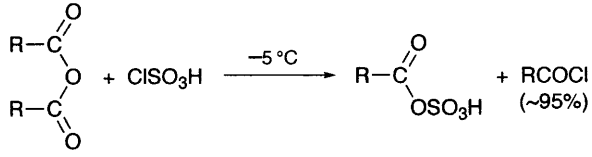
The use of chlorosulfonic acid for the synthesis of organic sulfonyl chlorides has been reviewed. The work before 1943 is described with extensive references

by Suter,[9] by Jackson[3] and, specifically for aromatic hydrocarbons, by Suter and Weston.[10]

More recent reviews of sulfonation were carried out by Gilbert,[11] Cerfontain,[12] Andersen[13] and Taylor[14] and of chlorosulfonation by Bassin, Cremlyn and Swinbourne.[15]

The use of chlorosulfonic acid for preparation of several important arylsulfonyl chlorides has been described.[16,17] However, depending on the nature of the substrate and the experimental conditions, reaction with chlorosulfonic acid may also yield diaryl sulfones[18] or chlorinated products.[19]

Chlorosulfonic acid is widely used in organic qualitative analysis to prepare solid derivatives from liquid or low melting aromatic compounds, *e.g.* hydrocarbons, halides and ethers.[16,20] The procedure involves conversion of the aromatic compound into the sulfonyl chloride, which is subsequently reacted with ammonia to yield the solid sulfonamide derivative which is suitable for melting point determination. Chlorosulfonic acid reacts with carboxylic acid anhydrides to give excellent yields of the acid chlorides[21] (Equation 11).



(11)

4 Safety

Chlorosulfonic acid reacts explosively with water producing fumes of hydrogen chloride and sulfuric acid; the pungent vapour is toxic and highly irritating to eyes, mucous membranes, skin and the respiratory tract.[22]

When using the reagent, protective clothing, gloves and safety goggles are needed, because chlorosulfonic acid is highly corrosive and causes severe burns in contact with skin. Experiments using chlorosulfonic acid must be performed in an efficient fume cupboard. The acid is not itself flammable, but it can cause fires by contact with combustible materials because of the heat of reaction.[4,22] Spills should be carefully diluted with large volumes of water. Absorption onto materials, such as expanded clay, diatomaceous earth, sand or soda ash mixture is effective, especially the latter since soda ash also partially neutralizes the acid.

5 Uses

Chlorosulfonic acid is employed in the manufacture of synthetic detergents such as sulfates of alkenes or unsaturated oils, polyoxypropylene glycol, long chain alcohols, alkylarenes or alkyl diphenyl ethers.[4] It is also extensively used in the manufacture of sulfonamide antibacterials (sulfa drugs), diuretics and other pharmaceuticals, pesticides, artificial sweeteners (saccharin), disinfectants (chloramine and dichloramine T), plasticizers, dyes and pigments, sulfonyl polymers as plastics, and ion exchange resins. Chlorosulfonic acid is an oxidizing and

dehydrating agent and functions as a catalyst in the esterification of aliphatic alcohols, alkylation of alkenes, and synthesis of alkyl halides from alkenic halides and isoalkanes containing tertiary hydrogen. It is used as a vulcanization accelerator, a source of anhydrous hydrogen chloride and in the tanning, textile and paper industries.

Overall, the approximate breakdown of the commercial applications of chlorosulfonic acid is as follows: detergents 40%; pharmaceuticals 20%; dyes 15%; pesticides 10% and miscellaneous uses, *e.g.* plasticizers, ion-exchange resins, *etc.* 15%.

6 References

1 A.W. Williamson, *Proc. R. Soc. London*, 1854, **7**, 11.
2 A.W. Williamson, *J. Chem. Soc.*, 1857, **10**, 97.
3 K.E. Jackson, *Chem. Rev.*, 1939, **25**, 83.
4 C.E. McDonald, 'Chlorosulfuric Acid' in Kirk-Othmer, *Encyclopaedia of Chemical Technology*, 4th Edn, Vol. 6, Wiley, New York, 1993, 168.
5 S.S. Dharmatti, *Proc. Indian Acad. Sci. Sect. A*, 1941, **13**, 359.
6 R.J. Gillespie and E.A. Robinson, *Can. J. Chem.*, 1962, **40**, 644.
7 H. Gerding, *J. Chem. Phys.*, 1948, **46**, 188.
8 R.B. Wagner and H.D. Zook, *Synthetic Organic Chemistry*, Wiley, New York, 1965, 822.
9 C.M. Suter, *The Organic Chemistry of Sulfur*, Wiley, New York, 1944. Reprinted edition by Intra-Science Research Foundation, Santa Monica, California, 1969.
10 C.M. Suter and A.W. Weston, *Org. React. (NY)*, 1946, **3**, 141.
11 E.E. Gilbert, *Sulfonation and Related Reactions,* Wiley, New York, 1965.
12 H. Cerfontain, *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation,* Interscience, New York, 1968.
13 K.K. Andersen, 'Sulfonic Acid and Derivatives' in *Comprehensive Organic Chemistry*, D.H.R. Barton and W. Ollis (eds), Vol. 3, Pergamon Press, Oxford, 1979, 331.
14 R. Taylor, *Electrophilic Aromatic Substitution,* Wiley, Chichester, 1990, 337.
15 J.P. Bassin, R.J. Cremlyn and F.J. Swinbourne, *Phosphorus, Sulfur and Silicon*, 1991, **56**, 245.
16 B.S. Furniss, A.J. Hannaford, V. Rogers, P.W.G. Smith and A.R. Tatchell (eds), *Vogel's Textbook of Practical Organic Chemistry*, 5th Edn, Longman, Harlow, 1989, 877, 883, 1234, 1238.
17 R.J. Cremlyn, *An Introduction to Organosulfur Chemistry*, Wiley, Chichester, 1996, 100, 103, 219.
18 A. Rieche and W. Fischer, *Angew. Chem.*, 1957, **69**, 482.
19 R.J. Cremlyn and T.N. Cronje, *Phosphorus and Sulfur*, 1979, **6**, 459.
20 H.T. Openshaw, *Laboratory Manual of Qualitative Organic Analysis,* Cambridge University Press, Cambridge, 1968, 27.
21 L.F. Fieser and M. Fieser, *Reagents for Organic Synthesis,* Wiley, New York, 1967, 139.
22 S.G. Luxon (ed), *Hazards in the Chemical Laboratory,* Royal Society of Chemistry, Cambridge, 1992, 302.

CHAPTER 2

Sulfonation and Chlorosulfonation of Organic Compounds

1 Introduction

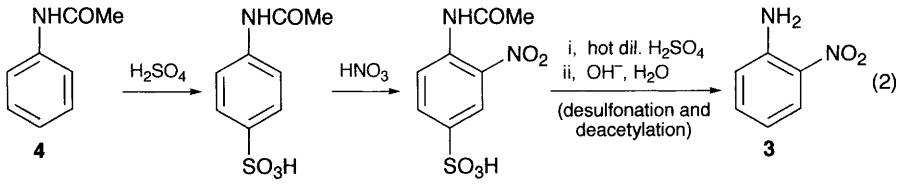
Sulfonation is a bimolecular electrophilic substitution reaction (S_E2) which may be depicted in general terms as shown (Equation 1):

$$ArH + E^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\mathbf{1}}{Ar(H)E^+} \xrightarrow[(B^-)]{k_2} \underset{\mathbf{2}}{ArE} + BH \qquad (1)$$

(ArH = aromatic hydrocarbon, E^+ = electrophilic species and B = conjugate base, *e.g.* $H_2SO_4^-$)

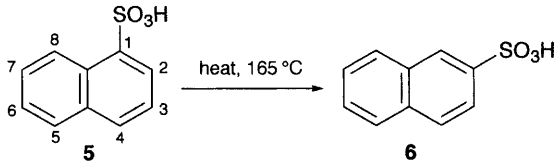
The general S_E2 mechanism involves addition of the electrophile (E^+) to the aromatic nucleus to form the σ-complex **1** which subsequently loses a proton to yield the substitution product **2**.[1] In this process either the first addition step or the second stage may be rate determining. In sulfonation, the sulfonic acid group is very bulky so that in the S_E2 reaction k_{-1} becomes large in comparison with k_2 which results in a kinetic isotope effect.[2] The latter causes increasing resistance to sulfonation when a degree of steric hindrance is present in the aromatic substrate. In sulfonation, the *ortho*:*para* substitution ratios vary widely according to the reaction conditions which indicates that different electrophilic species may be involved.

Sulfonation, unlike nitration, is a reversible process which enables the sulfonic acid group (SO_3H) to be employed in organic synthesis as a blocking and orientation-directing group. An example is provided by the synthesis of *o*-nitroaniline **3** from acetanilide **4** (Equation 2).



4 **3** (2)

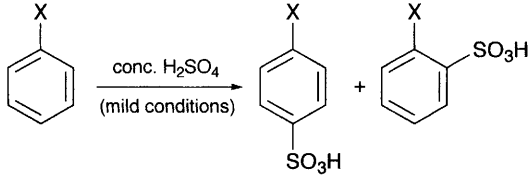
In acetanilide **4** the first sulfonation step causes the bulky sulfonic acid group to predominantly enter the *para*-position due to steric hindrance of the *o*-positions by the acetamido substituent. In the second nitration stage, the nitro group enters the aromatic nucleus *ortho* to the electron-donating acetamido group. In the last stage, the sulfonic acid moiety is removed by heating with dilute sulfuric acid (protiodesulfonation) which demonstrates the unique reversibility of sulfonation. The large size of the sulfonic acid group makes sulfonation especially sensitive to steric factors in the aromatic substrate and the severe resistance to sulfonation may cause the initial sulfonation products to rearrange to the most thermodynamically stable isomer in which steric hindrance is a minimum. The classic example of this phenomenon is the thermal rearrangement of naphthalene-1-sulfonic acid **5** into the 2-sulfonic acid **6** (Equation 3).



5 **6** (3)

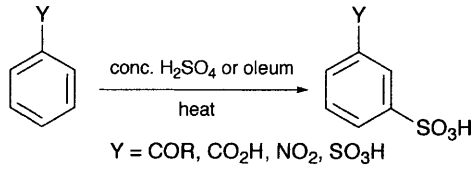
Thus, sulfonation of naphthalene with concentrated sulfuric acid at 80 °C afforded 96% of the 1-sulfonic acid **5**, whereas at 165 °C 85% of the 2-sulfonic acid **6** was obtained.

In the sulfonation of monosubstituted benzenes by concentrated sulfuric acid, electron-donating substituents (X) such as acetamido, alkoxy, hydroxy or alkyl groups facilitate the reaction and, in such cases, sulfonation occurs under relatively mild conditions (0–35 °C) to give a mixture of the *o*- and *p*-sulfonic acids[1] (Equation 4).



X = NHCOMe, OR, OH, R (4)

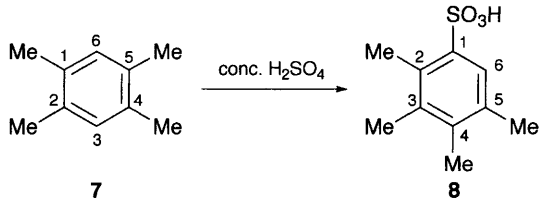
The *p*-isomer generally predominates because of the large steric size of the sulfonic acid group and is almost the sole product when other large substituents are present as in the case of acetanilide **4**. With benzenes containing electron-withdrawing substituents (Y), such as carbonyl, carboxy, nitro or sulfonic acid groups, sulfonation is more difficult and demands comparatively forcing conditions (a large excess of the sulfonating reagent and temperatures > 100 °C) then the resultant product is mainly the *m*-sulfonic acid (Equation 5).



(5)

The sulfonation of halobenzenes is anomalous because, although the halogen atom exerts a powerful electron-withdrawing (−I) inductive effect with deactivation, sulfonation of halobenzenes occurs in the *o/p*-positions and not in the *m*-position as would be anticipated for an electron-withdrawing group. The observed orientation of sulfonation is due to electron donation involving the electromeric (+E) effect from the lone electron pairs on the halogen atom in the presence of the electrophilic reagent. A similar effect is also observed with substituents of the type −CH=CHR (where R = an electron-withdrawing group such as nitro).

Sulfonation can be achieved by reaction of the organic substrate with reagents such as concentrated or fuming sulfuric acid (oleum), sulfur trioxide in aprotic solvents, or halosulfonic acids. In the sulfonation of polyalkylbenzenes, the strongly acid conditions may cause migration of an alkyl group (Jacobsen rearrangement) and this occurs after sulfonation so that 1,2,4,5-tetramethylbenzene **7** is converted to 2,3,4,5-tetramethylbenzenesulfonic acid **8** in which the methyl groups have moved closer together (Equation 6).



7 **8**

(6)

In sulfonation, disulfonation may occur and also formation of byproducts when free sulfur trioxide is present, *e.g.* sulfonic anhydrides (from intermolecular dehydration of monosulfonic acids or from intramolecular dehydration of *ortho*-disulfonic acids). Sulfones may also be produced by electrophilic substitution by the sulfonic acid or by the sulfonyl chloride when chlorosulfonic acid is the sulfonating reagent; the latter reagent also tends to form sulfonyl chlorides as byproducts.

2 Mechanism of Sulfonation

The reaction mechanism is complex because of the large number of different electrophilic species that may be present depending on the nature of the sulfonating reagent and the experimental conditions.[2] The mechanism of sulfonation by sulfuric acid has been extensively reviewed,[2–4] and it has been observed that the rate of sulfonation speeds up as the concentration of the sulfuric acid used increases. The rate increase is very pronounced in the region of 100 wt% acid;[5] this implies that the mechanism of sulfonation in sulfuric acid containing

free water is different from that obtained in sulfuric acid containing free sulfur trioxide. Sulfonation is accompanied by some degree of protiodesulfonation, but the latter is less pronounced in high concentrations of sulfuric acid; no by-products are observed in sulfonation in aqueous sulfuric acid. The complexity of the sulfonation mechanism arises from the large number of different species that may be present. Any water present in the medium will be ionized (Equation 7) and consequently the different equilibria resulting in the formation of potential electrophilic sulfonating species are as depicted by Equations 8–12.

$$H_2O + H_2SO_4 \rightleftharpoons H_3O^+ + HSO_4^- \quad (7)$$

$$2H_2SO_4 \rightleftharpoons H_3SO_4^+ + HSO_4^- \quad (8)$$

$$2H_2SO_4 \rightleftharpoons SO_3 + H_3O^+ + HSO_4^- \quad (9)$$

$$3H_2SO_4 \rightleftharpoons HSO_3^+ + H_3O^+ + 2HSO_4^- \quad (10)$$

$$4H_2SO_4 \rightleftharpoons S_2O_6 + 2H_3O^+ + 2HSO_4^- \quad (11)$$

$$H_2SO_4 + SO_3 \rightleftharpoons H_2S_2O_7 \quad (12)$$

Kinetic studies[3] supported the idea that, under some conditions, the precise nature of the electrophile remains in doubt because several kinetically equivalent species are possible. When the concentration of sulfuric acid is $< 85\%$, the predominant electrophilic species is $H_3SO_4^+$ and the sulfonation mechanism is shown by Equations 13–15.

$$ArH + H_3SO_4^+ \overset{\text{slow}}{\rightleftharpoons} \overset{+}{Ar}\overset{H}{\diagup}\underset{SO_3^-}{\diagdown} + H_3O^+ \quad (13)$$

$$\overset{+}{Ar}\overset{H}{\diagup}\underset{SO_3^-}{\diagdown} + HSO_4^- \overset{\text{fast}}{\rightleftharpoons} ArSO_3^- + H_2SO_4 \quad (14)$$

$$ArSO_3^- + H_3O^+ \overset{\text{fast}}{\rightleftharpoons} ArSO_3H + H_2O \quad (15)$$

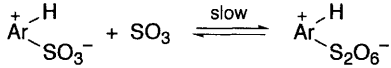
In 90–96 wt% acid, the electrophile becomes sulfuric acid solvated with sulfur trioxide (pyrosulfuric acid, $H_2S_2O_7$) and the mechanism is modified so that the first step is as shown in Equation 16.

$$ArH + H_2S_2O_7 \overset{\text{slow}}{\rightleftharpoons} \overset{+}{Ar}\overset{H}{\diagup}\underset{SO_3^-}{\diagdown} + H_2SO_4 \quad (16)$$

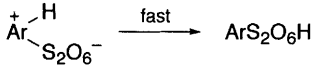
In 97–100 wt% acid, the observed isotope effect indicated that removal of the proton from the intermediate is rate decisive, consequently the reaction of the electrophile with the aromatic species (Equation 16) is now fast while Equation 14 is slow. In fuming sulfuric acid (oleum), the electrophile is probably free sulfur trioxide which is more reactive than the solvated species and reacts rapidly with the aromatic moiety (Equation 17).

$$ArH + SO_3 \overset{\text{fast}}{\rightleftharpoons} \overset{+}{Ar}\overset{H}{\diagup}\underset{SO_3^-}{\diagdown} \quad (17)$$

This step is subsequently followed by the reactions shown in Equations 14 and 15, one of which must be a relatively slow stage. When the sulfonation is effected by sulfur trioxide in aprotic solvents, the mechanism varies with the solvent because complexes are formed in nitromethane and nitrobenzene, but not in halogenated solvents. Hinshelwood and co-workers[6] showed that in nitrobenzene and nitromethane sulfonation was second order in sulfur trioxide which is in agreement with one molecule of sulfur trioxide assisting the polarization of the other. On the other hand, Cerfontain[4] proposed the mechanism depicted in Equations 18 and 19.

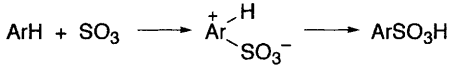


(18)



(19)

The last stage (Equation 19) of the mechanism is relatively fast but can be the rate-determining step when the site of sulfonation is sterically hindered. When the sulfonation is performed in halogenated solvents, the reaction is first order in both the aromatic substrate and sulfur trioxide[7] which agrees with the mechanism given by Equation 20.



(20)

3 Sulfonation by Halosulfonic Acids

Fluorosulfonic acid readily dissociates into sulfur trioxide and hydrogen fluoride and consequently is not a very useful sulfonating agent. With aromatic compounds, fluorosulfonic acid yields sulfonic acids, sulfones and sulfonyl fluorides, but no mechanistic studies have been reported.[2,9] In contrast, chlorosulfonic acid is more stable and is a valuable sulfonating agent; it similarly yields sulfonic acids, sulfones and sulfonyl chlorides. The latter are only formed in large amounts, when an excess of the reagent (at least two molar equivalents or more) is employed.[8a] Chlorosulfonic acid is a more powerful sulfonating agent than sulfuric acid[9] and sulfonation consequently generally occurs under mild conditions (approximately one molar equivalent of reagent at −5 to 25 °C in the presence of an inert solvent). The latter is important to reduce the amount of sulfonyl chloride formed as a byproduct. Under these conditions, sulfonation by chlorosulfonic acid generally gives high yields (75–80%) of the sulfonic acids. The following are some illustrative examples, thus 1-methylnaphthalene reacts with an equimolar quantity of the reagent in carbon tetrachloride at −7 to 0 °C to give potassium 1-methylnaphthalene-4-sulfonate (88%) after neutralization with potassium hydroxide.[10] Chlorobenzene has been sulfonated with chlorosulfonic acid,[11] and chlorosulfonic acid in acetic anhydride was found to be the best reagent for the mono- and disulfonation of ferrocene.[12] Schultz[13] discovered that biphenyl was selectively converted into the 4-sulfonic acid by treatment with

chlorosulfonic acid in chloroform. 2,6-Dialkylnaphthalenes react with chlorosulfonic acid (one molar equivalent) in dichloromethane at 0 °C to give the 3,7-dialkylnaphthalene-1-sulfonic acids.[14] 1-Nitronaphthalene with chlorosulfonic acid (one molar equivalent) in 1,2-dichloroethane at 0 °C affords mainly 1-nitronaphthalene-5-sulfonic acid (78–82%), with the 1,6- (8–16%) and the 1,7- (6–10%) isomers.[15] Cerfontain and van Albada[16] determined the kinetic isotope effect (k_H/k_D) in the sulfonation and sulfonylation of benzene by chlorosulfonic acid in nitromethane and dichloromethane; they also carried out detailed kinetic studies on these reactions.[17,18] The sulfonation of *o*-alkylphenols with chlorosulfonic acid has been examined and the kinetics shown to be first order in the intermediate phenyl hydrogen sulfate.[19]

Less mechanistic studies have been carried out with chlorosulfonic acid than with sulfuric acid and generally the precise nature of the electrophilic species involved remains uncertain and appears to vary with the nature of the substrate and the reaction conditions. Experimental data and thermodynamic studies indicated that when an aromatic substrate reacts with an equimolar quantity of chlorosulfonic acid, the first step yields the sulfonic acid (Equation 21). In the presence of an excess of the reagent, the initially formed sulfonic acid is slowly converted into the sulfonyl chloride with liberation of sulfuric acid[20] (Equation 22).

$$ArH + ClSO_3H \rightleftharpoons ArSO_3H + HCl \quad (21)$$

$$ArSO_3H + ClSO_3H \rightleftharpoons ArSO_2Cl + H_2SO_4 \quad (22)$$

The first stage may be driven to completion by removal of the hydrogen chloride gas and the progress of the reaction can be monitored by measurement of the volume of gas evolved.[21] Kinetic studies[22] demonstrated that the rate of the second stage (Equation 22) was slower than the observed overall rate of formation of the sulfonyl chloride and therefore the earlier proposed mechanism[20] shown by Equations 21 and 22 must be incorrect.[2]

Studies[22] of the reaction of benzene with chlorosulfonic acid (one molar equivalent) showed that the major product was benzenesulfonic acid (Equation 21) with a little diphenyl sulfone. When an excess of chlorosulfonic acid was used benzenesulfonyl chloride was obtained (Equation 22). Spryskov and Kuz'mina[23] demonstrated the reversibility of Equation 22 and measured the equilibrium constants for several different aromatic substrates.[4] In the benzene–chlorosulfonic acid reaction, the quantity of diphenyl sulfone produced was increased by addition of anhydrous benzenesulfonic acid, but not by benzenesulfonyl chloride.[16] The sulfone therefore apparently derived from reaction of benzenesulfonic acid and benzene under the influence of chlorosulfonic acid.[4,24] Sulfone formation appeared to be relatively favoured at low temperatures and this may be due to the formation of an intermediate pyrosulfuric acid[25] (Equations 23, 24).

$$ArSO_3H + ClSO_3H \longrightarrow ArS_2O_6H + HCl \quad (23)$$

$$ArS_2O_6H + ArH \longrightarrow ArSO_2Ar + H_2SO_4 \quad (24)$$

In chlorosulfonation, since the chlorination step (Equation 22) is reversible, the experimental conditions must be adjusted with a given aromatic substrate to obtain the maximum yield of the sulfonyl chloride. An excess of chlorosulfonic acid can be employed to drive this stage to completion and it has been shown[26] that where reaction costs are important a ratio of reagent to substrate of 5:1 was desirable. However, greater efficiency has been claimed[27] by a stepwise reaction of substrate with reagent at moderate temperatures. The yield of sulfonyl chloride may also be enhanced by removal of the sulfuric acid formed in Equation 22. This can sometimes be achieved by addition of sodium chloride,[21] but this may sometimes reduce the yield due to conversion of chlorosulfonic acid into the unreactive chlorosulfonate anion as shown (Equation 25).[8b,28] Ideally, the sulfuric acid may be removed by conversion into chlorosulfonic acid which can be effected by addition of carbon tetrachloride, sulfur and chlorine, or by treatment with sulfur trioxide in the presence of hydrogen chloride; in the latter case both byproducts are removed. Addition of a mixture of sodium chloride and carbon tetrachloride or the use of thionyl chloride as a chlorinating solvent has reduced the amount of chlorosulfonic acid required for chlorosulfonation of a given aromatic substrate.[21]

$$Cl^- + ClSO_3H \rightleftharpoons HCl + SO_3Cl^- \qquad (25)$$

The sulfonating power of pyrosulfuryl chloride or chlorosulfonic anhydride ($Cl_2S_2O_5$) is less than that of chlorosulfonic acid; however, addition of the anhydride to the reagent enhances the yield of the arylsulfonyl chloride. The anhydride probably acts by converting the sulfonic acid and sulfuric acid into the sulfonyl chloride and chlorosulfonic acid respectively (Equations 26, 27).

$$ArSO_3H + Cl_2S_2O_5 \longrightarrow ArSO_2Cl + ClS_2O_6H \qquad (26)$$

$$H_2SO_4 + Cl_2S_2O_5 \longrightarrow ClSO_3H + ClS_2O_6H \qquad (27)$$

The relative rates of sulfonation of sulfonyl chlorides, sulfonic acids and sulfonate anions with chlorosulfonic acid follow the order:

$$ArSO_2Cl > ArSO_3H > ArSO_3^-$$

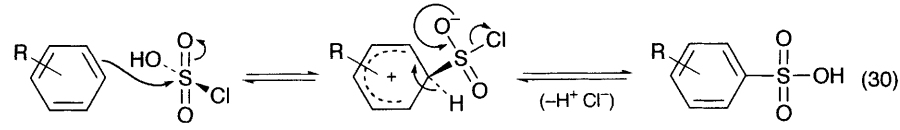
The order is in agreement with the conversion of the sulfonic acid into the sulfonyl chloride and can be explained in terms of the latter two substrates destroying part of the reagent[29] (Equations 28, 29).

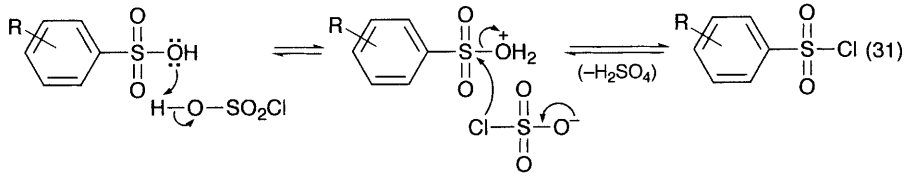
$$ArSO_3^- + ClSO_3H \rightleftharpoons ArSO_3H + SO_3Cl^- \qquad (28)$$

$$ArSO_3H + ClSO_3H \rightleftharpoons ArSO_3H_2^+ + SO_3Cl^- \qquad (29)$$

The kinetics of the conversion of benzenesulfonic acid into the sulfonyl chloride were studied in chlorosulfonic acid.[30] Other studies[31] showed that the equilibria between benzenesulfonyl chloride, sulfuric acid and chlorosulfonic acid

at 20–50 °C were acid-catalysed and the equilibrium constants were almost independent of the temperature. In the synthesis of the majority of aromatic sulfonyl chlorides by the action of chlorosulfonic acid, the reagent is used neat and in large excess without additional solvent. In view of the lack of precise detail on the stoicheiometric composition of chlorosulfonic acid and of the reactive entities present, all the mechanistic studies have been carried out with the reagent dissolved in suitable solvents, *e.g.* dichloromethane.[17]





However, the formation of the intermediate sulfonic acid and the sulfonyl chloride may possibly be depicted as shown (Equations 30, 31).[32] There is little precise mechanistic detail regarding these two reactions (Equations 30, 31). When the chlorosulfonation is performed under relatively mild conditions (low temperatures) using excess chlorosulfonic acid as solvent, it is possible that the initial electrophilic species may be intact chlorosulfonic acid.[32] On the other hand, at higher temperatures, (> 100 °C) chlorosulfonic acid slowly decomposes as indicated[21] (Equation 32).

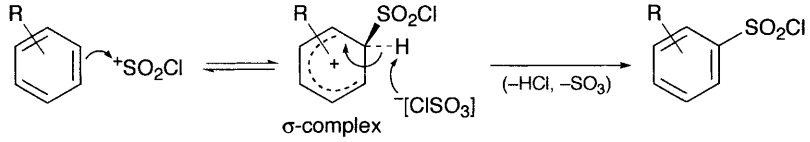
$$ClSO_3H \rightleftharpoons HCl + SO_3 \qquad (32)$$

At higher temperatures, therefore, appreciable amounts of hydrogen chloride and sulfur trioxide may be present in the reagent. Hence at elevated temperatures, sulfur trioxide may play a significant role in the sulfonation process either as itself or as chlorosulfonic acid solvated by SO_3 (namely ClS_2O_6H) as the electrophilic species.[32] Kinetic data for the chlorosulfonation of *p*-dichlorobenzene by chlorosulfonic acid agreed with the two-step reaction mechanism *via* the intermediate sulfonic acid.[33] The sulfonation of the secondary aromatic amines (*N*-methyl and *N*-ethylaniline) by chlorosulfonic acid in *o*-dichlorobenzene was determined to be an irreversible second order reaction which involved direct action of the amine with SO_3H^+.[34] On the other hand, the analogous reaction with the tertiary aromatic amines (*N,N*-dimethyl- and *N,N*-diethylaniline) was found to be a first order irreversible process involving initial formation of the amine–sulfur trioxide complexes which subsequently rearranged to give the *p*-aminobenzenesulfonic acids.[34] The kinetics of the chlorination of *p*-carbomethoxyaminophenylsulfonic acid have been examined photometrically at 295 nm.[35] The results indicated that the initial step was addition of two protons to the sulfonic acid, followed by equilibration with chlorosulfonic acid and the equilibrium constant

was 3.65 at 20–70 °C. Phenols react with chlorosulfonic acid to yield arylsulfates which with an excess of the reagent afforded the corresponding sulfonic acids and the kinetics of the complex sulfonation of tertiary butylphenols have been elucidated.[36] The sulfonation of naphthalene with chlorosulfonic acid at 0 and 170 °C gave the 1,1′- and 2,2′-dinaphthyl sulfones respectively as the major byproducts. The isomerization of naphthalene-1-sulfonic acid into the 2-sulfonic acid was concluded to be relatively fast in comparison with the conversion of the sulfonic acid into the sulfone.[37] The sulfonation of benzene by chlorosulfonic acid in dichloromethane as solvent has been studied.[38] The extent of the reaction at 0–20 °C was found to increase from 60% after a few minutes to 70% after 1 hour and at low temperatures (−30 to −7 °C), there was an induction period. The sulfonation was determined to be kinetically a third order reaction (first order with respect to benzene and second order with respect to chlorosulfonic acid). The mechanism was therefore concluded to involve the successive reaction of benzene with two moles of chlorosulfonic acid to yield benzenesulfonic anhydride.

In contrast, kinetic studies of the chlorosulfonation of benzene and toluene with chlorosulfonic acid in dichloromethane showed that the reaction was first order in the aromatic moiety and third order in chlorosulfonic acid.[22] The latter order is probably associated with the formation of the ion pair as the electrophile (Equation 33); this reacted with the aromatic substrate to give the σ-complex which subsequently decomposed to yield the sulfonyl chloride (Equation 34).

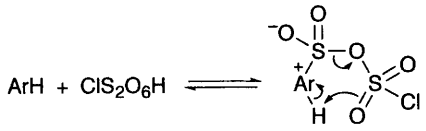
$$3ClSO_3H \rightleftharpoons SO_2Cl^+ + 2SO_3Cl^- + H_3O^+ \qquad (33)$$



(34)

In this work, toluene was observed to be five times more reactive than benzene. In the sulfonation of benzene, toluene and chlorobenzene by chlorosulfonic acid (just more than one molar equivalent) in dichloromethane or nitromethane, the major products were the corresponding arylsulfonic acids with only small amounts of the sulfones and sulfonyl chlorides.[17,18]

Kinetic and product studies were carried out on the reactions;[17] in dichloromethane for the reaction of chlorobenzene with chlorosulfonic acid, the electrophilic species was probably ClS_2O_6H. In the analogous reaction with benzene, unlike chlorobenzene, there was an induction period in the sulfonation. The sulfonating entity for the main reaction was concluded to be $PhS_2O_6H.ClSO_3H$, whereas for the initial reaction the electrophile was the same as for chlorobenzene, namely ClS_2O_6H. The sulfonation therefore may proceed as shown in Equations 35 and 36, in which the formation of the σ-complex is the rate-decisive step.



(35)

$$ArSO_3H + ClSO_3H \quad (36)$$

On the other hand, in nitromethane, kinetics indicated that the electrophile was probably $MeNO_2 \cdot SO_3H^+$.[2,17] From observations of the substituent effect on the rate of sulfonation, the reaction constant (ρ) was estimated as -10.[17] In the sulfonation of benzene by chlorosulfonic acid in dichloromethane and in nitromethane at 25 °C, the kinetic isotope effects (k_H/k_D) were 1.50–1.70.[16]

The sulfonation was discovered to be faster in dichloromethane than in nitromethane under otherwise identical reaction conditions. When sulfonation is performed by chlorosulfonic acid in acetic anhydride, the active electrophilic species is probably acetylsulfuric acid ($MeCO_2SO_3H$). The same electrophile is also involved in sulfonations using oleum, sulfuric acid or sulfur trioxide in acetic anhydride or acetic acid.[39]

In conclusion, the mechanistic studies of sulfonation and chlorosulfonation using chlorosulfonic acid are quite limited and somewhat contradictory. They indicate that the precise nature of the electrophile involved in these conversions appears to vary according to the polarity of the solvent, the reaction temperature and the nature of the aromatic substrate.

Chlorosulfonic acid (an excess of at least two molar equivalents) is the reagent of choice for the direct conversion of organic compounds, especially aromatic and heteroaromatic substrates, into their sulfonyl chlorides. The optimum conditions for chlorosulfonation vary widely and depend on the nature of the compound; as with sulfonation, the process is facilitated when the aromatic nucleus contains electron-donating groups when it occurs under mild conditions. For instance, a comparatively small excess (approx. two equivalents) of the reagent at fairly low temperatures (−5 to 25 °C) and a short reaction time. However, when electron-withdrawing substituents are present more vigorous conditions are needed (see p 8 and 16). For instance, prolonged treatment with a very large excess of chlorosulfonic acid (five to ten equivalents or more) at temperatures of 100–150 °C is often required to optimise the yield of the sulfonyl chloride.[40]

In some cases, chlorosulfonation has been promoted by using a mixture of chlorosulfonic acid and thionyl chloride; sometimes it was found preferable to react the substrate with chlorosulfonic acid alone first and then add the thionyl chloride later.[10] This modification allows the amount of chlorosulfonic acid to be reduced sometimes to just one molar equivalent, and may convert the intermediate sulfonic acid to the sulfonyl chloride where the conversion does not occur effectively in the absence of thionyl chloride. An example would be a substrate containing a substituent capable of hydrogen bonding with the sulfonic acid group, such as an *ortho*-hydroxy or amino group. The use of sulfuryl chloride, instead of thionyl chloride, as a chlorinating solvent was not successful because it

resulted in the formation of many chlorinated byproducts. Chlorosulfonation is a two-stage process (p 12) and it is vital that adequate time is allowed for the excess of chlorosulfonic acid to convert the intermediate sulfonic acid into the sulfonyl chloride, since the chlorination stage is a relatively slow reaction.

In the synthesis of arylsulfonyl chlorides, it is generally preferable to add the aromatic substrate gradually to the excess of chlorosulfonic acid rather than the other way about. Under these conditions, the reagent is mostly present in a large excess during the reaction which minimizes the formation of both the diaryl sulfone and the arylsulfonic acid. With highly reactive substrates, an inert solvent is used and the reaction temperature must be carefully controlled and kept as low as feasible to avoid unwanted di- and trisulfonation.[9]

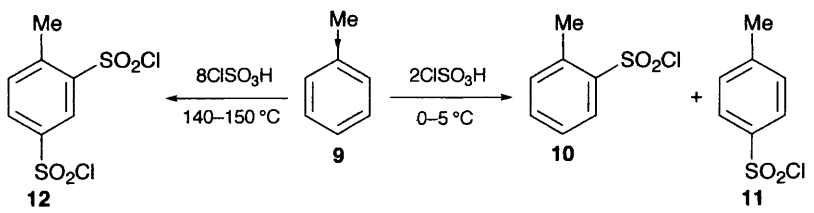
The following are some well-known examples of the application of chlorosulfonic acid in the synthesis of arylsulfonyl chlorides. They provide illustrations of the effect of electron-donor and electron-withdrawing substituents on the ease and orientation of chlorosulfonation.

Sulfonic acid groups (SO_3H) are both bulky and electron-withdrawing; consequently once one sulfonic acid group has been introduced into the aromatic nucleus, the resultant arylsulfonic acid will be more resistant towards further sulfonation. The latter will require more drastic conditions and the product will contain the two sulfonic acid groups in the 1,3-position with respect to each other. With reactive substrates, *e.g.* aromatic hydrocarbons, halides or ethers, monochlorosulfonation is often best achieved at low temperature in the presence of chloroform, dichloromethane or 1,2-dichloroethane to moderate the reaction and avoid disulfonation. Suter and Weston[41] described the experimental procedures for the sulfonation of aromatic hydrocarbons, halides and ethers and many early references and details of the synthesis of sulfonic acids and sulfonyl chlorides are included in Suter's comprehensive text.[42]

Benzenesulfonyl chloride is easily prepared by addition of benzene to excess chlorosulfonic acid (3 equivalents) at 20–25 °C (1 hour). The reaction yields the product (75%) together with a little diphenyl sulfone.[41–43]

When benzene is heated with a large excess of chlorosulfonic acid (~10 equivalents) at 150–160 °C (2 hours), the major product is benzene-*m*-disulfonyl chloride.

Toluene **9** is more reactive towards sulfonation than benzene due to the electron-donating (+I) methyl group, and treatment with chlorosulfonic acid (two molar equivalents) at 0–5 °C yields a mixture of the *ortho*- (58%) and *para*- (14%) toluenesulfonyl chlorides **10** and **11**[42] (Equation 37).

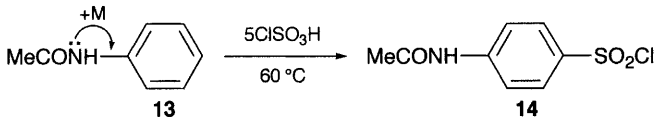


(37)

When the oily product mixture is cooled (−10 to −20 °C), the *p*-sulfonyl

chloride **11** crystallizes out and is filtered off, leaving the liquid *o*-isomer **10** in the filtrate; the latter is used in the manufacture of the artificial sweetener saccharin.[1,43] In this reaction, low temperatures tend to favour *o*-sulfonation; thus when toluene is reacted with chlorosulfonic acid (two equivalents) at 36 °C, the product contained 59% *p*- and 37% *o*-sulfonyl chloride.[43] However, at 80 °C the *p*-sulfonyl chloride (95%) was much more predominant. When toluene was heated with a large excess of the reagent (eight equivalents) at 140–150 °C (5 hours), the 2,4-disulfonyl chloride **12** (60%) was isolated (Equation 37).

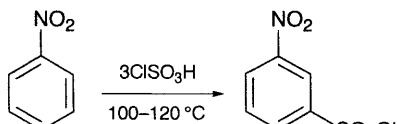
One of the most important examples is the chlorosulfonation of acetanilide **13** to *p*-acetamidobenzenesulfonyl chloride **14**[44] (Equation 38), since the latter is used as an intermediate in the manufacture of sulfonamide antibacterial drugs.[1] The optimum reaction conditions were found to be the use of a relatively large excess of the reagent (five equivalents) at 60 °C (2 hours). In acetanilide (*N*-phenylacetamide) **13**, the bulky acetamido (MeCONH) group is electron-donating (+M effect) and its large size virtually excludes *o*-sulfonation, so the *p*-sulfonyl chloride **14** is isolated as almost the sole product.



13 **14** (38)

Anisole (methyl phenyl ether) is extremely reactive towards sulfonation due to the presence of the strongly electron-donating (+M) methoxy group. It therefore reacts with chlorosulfonic acid (two equivalents) at 0 °C to give mainly *p*-methoxybenzenesulfonyl chloride.[42] With chlorobenzene, the chlorine atom exerts a strong electron-withdrawing (–I effect) so sulfonation will be rather less easy than for benzene. Treatment of chlorobenzene with chlorosulfonic acid (four equivalents) at 25 °C (3 hours) afforded *p*-chlorobenzenesulfonyl chloride (84%) and di(*p*-chlorophenyl sulfone) (6%).[43] Chlorobenzene with chlorosulfonic acid (six equivalents) at 150–160 °C (8 hours) gave the 2,4-disulfonyl chloride.

With *p*-dichlorobenzene, the molecule is more deactivated due to the presence of the two chlorine atoms; consequently chlorosulfonation to yield 2,5-dichlorobenzenesulfonyl chloride requires more drastic conditions; namely heating with chlorosulfonic acid (five equivalents) at 150 °C (1 hour).[41] Other examples involving electron-withdrawing groups include nitrobenzene and benzoic acid. In the former compound **15**, the nitro group is strongly electron-withdrawing (–I, –M effects) so forcing conditions are required for chlorosulfonation. Heating nitrobenzene **15** with excess chlorosulfonic acid (four equivalents) at 100–120 °C (8 hours) yields the *m*-sulfonyl chloride **16** (60%) (Equation 39).[45]

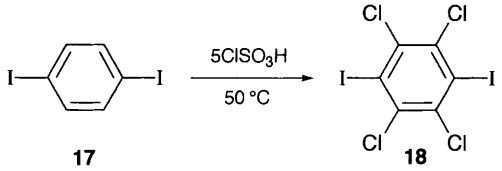


15 **16** (39)

Benzoic acid, containing the electron-withdrawing carboxy group also needs

forcing conditions for chlorosulfonation, namely heating with a large excess of chlorosulfonic acid (five equivalents) at 125 °C (1 hour) to yield *m*-chlorosulfonylbenzoic acid.[46]

Chlorosulfonic acid is known[47] to act as a chlorinating agent for aromatic compounds at high temperatures and consequently in chlorosulfonation by chlorosulfonic acid under forcing conditions chlorinated byproducts may be formed. Iodine has been demonstrated[48] to catalyse chlorination by chlorosulfonic acid even under comparatively mild conditions. This effect causes problems when attempting the chlorosulfonation of aromatic compounds containing iodine; thus the action of excess chlorosulfonic acid (five equivalents) on *p*-diiodobenzene **17** at 50 °C did not yield the expected sulfonyl chloride, but instead chlorination occurred to give 2,3,5,6-tetrachloro-1,4-diiodobenzene **18**[49] (Equation 40).

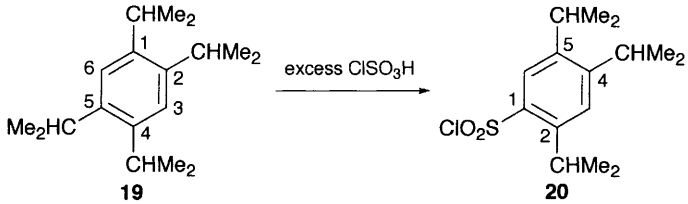


17 **18** (40)

A general procedure for the chlorosulfonation of reactive aromatic substrates, *e.g.* hydrocarbons, ethers and halides has been developed by Huntress and coworkers.[49,50] The method involves the dropwise addition of an excess of chlorosulfonic acid to a solution of the aromatic compound in chloroform at 0 °C, and then allowing the solution to warm to room temperature.

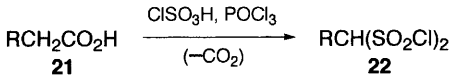
In the sulfonation of polyalkylbenzenes, an intramolecular rearrangement of an alkyl group may occur (see p 9). Similarly during the chlorosulfonation of polyalkylbenzenes, alkyl groups are sometimes displaced from the aromatic nucleus.

For example, when 1,2,4,5-tetraisopropylbenzene **19** is reacted with excess chlorosulfonic acid, the product is 2,4,5-triisopropylbenzenesulfonyl chloride **20** (Equation 41) involving displacement of the 5-isopropyl moiety.[51]



19 **20** (41)

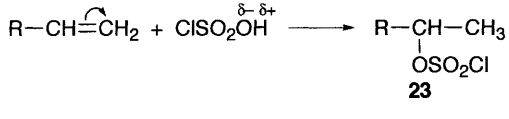
Chlorosulfonic acid also reacts with aliphatic compounds, but the yields of the sulfonyl chlorides are usually poor.[21] However, chlorosulfonic acid does react with aliphatic carboxylic acids **21** in the presence of phosphorus oxychloride to form the disulfonyl chlorides **22** in excellent yields (Equation 42).[52]



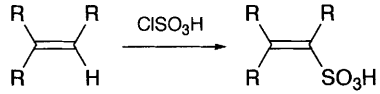
21 **22** (42)

Chlorosulfonic acid is an important reagent for the sulfation of alcohols to

prepare alkyl sulfates, many of these are used as commercial detergents (see Chapter 1, p 5). Chlorosulfonic acid also reacts with alkenes to form alkyl chlorosulfonates **23** (Equation 43)[21] and the reagent will sulfonate a vinylic hydrogen atom (Equation 44).[53]



(43)



(44)

4 References

1 R.J. Cremlyn, *An Introduction to Organosulfur Chemistry*, Wiley, Chichester, 1996, 97.
2 R. Taylor, *Electrophilic Aromatic Substitution*, Wiley, Chichester, 1990, 337.
3 R. Taylor, *Comprehensive Chemical Kinetics*, Elsevier, Amsterdam, 1972, Vol 13, 56.
4 H. Cerfontain, *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Interscience, New York, 1968.
5 H. Cerfontain, *Recl. Trav. Chim Pays-Bas*, 1961, **80**, 296; H. Cerfontain, *Recl. Trav. Chim Pays-Bas*, 1965, **84**, 551.
6 C.N. Hinshelwood and D.R. Vicary, *J. Chem. Soc.*, 1932, 1372; C.N. Hinshelwood and E. Dresel, *J. Chem. Soc.*, 1944, 649.
7 J.K. Bosscher and H. Cerfontain, *Recl. Trav. Chim Pays-Bas*, 1968, **57**, 873; *Tetrahedron*, 1968, **24**, 6543.
8 (a) L. Harding, *J. Chem. Soc.*, 1921, 1261; (b) L.H. Levina, S.N. Patrakova and D.A. Patruskev, *J. Gen. Chem.*, USSR, 1958, **28**, 2464.
9 J. Hoyle, *Preparation of Sulfonic Acids, Esters, Amides and Halides*, in *The Chemistry of Sulfonic Acids and their Derivatives*, S. Patai and Z. Rappoport (Eds), Wiley, Chichester, 1991, 354, 379.
10 L.F. Fieser and D.M. Bowen, *J. Am. Chem. Soc.*, 1940, **62**, 2105.
11 W.A. Cook and K.H. Cook, *J. Am. Pharm. Assoc.*, 1949, **38**, 239.
12 G.R. Knox and P.L. Pauson, *J. Chem. Soc.*, 1958, 692.
13 R.G. Schultz, *J. Org. Chem.*, 1961, **26**, 5195.
14 D.C.F. Garbutt, K.G.R. Pachler and J.R. Parrish, *J. Chem. Soc.*, 1965, 2324.
15 B.I. Karavaev and V.V. Paramonova, *Izv. Vyssh. Ucheb. Zaved, Khim. Khim. Tekhnol.*, 1967, **10**, 57; *Chem. Abs.*, **67**, 53907.
16 M.P. van Albada and H. Cerfontain, *Recl. Trav. Chim. Pays-Bas*, 1972, **91**, 499.
17 M.P. van Albada and H. Cerfontain, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1548.
18 M.P. van Albada and H. Cerfontain, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1557.
19 A. Brändstrom, G. Strandlund and P. Langerström, *Acta. Chem. Scand.*, 1979, **B33**, 567.
20 B.Y. Yasnitskii, *Zh. Obshch. Khim.*, 1953, **23**, 107, *Chem. Abs.*, **48**, 625.
21 E.E. Gilbert, *Sulfonation and Related Reactions*, Interscience Publishers, New York, 1965.
22 S.M. Chizhlik and B.V. Passet, *Zh. Org. Khim.*, 1975, **11**(8), 1649; *Chem. Abs.*, **83**, 177739.
23 A.A. Spryskov and Y.L. Kuz'mina, *J. Gen. Chem. USSR*, 1958, **28**, 184.

24 A. Rieche and W. Fisher, *Angew. Chem.*, 1957, **69**, 482.
25 V.O. Lukashevich, *Dokl. Akad. Nauk. SSSR*, 1957, **112**, 872; *Chem. Abs.*, **51**, 14591.
26 F. Caragna, T. Grewer, O. Jaenicke and H. Zeininger, *Chem. Ing.-Tech.*, 1978, **50**(1), 51; *Chem. Abs.*, **88**, 111158.
27 A. Swinarski, A. Grodzicki and J. Glowinska, *Przem. Chem.*, 1973, **52**(8), 553; *Chem. Abs.*, **80**, 59618.
28 A.A. Spryskov and B.I. Karavev, *Zh. Obshch. Khim.*, 1952, **22**, 661; *Chem. Abs.*, **47**, 8709.
29 A.A. Spryskov and B.G. Gnedin, *Izv. Vyssh. Ucheb. Zaved., Khim. Khim. Tekhnol.*, 1964, **7**(6), 935; *Chem. Abs.*, **62**, 14440.
30 N.I. Rudakova and B.G. Gnedin, *Tr. Ivanov. Khim.-Tekhnol. In-ta.*, 1976, **19**, 77; *Chem. Abs.*, **86**, 139017.
31 B.G. Gnedin, S.N. Ivanov, N.I. Rudakova and A.A. Spryskov, *Izv. Vyssh. Ucheb. Zaved., Khim Khim. Tekhnol.*, 1975, **18**(7), 1039; *Chem. Abs.*, **83**, 177735.
32 J.P. Bassin, R.J. Cremlyn and F.J. Swinbourne, *Phosphorus, Sulfur and Silicon*, 1991, **56**, 245.
33 V.I. Koshelev and S.V. Borodaev, *Zh. Prikl. Khim.*, 1980, **53**(10), 2298; *Chem. Abs.*, **94**, 64784.
34 R.N. Khelevin, *Zh. Org. Khim.*, 1987, **23**(9), 1925; *Chem. Abs.*, **108**, 166776.
35 V.A. Pal'm, *Dokl. Akad. Nauk. SSSR*, 1956, **108**, 487; *Chem. Abs.*, **51**, 1066.
36 A. Brandström, G. Strandlund and P. Langerström, *Acta. Chim. Scand.*, 1980, **B34**, 467; *Chem. Abs.*, **94**, 120495.
37 V.V. Kozlov, T.I. Vol'fson, N.A. Kozlova and G.S. Tubyarskaya, *J. Gen. Chem. USSR*, 1962, **32**, 3373; *Chem. Abs.*, **58**, 11289.
38 B.G. Gnedin and N.I. Rudakova, *Izv. Vyssh. Ucheb. Zaved., Khim. Khim. Tekhnol*, 1972, **15**(5), 716; *Chem. Abs.*, **77**, 87401.
39 A. Carsadevall, A. Commeyras, P. Paillous and H. Collet, *Bull. Soc. Chim. Fr.*, 1970, 719; M. Schmidt and K.E. Pichl, *Z. Anorg. Allg. Chem.*, 1961, 335, 244.
40 R.B. Wagner and H.D. Zook, *Synthetic Organic Chemistry*, Wiley, New York, 1965, 822.
41 C.M. Suter and A.W. Weston, *Org. React.* (NY), 1946, **3**, 141.
42 C.M. Suter, *The Organic Chemistry of Sulfur*, Wiley, New York, 1944. Reprinted edition by Intra-Science Research Foundation, Santa Monica, California, 1969, Chapter 3.
43 B.S. Furniss, A.J. Hannaford, V. Rogers, P.W.G. Smith and A.R. Tatchell (eds), *Vogel's Textbook of Practical Organic Chemistry*, 5th edn., Longman, Harlow, 1989, 877, 883.
44 S. Smiles and J. Stewart, *Org. Synth.*, Coll. Vol 1, Wiley, New York, 1941, 8.
45 H.H. Hodgson and J.S. Whitehurst, *J. Chem. Soc.*, 1944, 482.
46 S. Smiles and J. Stewart, *J. Chem. Soc.*, 1921, **119**, 1795.
47 M. Ballester and S. Olivella, 'Aromatic and Alkaromatic Chlorocarbons' in *Polychloroaromatic Compounds*, H. Suschitzky, (ed), Plenum Press, London, 1974, 6.
48 R.J. Cremlyn and T.N. Cronje, *Phosphorus and Sulfur*, 1979, **6**, 495.
49 E.H. Huntress and F.H. Carten, *J. Am. Chem. Soc.*, 1940, **62**, 511, 603.
50 E.H. Huntress and J.S. Authenrieth, *J. Am. Chem. Soc.*, 1941, **63**, 3446.
51 A. Newton, *J. Am. Chem. Soc.*, 1943, **65**, 2439.
52 M. Fild and H.P. Rieck, *Chem. Ztg.*, 1976, **100**, 391; *Chem. Abs.*, **85**, 159332.
53 S. Miron and G.H. Richter, *J. Am. Chem. Soc.*, 1949, **71**, 453.

CHAPTER 3

Reactions of Organic Sulfonyl Chlorides

1 Reactions with Nucleophilic Reagents

As mentioned in Chapter 2, chlorosulfonic acid is a valuable reagent for the conversion of organic compounds into their sulfonyl chlorides. The latter are of considerable importance because they are valuable synthetic intermediates in the preparation of a wide range of sulfonyl derivatives.[1] The synthetic utility of sulfonyl chlorides depends on their ability to undergo substitution reactions with various nucleophilic reagents. Organic sulfonyl chlorides are generally liquids or low melting solids and they are not easily purified by recrystallization or distillation. The relatively low melting point makes crystallization difficult and they tend to decompose on distillation even under reduced pressure. Sulfonyl chlorides are also prone to hydrolysis when traces of moisture are present, since this results in the formation of hydrogen chloride which catalyses further hydrolytic decomposition. Sulfonyl chlorides are therefore generally characterized by condensation with amines to form the corresponding sulfonamides which are stable, well-defined, crystalline solids with fairly high, sharp melting points. The sulfonyl transfer reaction is illustrated by the condensation of an arylsulfonyl chloride **1** with nucleophilic reagents, *e.g.* water, alcohols, phenols, amines, hydrazine, hydroxylamine and azide ion to yield the corresponding sulfonic acids **2**, sulfonates **3**, sulfonamides **4**, sulfonyl hydrazides **5**, sulfonyl hydroxylamines **6** and sulfonyl azides **7** (Equations 1–6).

$$\underset{\mathbf{1}}{ArSO_2Cl} + H_2O \longrightarrow \underset{\mathbf{2}}{ArSO_3H} + HCl \qquad (1)$$

$$\underset{\mathbf{1}}{ArSO_2Cl} + ROH \longrightarrow \underset{\mathbf{3}}{ArSO_3R} + HCl \qquad (2)$$

(R = aliphatic or aromatic radical)

$$\underset{\mathbf{1}}{ArSO_2Cl} + 2R^1R^2NH \longrightarrow \underset{\mathbf{4}}{ArSO_2NR^1R^2} + R^1R^2\overset{+}{N}H_2Cl^- \qquad (3)$$

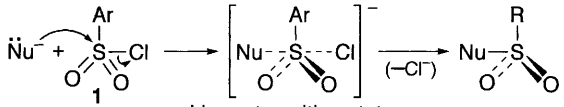
$$\underset{\mathbf{1}}{ArSO_2Cl} + 2NH_2\text{–}NH_2 \longrightarrow \underset{\mathbf{5}}{ArSO_2NHNH_2} + NH_2\overset{+}{N}H_3Cl^- \quad (4)$$

$$\underset{\mathbf{1}}{ArSO_2Cl} + 2NH_2OH \longrightarrow \underset{\mathbf{6}}{ArSO_2NHOH} + \overset{+}{N}H_3OHCl^- \quad (5)$$

$$\underset{\mathbf{1}}{ArSO_2Cl} + \overset{+}{N}aN_3^- \longrightarrow \underset{\mathbf{7}}{ArSO_2N_3} + NaCl \quad (6)$$

In the reactions with amines or amino derivatives (Equations 3–5), either an excess of the amino compound is employed or the reaction is carried out in the presence of a tertiary base, *e.g.* pyridine or triethylamine. It is preferable for the reaction to be performed in non-aqueous media, *e.g.* acetone or acetonitrile to avoid competing base-catalysed hydrolysis.

The mechanism of the reaction of arylsulfonyl halides with nucleophilic reagents has been widely studied and reviewed.[2–4] The majority of kinetic and other evidence indicates that the reactions of an arylsulfonyl chloride **1** with a nucleophile (Nu^-) generally follow the concerted bimolecular S_N2-type mechanism as depicted in Equation 7 with a linear bipyramidal transition state which is similar to the S_N2 (acyl) pathway established for acyl halides.[5]



(7)

Linear transition state

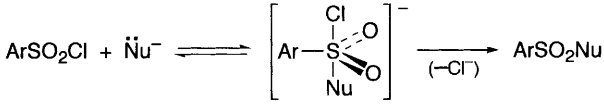
S_N2 mechanism

The main evidence in support of this mechanism derives from studies of stereochemical inversions as in the reaction of a chiral sulfonate with a Grignard Reagent;[6] isotopic experiments on the hydrolysis of arylsulfonates;[7] and the rates of hydrolysis of alkyl and arylsulfonyl halides.[8–10]

Various other workers have proposed alternative reaction mechanisms, namely the unimolecular (S_N1) and the stepwise addition–elimination pathway (S_AN) (Equations 8 and 9 respectively).

$$ArSO_2Cl \underset{(-Cl^-)}{\overset{\text{slow}}{\rightleftharpoons}} ArSO_2^+ \xrightarrow[\text{fast}]{Nu^-} ArSO_2Nu \quad (8)$$

S_N1 mechanism



(9)

S_AN mechanism

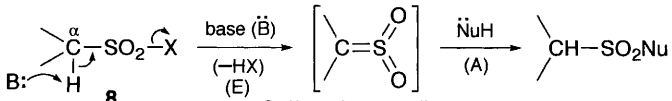
By analogy with acyl halides, the S_N1 mechanism (Equation 8) should be possible for arylsulfonyl halides, provided they contain sufficiently electron-donating substitutents as in the hydrolysis of 2,4,6-trimethylbenzenesulfonyl chloride.[9,11] However, this evidence has been disputed by the work of Rogne in Norway in a series of papers;[12–15] thus in the reaction of imidazole with substituted

benzenesulfonyl chlorides in protic and aprotic media the kinetics indicated the operation of a direct concerted S_N2 process.[15]

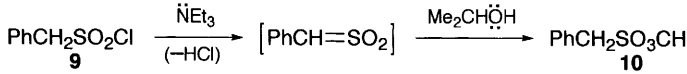
The S_AN mechanism (Equation 9) has been favoured by other workers[16] to explain the similar leaving group mobility of a series of benzenesulfonyl halides (chlorides, bromides and iodides) in reactions with amines and hydroxide ion in aqueous acetonitrile. Further evidence for the operation of the S_AN mechanism was claimed in studies of the alkaline hydrolysis of *para*-substituted benzenesulfonyl fluorides[17] in aqueous dioxane; for the reactions of thiophene-2-sulfonyl halides in methanol[18] and in other papers[19,20] by this Italian group. In the addition–elimination (S_AN) mechanism, the trigonal bipyramidal transition state contains both the nucleophile and nucleofuge in apical positions (Equation 9). The attack of the nucleophile was considered to be the rate-determining step, which accounted for the reduced influence of the sulfur–halogen bond strength on the overall rate of reaction. The S_AN mechanism involves the formation of a transition state containing a pentacoordinate sulfur atom. This is possible, since sulfur can accommodate up to twelve electrons in its valence shell by utilizing the d-orbitals and, indeed, stable analogues of such structures are known.[21]

Later studies from Italy, however, discounted much of the earlier work and reinterpreted the results in terms of an S_N2-type mechanism which can involve both 'loose' and 'tight' transition states.[22]

For nucleophilic substitutions involving alkylor arylsulfonyl halides **8** possessing at least one α-hydrogen atom, a different reaction mechanism is possible as shown (Equation 10):



This is an elimination–addition (E–A) pathway involving a transient, highly reactive, sulfene intermediate.[23–25] An illustrative example is provided by the reaction of benzylsulfonyl chloride **9** with isopropanol in the presence of a base, triethylamine, to yield the isopropyl sulfonate **10** (Equation 11).

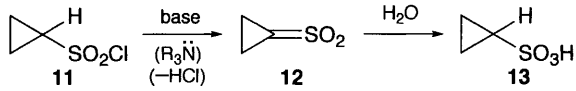


The evidence for the formation of the sulfene intermediate, probably *via* a concerted E_2 type elimination reaction, has been reviewed by King and Rathore.[26] For instance, when the reaction shown in Equation 11 was performed using deuterated isopropanol (Me_2CHOD), the monodeuterated isopropyl sulfonate **10** was obtained (90% yield).[27] The presence of a free sulfene intermediate was also indicated by mass spectral evidence in the reaction of ethylsulfonyl chloride with deuterated methanol (MeOD) in the presence of 3-methylpyridine.[28] Further evidence for sulfene formation derived from kinetic studies of the reaction of methylsulfonyl chloride with isopropanol in the presence of triethylamine. The

dehydrohalogenation was found to be an overall second order reaction (first order in both sulfonyl chloride and triethylamine), but zero order with respect to isopropanol. These results indicate the formation of an intermediate (sulfene) in the rate-determining step; the final reaction of the sulfene with the alcohol being relatively fast.

Experiments on the hydrolysis and related nucleophilic substitution reactions of alkylsulfonyl chlorides showed the mechanisms were dependent on pH and deuterium substitution patterns. For instance, in the hydrolysis of methylsulfonyl chloride by 0.1 M aqueous KCl at 25 °C overlapping mechanisms were identified.[29] At a pH of 1–6.7 there was direct attack by H_2O on the sulfonyl chloride, whereas at higher pH (6.8–11.8), there was slow attack by OH^- to form the sulfene, and at pH > 11.8, the sulfene was trapped by the OH^- ion. Deuterated benzylsulfonyl chloride ($PhCD_2SO_2Cl$) was hydrolysed in aqueous dioxane (1 : 1) to give $PhCD_2SO_3H$ without hydrogen–deuterium exchange indicating the operation of the bimolecular S_N2 mechanism. On the other hand, benzylsulfonyl chloride reacted with NaOD in D_2O–dioxane (1 : 5) to yield the mono-deuterated product, $PhCHDSO_3Na$, suggesting that reaction proceeds by the elimination–addition mechanism *via* the sulfene ($PhCH{=}SO_2$).[30]

In the nucleophilic substitution reactions of alkylsulfonyl chlorides and ring-substituted benzylsulfonyl chlorides, the operation of two competing reaction pathways has been established: (a) E–A (sulfene) mechanism and (b) direct nucleophilic substitution at sulfur (general base catalysis).[31,32] The relative significance of these competing mechanisms depends on the nature of the substrate and the precise reaction conditions. In the hydrolysis of cyclopropanesulfonyl chloride **11** with tertiary amines in organic media, the sulfene **12** appears to be the crucial intermediate in the formation of cyclopropanesulfonic acid **13** (Equation 12).[33]



(12)

Kinetic and deuteration experiments demonstrated that the hydrolysis of (trimethylsilyl) methylsulfonyl chloride **14** in water (0.01 M KCl) involves the sulfenes **15** and **16**[34] (Equation 13).

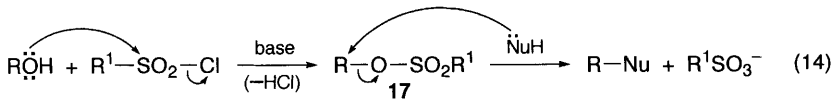
$$\underset{\mathbf{14}}{Me_3Si{-}CH_2SO_2Cl} \xrightarrow[(KCl)]{H_2O} \underset{\mathbf{15}}{[CH_2{=}SO_2]} + \underset{\mathbf{16}}{[Me_3SiCH{=}SO_2]} \qquad (13)$$

More recent experiments by King and co-workers[35] studied the hydrolysis of other alkylsulfonyl chlorides, including 2,2,2-trifluoroethyl- and tertiary butyl-sulfonyl chlorides. The results showed that most of the reactions occurred *via* sulfenes, although with the tertiary butyl derivatives, hydrolysis involved initial formation of the tertiary butyl cation.[35]

The sulfene mechanism appears to be facilitated by (a) the use of substrates with good leaving groups (*e.g.* halogens) and electron-accepting substituents at the α-carbon atom of alkylsulfonyl halides; (b) the use of catalysts with

pronounced basic properties; and (c) the use of a polar reaction medium.[26,31] The combined use of all these favourable conditions may result in reactions proceeding almost entirely *via* the sulfene mechanistic pathway.

Organic sulfonyl chlorides are important reagents in organic chemistry for the activation of alcohol groups by their conversion into the corresponding sulfonate esters **17** which are then easily displaced by nucleophiles since the sulfonate moiety is an excellent leaving group (Equation 14).[36]



$$R\ddot{O}H + R^1{-}SO_2{-}Cl \xrightarrow[(-HCl)]{\text{base}} R{-}O{-}SO_2R^1 \xrightarrow{\ddot{N}uH} R{-}Nu + R^1SO_3^- \quad (14)$$

The hydroxyl group of an alcohol is a poor leaving group and so sulfonation by treatment with the appropriate sulfonyl chloride provides a valuable method of activating the hydroxyl group towards nucleophilic substitution. The tosylate derivatives (**17**, R′ = *p*-MeC_6H_4) obtained by treatment of the alcohol with *p*-toluenesulfonyl chloride (tosyl chloride) in pyridine are widely used for the activation of the hydroxyl group.

Theoretical studies of the gas-phase hydrolysis or methanolysis of methylsulfonyl chloride indicated a concerted S_N2 process involving a four-membered cyclic transition state.[37,38] The tertiary amine-catalysed hydrolysis of benzenesulfonyl chloride was shown to be inhibited by chloride ion and a nucleophilic mechanism of catalysis was favoured.[39] Kinetic studies[40–42] of the solvolysis of *p*-substituted benzenesulfonyl chlorides in aqueous binary mixtures with acetone, methanol, ethanol, acetonitrile and dioxane showed that the reactions were third order processes, with first order rate constants determined mainly by the molar concentrations of the protic solvent, so that the reaction rates appear to be dominated by solvent stoichiometry. The solvolyses in methanol and ethanol yield both an alcoholysis (ap) and a hydrolysis product (hp). Solvolyses of electron-rich arylsulfonyl chlorides, under neutral or acidic conditions, exhibited surprising maxima in solvent-dependent S values as defined by Equation 15.

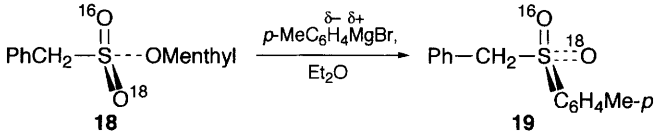
$$S = \frac{[ap]\,[water\ solv.]}{[hp]\,[alcohol\ sov.]} \quad (15)$$

These effects were hidden in previous studies,[8,43–45] which were restricted to hydrolysis in mixtures with aprotic solvents or in sulfuric acid where only one product is obtained.[46] The experimental data indicated changes in reaction mechanism depending on water content and solvent polarity.[47] In agreement with previous studies,[48,49] they indicated the operation of two simultaneous reaction channels in the different media used, with an S_N1-type reaction favoured in more aqueous media. In the methanolysis of *p*-substituted benzenesulfonyl chlorides in various solvent combinations, the mechanism appeared to consist of a mixture of the S_N1 and S_N2 reaction pathways, but in methanol–ethylene glycol mixture, the results favoured the S_N2 mechanism.[50]

In the solvolysis of thiophene-2-sulfonyl chloride in low polarity solvents,

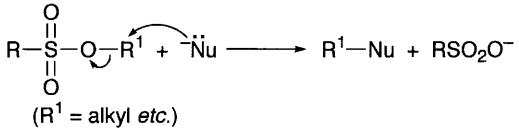
kinetic studies indicated the operation of general base catalysis and/or an addition–elimination mechanism.[49] Other studies[40,51] have suggested that the unimolecular S_N1 reaction channel is unfavourable even with electron-rich sulfonyl chlorides. On the other hand, kinetic data and cross interaction constants for the solvolysis of α-tertiary butylbenzenearenesulfonates indicate the operation of a typical S_N1 reaction mechanism.[52]

Organic sulfonate esters, like sulfonyl halides, also readily undergo nucleophilic substitution reactions as previously mentioned (p 23). For example, oxygen-labelled (–)menthyl phenylmethanesulfonate **18** reacted with *p*-tolylmagnesium bromide to give labelled benzyl *p*-tolyl sulfone **19** with inversion of stereochemical configuration at the chiral sulfur atom (Equation 16).

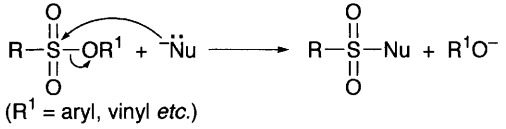


(16)

This observation clearly indicated that the substitution reaction followed the bimolecular (S_N2) mechanism.[6] Nucleophilic attack on sulfonate esters may occur *via* two possible pathways: either with carbon–oxygen bond cleavage (Equation 17) or by cleavage of the sulfur–oxygen bond (Equation 18).

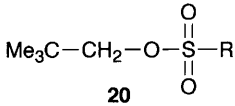


(17)



(18)

The former generally predominates over the competing sulfur–oxygen cleavage,[36] so that the sulfonate moiety functions as a leaving group. The early work on the chemistry of alkyl and aryl sulfonates has been discussed by Suter[53a] and more recently by Kaiser.[54] The general consensus is that sulfur–oxygen cleavage (Equation 18) only becomes significant when carbon–oxygen bond cleavage (Equation 17) is sterically and/or electronically unfavourable: for instance, when R is aryl[55] or vinyl[56] or in neopentyl sulfonates **20** in which nucleophilic attack on the methylene carbon atom is hindered by the adjacent bulky tertiary butyl moiety.[57]



20

Steric effects and polarizability of the attacking nucleophilic reagent may also be important;[54] thus less polarizable nucleophiles, *e.g.* methoxide[55] and fluoride[58]

appear to facilitate sulfur–oxygen bond cleavage (Equation 18). As was observed in nucleophilic substitution reactions involving sulfonyl halides (see p 24), sulfonates possessing α-hydrogen atoms may react by the elimination–addition (sulfene) mechanism. Indeed, Williams and his group at Kent[59] showed that alcoholysis of aryl arylmethanesulfonates **21** proceeded *via* the sulfene intermediate (Equation 19).

$$\underset{\mathbf{21}}{ArCH_2SO_2OAr^1} + ROH \xrightarrow[(-Ar^1OH)]{\text{base}} [ArCH{=}SO_2] \xrightarrow{ROH} ArCH_2SO_3R \qquad (19)$$

The sulfene formation may occur by either a stepwise E1cB or a bimolecular E2 elimination mechanism depending on the particular reaction.

Research into the aminolysis and hydrolysis of sulfamate esters **22** in *aqueous* organic media (*e.g.* chloroform, acetonitrile) indicated predominately the operation of an E1cB elimination mechanism *via* a sulfonylamine **23**[60,61] (Equation 20).

$$\underset{\mathbf{22}}{RNHSO_2OC_6H_4X} + R^1NH_2 \longrightarrow \underset{\mathbf{23}}{[RN{=}SO_2]} \xrightarrow[(-HOC_6H_4X)]{R^1NH_2} \underset{\mathbf{24}}{RNHSO_2NHR^1} \qquad (20)$$

However, recent studies[62] suggested that in *non-aqueous* organic media, the reaction appears to follow the concerted E2-type mechanism with some E1cB character, but probably not involving sulfonylamines. The relative order of nucleophilicity towards the sulfonyl sulfur atom is similar to that obtained at a carbonyl carbon atom[2] and is shown in Figure 1.

$$HO^- > RNH_2 > N_3^- > F^- > OAc^- > Cl^- > H_2O > I^-$$

decreasing nucleophilicity

Figure 1

In the majority of substitution and elimination reactions, the sulfonate moiety functions as a leaving group (*i.e.* reaction as shown by Equation 17 involving carbon–oxygen cleavage).

Certain sulfonates, *e.g.* methanesulfonate (mesylate), *p*-toluenesulfonate (tosylate) and trifluoromethanesulfonate (triflate) are exceptionally good leaving groups, and hence their introduction greatly facilitates nucleophilic substitution reactions. The triflate is the best leaving group and will undergo acetolysis some 10^4 times faster than the analogous tosylate.

In the nucleophilic substitution reactions of isopropyl *p*-substituted benzenesulfonates with amines in acetonitrile an S_N1-type mechanism was favoured.[63] The alkaline hydrolyses of a range of *ortho*- and *para*- substituted phenyl tosylates in various solvents from pure water to 80% DMSO have been studied at different temperatures.[64,65] The results showed that altering the concentration of hydroxide ion affected the activation entropy, especially for the *ortho*-isomers.

The solvolysis of 3-chlorobenzyl 4-substituted benzenesulfonates has been

examined kinetically in aqueous 2,2,2-trifluoroethanol at various temperatures.[66] The ratio of the alcoholysis product (ether) to the hydrolysis product (alcohol) was found to be independent of the nucleofuge. The reaction mechanism was considered to be a solvent induced, concerted, but not synchronous S_N2 process.

In the reactions of organic sulfonyl chlorides and sulfonates with nucleophilic reagents; it is now generally considered that in the absence of α-hydrogens, the favoured reaction pathway is probably the bimolecular (S_N2) process (see p 23). The alternative addition–elimination (S_AN) mechanism may also intervene in certain cases. For sulfonyl chlorides and sulfonates possessing α-hydrogens, the elimination–addition (sulfene mechanism) is often a major reaction channel. The unimolecular (S_N1) mechanism is generally considered unfavourable, even in reactions involving electron-rich substrates.

2 Sulfonylation

Sulfonyl chlorides can also undergo nucleophilic substitution reactions with arenes to give the corresponding sulfones **24** (Equation 21).

$$ArH + RSO_2Cl \xrightarrow{AlCl_3} ArSO_2R + HCl \quad (R = \text{alkyl/aryl radical}) \qquad (21)$$

Sulfonylation involves the replacement of a hydrogen atom by the sulfonyl (RSO_2) group. The early work on the chemistry of sulfones was reported by Suter[53b] and the mechanism of sulfonylation has been reviewed by Taylor.[67] In sulfonylation, the reaction is catalysed by Lewis acids and aluminium chloride is usually the favoured catalyst since the relative activities of the catalysts in methylsulfonation are as depicted (Figure 2).[68]

$$AlCl_3 > FeCl_3 > SbCl_5$$

Figure 2

In sulfonylation, the catalyst coordinates with both the sulfonyl chloride and the sulfone product so the latter is accordingly isolated as the 1 : 1 adduct.[69]

The mechanism of sulfonylation is analogous to that obtaining in acylation: reactive aromatic substrates attack the undissociated sulfonyl chloride, but less reactive aromatics only react with the dissociated species.

Early studies of the kinetics of sulfonylation were carried out by Olivier,[69] who examined the benzenesulfonylation of benzene, toluene and chlorobenzene using excess *of benzenesulfonyl chloride as solvent* and aluminium chloride catalyst. In all cases, the rate constants varied markedly with the concentration of the catalyst. Further kinetic studies[70] of these sulfonylations showed that the order of reaction depends on the reactivity of the aromatic compound. The benzenesulfonylation of the more reactive substrate toluene showed second order kinetics, rate = $k_2[AlCl_3][PhMe]$. For benzene, the kinetic order is mixed, while for the less reactive chlorobenzene the rate was claimed[70] to be three-halves, rate =

$k_{3/2}[AlCl_3]^{1/2}[PhCl]$. The rate of benzenesulfonylation of toluene was reduced by substituting a less polar solvent, cyclohexane, suggesting that the adduct with aluminium chloride is ionized before reaction (Equation 22). The suggested steps in the benzenesulfonylation reaction are shown in Equations 22–24.

$$PhSO_2Cl + AlCl_3 \rightleftharpoons PhSO_2^+ AlCl_4^- \quad (22)$$

$$ArH + PhSO_2^+ AlCl_4^- \rightleftharpoons ArSO_2Ph{\cdot}AlCl_3 + HCl \quad (23)$$

$$PhSO_2^+ AlCl_4^- \rightleftharpoons PhSO_2^+ + AlCl_4^- \quad (24)$$

The rate-determining stage is the subsequent reaction of the aromatic compound with the ionized complex (Equation 23). The three-halves order kinetics for the benzenesulfonylation of chlorobenzene was claimed[70] to give better agreement with Olivier's kinetic data than the second order kinetics originally proposed[69] for this reaction, and was suggested to require pre-dissociation of the ionized complex (Equation 24). However, Taylor[67] disputes this argument since it contradicts the conclusion by Jensen and Brown[70] that acylation by a similarly ionized complex would result in second order kinetics. The relative effects of various *para*-substituents in the arylsulfonyl halide on the sulfonylation of benzene are as follows: OMe (3.0), I (0.7), Br (Cl) (0.5) and for the *meta*-NO_2 group (0.06).[69] Similar substituent effects were observed in the sulfonylation of naphthalene[71] and are in agreement with attack of aromatic compound on the polarized complex (Equation 23). Determination of the kinetic isotope effect ($k_H : k_D = 0.86$) by Cerfontain and co-workers[72,73] suggested that the last step of the reaction, namely proton removal from the complex, was not rate-contributory, but this argument may not be valid since a more recent publication[74] reported a higher value of the kinetic isotope effect ($k_H : k_D$) of 1.9–2.5. In sulfonylation using alkylsulfonyl chlorides, there is competing alkylation; the latter is enhanced by increasing stability of the alkyl cation.[75,76] Thus reaction of isopropyl, tertiary butyl and benzylsulfonyl chlorides caused facile alkylation of aromatic substrates in the presence of aluminium chloride in nitromethane at 25 °C.[75]

With isomeric chlorosulfonylbenzoyl chlorides, the reaction with an aromatic substrate and aluminium chloride yields the products of benzoylation and not sulfonylation indicative of the comparatively powerful electrophilic character of the acyl chloride (COCl) group as compared with the chlorosulfonyl (SO_2Cl) moiety.[77]

Sulfonylation has also been studied using solvents when the sulfonyl chloride is *not* in excess.

Under these conditions, the sulfonyl chloride appears directly in the rate equations and for benzenesulfonylation in nitrobenzene solvent, the greater polarity of the solvent should enhance ionization of the sulfonyl chloride–catalyst complex (Equation 24). Studies[70] of the sulfonylation of aromatic substrates with aluminium chloride catalyst in nitrobenzene showed that with more reactive substrates, *e.g.* 1,3,5-trimethylbenzene (mesitylene), the reaction exhibits overall second order kinetics; rate $= k_2$ $[AlCl_3]$ $[PhSO_2Cl]$, the rate was independent of the concentration of the aromatic compound.

On the other hand, with less reactive aromatics of the order of benzene, or less, the reaction obeys third order kinetics; rate = k_3 [ArH] [$AlCl_3$] [$PhSO_2Cl$]. With reactive substrates, the rate-decisive step is the ionization of the addition complex (Equation 22). However, for less reactive aromatics, the rate-determining step is the subsequent reaction of the ionized complex with the aromatic compound (Equation 23).[70] The kinetic isotope effect ($k_H : k_D$) was ~1.0 for benzenesulfonylation in nitrobenzene, nitromethane and trichlorofluoromethane;[70,74,78] while for *p*-toluenesulfonylation in nitromethane and in dichloromethane the values were determined to be 1.5 and 3.3 respectively.[79]

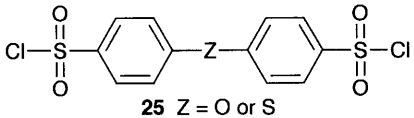
Holt and co-workers[80] demonstrated that aluminium chloride readily dissolved in dichloromethane and they successfully sulfonylated several aromatic compounds by treatment with this homogeneous reagent. Studies of the *p*-toluenesulfonylation of benzene and bromobenzene using *p*-toluenesulfonyl chloride and aluminium chloride in dichloromethane showed that the reaction followed third order kinetics with substantial kinetic isotope effects ($k_H : k_D$ 2.0–2.8). The IR spectra showed no evidence of free cations and the *p*-toluenesulfonylation therefore probably involves the loss of a proton from the unionized aromatic sulfonyl chloride–catalyst complex as the rate-determining step.[81]

Studies of substituent effects on the sulfonylation reaction are confusing and suggest that the mechanism may be affected by both reaction conditions and mixing control.[67,82] In the benzensulfonylation of toluene in nitrobenzene, the toluene:benzene rate ratio is 8.0 and the *ortho*, *meta*, *para* partial rate factors are 6.8, 2.1 and 30.2 respectively. Alkylbenzenes gave the Baker–Nathan activation order as expected under the highly solvating conditions.[70] The results surprisingly indicate that the electrophile is more reactive than the nitronium ion and it is possible that mixing control is involved.

For instance, *p*-methoxybenzenesulfonylation afforded a toluene:benzene ratio of 8.2, whereas for *p*-nitrobenzenesulfonylation, the ratio was only 2.8;[82] mixing control is clearly implicated in the latter reaction. In *p*-bromobenzenesulfonylation (without any solvent) a toluene:benzene rate ratio of 41.3 was obtained,[69] indicating that the electrophile was less reactive than that involved in benzenesulfonylation. But if the electrophile is the free cation, then it should be more reactive so nucleophilic displacement by the aromatic substrate on the electrophile complex may occur in this reaction. Methylsulfonylation shows a *para:meta* ratio of 2.4[68] (*cf.* 7.2 for benzenesulfonylation) indicating the electrophile to be less selective and hence more reactive which is not consistent with both reagents substituting by the same reaction mechanism, because the positive charge on the sulfur atom should be larger in benzenesulfonylation. The absence of *ortho*-substitution in the reaction of methylsulfonyl chloride with halobenzenes is also surprising.[68]

The methylsulfonylation of toluene by reaction with methylsulfonyl chloride in the presence of aluminium chloride catalyst affords methyl tolyl sulfone (52% yield) with an *ortho:meta:para* isomer ratio of 53 : 14 : 33.[82] Attempts have been made to obtain greater selectivity in sulfonylations: a supported Lewis acid catalyst has been recommended for selective sulfonylation, but it did not give good results in the methylsulfonylation of toluene.[83] The best *para*-selectivity

(81%) in this reaction was obtained by the use of a protonated form of zeolite β as catalyst.[84]



25 Z = O or S

The kinetics of the sulfonylation of aniline by aryldisulfonyl chlorides of type **25** has been studied. The reactivity of the disulfonyl chloride was greater than that of benzenesulfonyl chloride, but was significantly less than that of benzene-4,4′-disulfonyl chloride.[85]

3 References

1 R.J. Cremlyn, *An Introduction to Organosulfur Chemistry*, Wiley, Chichester, 1996, 104, 106, 107.
2 J. March, *Advanced Organic Chemistry*, Wiley, New York, 1992, 496.
3 I.M. Gordon, H. Maskell and M.-F. Ruasse, *Chem. Soc. Rev.*, 1989, **18**, 123.
4 J.L. Kice, *Adv. Phys. Org. Chem.*, 1980, **17**, 65.
5 M.L. Bender, *Chem. Rev.*, 1960, **60**, 53.
6 M.A. Sabol and K.K. Andersen, *J. Am. Chem. Soc.*, 1969, **91**, 3603.
7 C.A. Bunton and C.F. Frei, *J. Chem. Soc.*, 1951, 1872.
8 F.E. Jenkins and A.N. Hambly, *Aust. J. Chem.*, 1961, **14**, 190, 205.
9 M.L. Tonnet and A.N. Hambly, *Aust. J. Chem.*, 1971, **24**, 703.
10 R.J. Cremlyn, P.H. Gore, A.O.O. Ikejiani and D.F.C. Morris, *J. Chem. Res. (S)*, 1982, 194.
11 R.V. Vizgert, *Russ. Chem. Rev.*, 1963, **32**, 1.
12 O. Rogne, *J. Chem. Soc. (B)*, 1968, 1294.
13 O. Rogne, *J. Chem. Soc. (B)*, 1969, 663.
14 O. Rogne, *J. Chem. Soc. (B)*, 1970, 1056.
15 O. Rogne, *J. Chem. Soc., Perkin Trans. 2*, 1973, 823, 1760.
16 E. Ciuffarin, L. Senatore and M. Isola, *J. Chem. Soc. Perkin Trans. 2*, 1972, 468.
17 E. Ciuffarin and L. Senatore, *Tetrahedron Lett.*, 1974, 1635.
18 E. Maccarone, G. Musumarra and G.A. Tomaselli, *J. Org. Chem.*, 1974, **39**, 3286.
19 A. Arcoria, V. Librando, E. Maccarone, G. Musumarra and G.A. Tomaselli, *Tetrahedron*, 1977, **33**, 105.
20 A. Arcoria, F.P. Ballisteri and G.A. Tomaselli, *Tetrahedron*, 1978, **34**, 2545.
21 E.E. Perozzi, J.C. Martin and I.C. Paul, *J. Am. Chem. Soc.*, 1974, **96**, 6735.
22 F.P. Ballisteri, A. Cantone, E. Macarone, G.A. Tomaselli and M. Tripolone, *J. Chem. Soc., Perkin Trans. 2*, 1981, 438.
23 G. Opitz, *Angew. Chem. Int. Ed. Engl.*, 1967, **6**, 107.
24 T.J. Wallace, *Q. Rev. Chem. Soc.*, 1966, **20**, 67.
25 J.F. King, *Acc. Chem. Res.*, 1975, **8**, 10.
26 J.F. King and R. Rathore, 'Sulfenes' in *The Chemistry of Sulfonic Acids, Esters and their Derivatives*, S. Patai and Z. Rappoport (eds), Wiley, Chichester, 1991, Chapter 17, 697.
27 J.F. King and T. Durst, *J. Am. Chem. Soc.*, 1964, **86**, 287; J.F. King and T. Durst, *J. Am. Chem. Soc.*, 1965, **87**, 5684.
28 T.S. Uhn, J.P. Lee, H.S. Park, H.T. Kim and Z.H. Ryn, *Bull. Korean. Chem. Soc.*, 1990, **11**, 60; *Chem. Abs.*, **113**, 22817.

29 J.F. King, J.Y.L. Lam and S. Skonieczny, *J. Am. Chem. Soc.*, 1992, **114**, 1743.
30 J.F. King and K.C. Khemani, *Can. J. Chem.*, 1989, **67**, 2162.
31 S.N. Lyashchuk, Yu. G. Skrypnik and V.P. Besrodnyni, *J. Chem. Soc., Perkin. Trans. 2*, 1993, 1153.
32 Yu. G. Skrypnik and S.N. Lyashchuk, *Zh. Org. Khim.*, 1992, **28**, 906; *Chem. Abs.*, **118**, 168482.
33 J.F. King, J.Y.L. Lam and G. Ferrazzi, *J. Org. Chem.*, 1993, **58**, 1128.
34 J.F. King and J.Y.L. Lam, *J. Org. Chem.*, 1993, **58**, 3429.
35 J.F. King, M.S. Gill and D.F. Klassen, *Pure Appl. Chem.*, 1996, **68**, 825.
36 T.W. Bentley, 'Directing and Activating Effects in Reactions involving Sulfonic Acids and Derivatives' in *The Chemistry of Sulfonic Acids, Esters and their Derivatives*, S. Patai and Z. Rappoport (eds), Wiley, Chichester, 1991, Chapter 16, 671.
37 K. Yang, I.S. Koo, D.H. Kang and I. Lee, *Bull. Korean Chem. Soc.*, 1994, **15**, 419; Chem. Abs., **121**, 107707.
38 K. Yang, I.S. Koo and I. Lee, *J. Phys. Chem.*, 1995, **99**, 15035; *Chem. Abs.*, **123**, 2247420.
39 Yu.G. Skrypnik, V.P. Bezrodnyi, A.V. Kiprya and S.N. Lyashchuk, *Zh. Org. Khim.*, 1993, **29**, 1530; *Chem. Abs.*, **121**, 107716.
40 I.S. Koo, T.W. Bentley, G. Llewellyn and K. Yang, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1175.
41 I.S. Koo, T.W. Bentley, G. Llewellyn and S.J. Norman, *Croat. Chem. Acta*, 1992, **65**, 575.
42 I.S. Koo, K.W. Bentley, D.H. Kang and I. Lee, *J. Chem. Soc., Perkin Trans. 2*, 1991, 175.
43 R.M. Laird and M.J. Spence, *J. Chem. Soc. Perkin Trans. 2*, 1975, 637.
44 A. Arcoria, F.P. Ballistreri, E. Spina, G.A. Tomaselli and E. Maccarone, *J. Chem. Soc., Perkin Trans. 2*, 1988, 1793.
45 R.V. Vizgert, L.I. Rubleva and N.W. Maksimenko, *Zh. Org. Khim.*, 1989, **25**, 810.
46 B.G. Gnedin, S.N. Ivanov and M.V. Shchukina, *Zh. Org. Khim.*, 1988, **24**, 810.
47 T.W. Bentley, R.O. Jones and I.S. Koo, *J. Chem. Soc., Perkin Trans. 2*, 1994, 753.
48 I.S. Koo, I. Lee, J. Oh, K. Yang and T.W. Bentley, *J. Phys. Org. Chem.*, 1993, **6**, 223.
49 J.C. Choi, J. Oh, D.H. Kang, I.S. Koo and I. Lee, *J. Korean Chem. Soc.*, 1993, **37**, 695; *Chem. Abs.*, **120**, 53991.
50 D.D. Sung, Y.H. Kim, Y.M. Park, Z.H. Ryu and I. Lee, *Bull. Korean Chem. Soc.*, 1992, **13**, 599; *Chem. Abs.*, **118**, 101347.
51 R.M. Forbes and H. Maskill, *J. Chem. Soc., Chem. Comm.*, 1991, 854.
52 I. Lee, M.S. Choi and H.W. Lee, *J. Chem. Res. (S)*., 1994, **3**, 92; *Chem. Abs.*, **121**, 8398.
53 C.M. Suter, *The Organic Chemistry of Sulfur*, Wiley, New York, 1944. Reprinted edition by Intra-Science Research Foundation, Santa Monica, California, 1969, (a) 514; (b) 658.
54 E.M. Kaiser in *Organic Chemistry of Sulfur*, S. Oae (ed), Plenum Press, New York, 1977, 652.
55 A. Streitwieser and A. Dafforn, *Tetrahedron Lett.*, 1976, 1435.
56 P.J. Stang, Z. Rappoport, M. Hanack and L.R. Subramanian, *Vinyl Cations*, Academic Press, New York, 1979, 215, 282.
57 F.G. Bordwell, B.M. Pitt and M. Knell, *J. Am. Chem. Soc.*, 1951, **73**, 5004.
58 M.J.V. De Oliveira Baptista and D.A. Widdowson, *J. Chem. Soc., Perkin Trans. 1*, 1978, 295.
59 A. Williams, K.T. Douglas and J.S. Loran, *J. Chem. Soc., Chem. Comm.*, 1974, 689.

60 A. Williams and K.T. Douglas, *J. Chem. Soc., Perkin Trans. 2*, 1974, 1727.
61 S. Thea, G. Cevasco, G. Guanti and A. Williams, *J. Chem. Soc., Chem. Comm.*, 1986, 1582.
62 W.J. Spillane, G. Hogan, P. McGrath, J. King and C. Brack, *J. Chem. Soc., Perkin Trans. 2*, 1996, 2099.
63 H. Oh, Y.B. Kwon and I. Lee, *J. Phys. Org. Chem.* 1993, **6**, 357.
64 V. Nummert, M. Piirsalu and V. Palm, *Org. React. (Tartu)*, 1990, **27**, 99; *Chem. Abs.*, **116**, 193427.
65 V. Nummert and M. Piirsalu, *Org. React. (Tartu)*, 1990, **27**, 217; *Chem. Abs.*, **116**, 193432.
66 I.M. Gordon and H. Maskill, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1951.
67 R. Taylor, *Electrophilic Aromatic Substitution*, Wiley, Chichester, 1990, 334.
68 W.E. Truce and C.W. Vrieson, *J. Am. Chem. Soc.*, 1953, **75**, 5053.
69 S.C.J. Olivier, *Recl. Trav. Chim. Pays-Bas*, 1914, **33**, 91, 244; S.C.J. Olivier, *Recl. Trav. Chim. Pays-Bas*, 1915, **35**, 109, 166.
70 F.R. Jensen and H.C. Brown, *J. Am. Chem. Soc.*, 1958, **80**, 4038, 4042, 4046.
71 Y. Yoshi, A. Ito, T. Hirashima, S. Shinkai and O. Minabe, *J. Chem. Soc. Perkin Trans. 2*, 1988, 777.
72 H. Cerfontain and A. Telder, *Recl. Trav. Chim. Pays-Bas*, 1965, **84**, 1613.
73 H. Cerfontain, H.J. Hofman and A. Telder, *Recl. Trav. Chim. Pays-Bas*, 1964, **83**, 493.
74 M. Kobayashi, K. Honda and A. Yamaguchi, *Tetrahedron Lett.*, 1968, 487.
75 G.A. Olah, J. Nishimura and Y. Yamada, *J. Org. Chem.*, 1974, **39**, 2430.
76 E.G. Willard and H. Cerfontain, *Recl. Trav. Chim. Pays-Bas*, 1973, **92**, 739.
77 E.C. Dart and G. Holt, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1403.
78 J.K. Bosscher and H. Cerfontain, *J. Chem. Soc. (B)*, 1968, 1524.
79 M.P. van Albada and H. Cerfontain, *Recl. Trav. Chim. Pays-Bas*, 1972, **91**, 499.
80 G. Holt and B. Pogdin, *J. Chem. Soc.*, 1960, 2508; E.C. Dart, G. Holt and K.D. Jeffreys, *J. Chem. Soc.*, 1964, 5663.
81 M. Kobayashi, H. Minato and Y. Kohara, *Bull. Chem. Soc. Jpn.*, 1970, **43**, 234, 520.
82 G.A. Olah, S. Kobayashi and J. Nishimura, *J. Am. Chem. Soc.*, 1973, **95**, 564.
83 K. Smith, G.M. Ewart and K.R. Randles, *J. Chem. Soc., Perkin Trans. 1*, 1997, 1085.
84 S. Daley, K.A. Trevor, K.R. Randles and B.D. Gott, *PCT Int. Appl. WO* 9318000 (1993); *Chem. Abs.*, **120**, 54320.
85 L.V. Kuritsyn, T.P. Kustora, Y.A. Moskvichev and A.V. Nikiforov, *Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol.*, 1996, **39**, 183; *Chem. Abs.*, **126**, 211710.

CHAPTER 4

Sulfonation and Chlorosulfonation of Aromatic Compounds using Chlorosulfonic Acid

1 Introduction

Chlorosulfonic acid can be used for the sulfonation or chlorosulfonation of a wide range of aromatic compounds. Generally for sulfonation only approximately one molar equivalent of the reagent is employed in an inert solvent, *e.g.* chloroform, to avoid formation of large amounts of sulfonyl chlorides as byproducts. On the other hand, for chlorosulfonation, an excess of the reagent is used either neat or in the presence of a solvent to drive the reversible reaction to completion. The optimum conditions in each case will depend on the nature of the aromatic substrate which it is desired to sulfonate or chlorosulfonate (see Chapter 2, p 16).

2 Aromatic Hydrocarbons

2.1 Monocyclic Systems

2.1.1 Benzene and its Alkyl Derivatives

Aromatic hydrocarbons are readily protonated in strongly acidic media, *e.g.* sulfuric and chlorosulfonic acid (Equation 1).

$$ArH + H^+ \rightleftharpoons ArH_2^+ \quad (1)$$

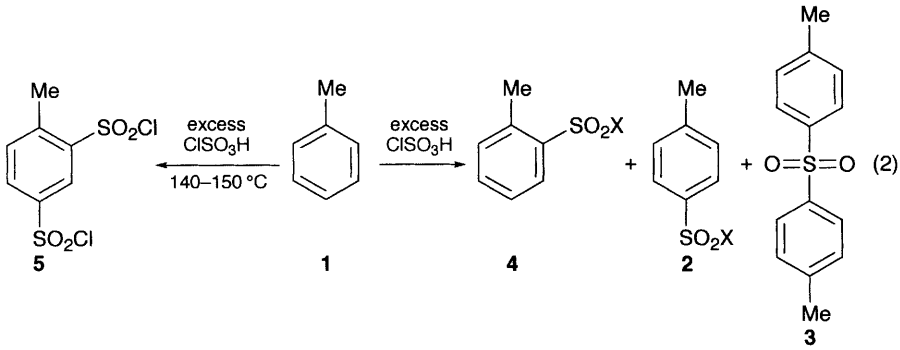
The protonated form of the hydrocarbon is considerably less reactive towards electrophilic substitution than the unprotonated substrate.

The early work on the sulfonation and chlorosulfonation of aromatic compounds has been extensively documented in Suter's book[1] and for aromatic hydrocarbons and their halogen derivatives by Suter and Weston.[2] More recently, the chlorosulfonation of aromatic and heteroaromatic systems was reviewed by

Bassin, Cremlyn and Swinbourne.[3] Details of kinetic and mechanistic studies on sulfonation and chlorosulfonation of aromatic hydrocarbons and other derivatives have been described in Chapter 2. Chlorosulfonic acid is a very active sulfonating agent and when benzene is added to an excess of the reagent at room temperature, benzenesulfonyl chloride is formed (> 70%) with only a trace of diphenyl sulfone.[1–4] On the other hand, when an excess of benzene is present, the major products are diphenyl sulfone and benzenesulfonic acid.[1,4,5]

Early studies of the reaction of chlorosulfonic acid on benzene were carried out by Armstrong[6] who obtained a mixture of benzenesulfonic acid, diphenyl sulfone and benzenesulfonyl chloride. When benzene is heated with a large excess of chlorosulfonic acid (ten equivalents) at 150–160 °C for 2 hours, the major product was benzene *m*-disulfonyl chloride (28%), together with small amounts of dichlorosulfonyldiphenyl sulfone and benzene *p*-disulfonyl chloride.[2,7,8] Several patents[9–15] have demonstrated that the reaction of chlorosulfonic acid on benzene is capable of producing high yields of benzenesulfonyl chloride, including its manufacture in 87.6% yield by a continuous process at 31 °C.[16] The reaction in 1,2-dichloroethane at 20 °C was sensitive to the reaction conditions: the maximum yield of benzenesulfonic acid (83%) was obtained using an approximately 10:1 ratio of C_6H_6:$ClSO_3H$.[17] Addition of sodium sulfate to the reaction was demonstrated to reduce the yield of benzenesulfonyl chloride.[18] Chlorosulfonic acid (< 1 molar equivalent) in dichloromethane or nitromethane converts benzene into the sulfonic acid with only small amounts of the sulfonyl chloride or sulfone being formed.[19] The kinetics of the sulfonation of benzene by chlorosulfonic acid in dichloroethane solution have been examined: the reaction was found to be kinetically third order (first and second order with respect to C_6H_6 and $ClSO_3H$).[20]

The first report of the use of chlorosulfonic acid for the conversion of toluene **1** into the *p*-sulfonic acid (**2**; X = OH) and di-*p*-tolyl sulfone **3** (Equation 2) was in 1878;[21] it was mentioned that some *o*-sulfonic acid (**4**; X = OH) may also be formed.



The reaction of toluene **1** with chlorosulfonic acid (two equivalents) at 10 °C gives mainly a mixture of the *o*- and *p*-sulfonyl chlorides (**4** and **2**; X = Cl).[1,2] Harding[22] was able to obtain toluene-*p*-sulfonyl chloride (**2**; X = Cl) in high yields (95%) by reaction of excess chlorosulfonic acid on toluene at 75–80 °C; low temperatures favoured *o*-sulfonation[23] (see also Chapter 2; p 18).

However, the relative proportion of the *o*-isomer is never greater than 45%, even under the optimum conditions for the formation of this isomer;[2,24,25] the two isomers can be separated by freezing out the solid *p*-isomer (Chapter 2, p 17). The reaction generally affords a mixture of isomers,[26] in which the yield of the *p*-isomer was substantially increased by addition of ammonium chloride[27] and catalysts;[28] sometimes it was possible to isolate the *p*-isomer as the sole product.[29] The ratio of the *o*- to *p*-isomers is dependent on the molar ratio of toluene and reagent.[26] The isomers of toluenesulfonyl chloride can be prepared in a continuous process,[30] and the reaction can be improved by use of an additive.[30a] Toluene **1** by heating with a large excess of chlorosulfonic acid at 140–150 °C affords mainly the 2,4-disulfonyl chloride **5** (Equation 2).[7,8]

2.1.2 Higher Alkylbenzenes

In contrast to the behaviour of toluene, ethylbenzene with chlorosulfonic acid only yields the *p*-sulfonic acid,[31,32] which agrees with observation that the *o*-isomer (obtained indirectly) is rapidly converted into the *p*-isomer at 100 °C.[1] 1-Phenyloctane,[23] phenylcyclohexane,[23] isopropylbenzene (cumene)[23,33] and tertiary butylbenzene[38] were also chlorosulfonated in the *p*-position; presumably this orientation is dictated by steric hindrance and thermodynamic stability. The observed regioselectivity of sulfonation in a series of monoalkylbenzenes (PhR) indicates the importance of steric effects.[33] In the sulfonation of cumene by chlorosulfonic acid, the formation of the *o*-isomer was favoured by low temperatures (0–25 °C) and by adding the substrate to the reagent. Higher molecular weight alkylbenzenes,[34] *e.g.* decyl-[35] and dodecylbenzene, similarly gave the corresponding *p*-sulfonyl chlorides on treatment with excess chlorosulfonic acid.[36,37]

The reaction is claimed[37a] to be improved by use of an equimolar mixture of chlorosulfonic acid and sulfuryl chloride; apparently chlorinated byproducts were not formed. *o*-Xylene (1,2-dimethylbenzene) reacts with excess chlorosulfonic acid to give the expected 4-sulfonyl chloride (74–86% yield),[38] and by treatment with the reagent (seven equivalents) at 8 °C, the reaction also produces some of the 3-sulfonyl chloride (26%).[39]

This orientation of sulfonation would be unfavourable on steric grounds and, indeed, it is known[1] that on heating, the 3-sulfonic acid rearranges to the 4-isomer.

m-Xylene (1,3-dimethylbenzene) is slightly more easily sulfonated than the *o*-isomer and treatment with excess chlorosulfonic acid gives the 4,6-disulfonyl chloride.[1,8] *p*-Xylene (1,4-dimethylbenzene) is the least reactive isomer, however, heating with a large excess of the reagent yields a mixture of the 2,6- and 2,5-disulfonyl chlorides in the ratio of 10:1.[40] In both the latter reactions, the *m*- and *p*-xylyl sulfones are significant byproducts. Cymene (1-methyl-4-isopropylbenzene) with chlorosulfonic acid at 20–25 °C yields 2-methyl-5-isopropylbenzenesulfonyl chloride.[41]

Mesitylene (1,3,5-trimethylbenzene), by heating with a mixture of chlorosulfonic acid and sulfuryl chloride at 100 °C (10 hours), gives a high yield of 2,4,6-trimethylbenzene-1,3-disulfonyl chloride;[1] the same compound (70% yield) also

results from the action of chlorosulfonic acid at −5 °C.[2,42] In the reaction using hot chlorosulfonic acid and sulfuryl chloride, it is rather surprising that extensive chlorination of the substrate did not occur so reducing the yield of the desired disulfonyl chloride.

5-Tertiary butyl-1,3-dimethylbenzene reacts with excess chlorosulfonic acid in chloroform solution to give a high yield of the 2-sulfonyl chloride.[38]

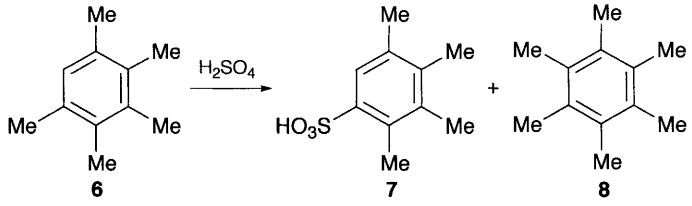
1,2,4- and 1,3,5-Triisopropylbenzene react with chlorosulfonic acid in carbon tetrachloride (30–50 °C) to yield the 5- and 2-sulfonyl chlorides respectively,[43] and 1-methyl-3,5-diisopropylbenzene gives the 2-sulfonyl chloride.[44]

The chlorosulfonation of 1,3,5-triisopropylbenzene by excess chlorosulfonic acid is enhanced by the presence of sodium or potassium chloride and the use of a promoter, *e.g.* H_2O, HOAc, HCO_2H, EtOH or 35% aq. HCl.[44a]

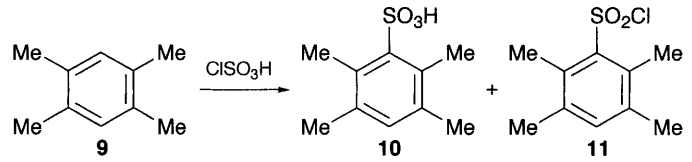
A general preparative route to arylsulfonyl chlorides involves treatment of the aryl compound with a mixture of chlorosulfonic acid and oxalyl chloride at 40 °C (4 hours); the mixture may also include an auxillary, *e.g.* dimethylformamide or phosphoric acid.[10,11]

2.1.3 *Polyalkylbenzenes*

Sulfonation of tetra- and pentaalkylbenzenes is often complicated by competing alkyl group migration (the Jacobsen rearrangement).[1,45] For example, pentamethylbenzene **6** by prolonged reaction with sulfuric acid gives a mixture of tetramethylbenzenesulfonic acid **7** and hexamethylbenzene **8** (Equation 3). The latter compound arises from the initially formed pentamethylbenzenesulfonic acid by methyl group migration. Polyalkylbenzenesulfonic acids and sulfonyl chlorides can, however, often be easily prepared because the alkyl group rearrangement is relatively slow compared with sulfonation; thus rapid treatment of 1,2,4,5-tetramethylbenzene (durene) **9** with chlorosulfonic acid yields a mixture of the sulfonic acid **10** and the sulfonyl chloride **11** without appreciable rearrangement (Equation 4);[1,2,46] also 1,2,3,4-tetramethylbenzene with excess chlorosulfonic acid in chloroform affords the 5-sulfonyl chloride in high yield (95%).[38]



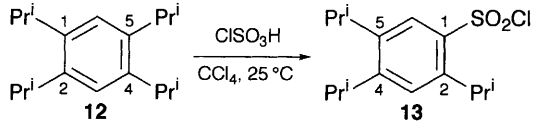
(3)



(4)

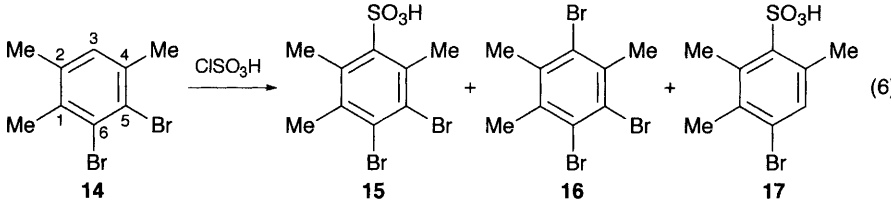
In some cases, as with pentamethylbenzenes, the alkyl group rearrangement is

rapid. For instance, 1,2,4,5-tetraisopropylbenzene **12** by treatment with excess chlorosulfonic acid (three equivalents) in carbon tetrachloride at room temperature gives a very high yield (97%) of 2,4,5-triisopropylbenzenesulfonyl chloride **13** (Equation 5).[43]



12 **13** (5)

The Jacobsen rearrangement has been reviewed by Smith;[45] it definitely involves the sulfonic acids and not the hydrocarbons and may involve migration of halogen as well as alkyl groups. One example using chlorosulfonic acid is the rearrangement of 5,6-dibromo-1,2,4-trimethylbenzene **14** to give a mixture of the compounds **15–17** (Equation 6). In this example, the Jacobsen reaction involves the rearrangement of the bromine atom and the major product was the tribromo derivative **16.**



14 **15** **16** **17** (6)

Other examples of the action of chlorosulfonic acid on polyalkylbenzenes[2] include; 1-ethyl-2,4,6-trimethylbenzene to give the 3-sulfonic acid;[47] 1,2,3,5- and 1,2,4,5-tetraethylbenzenes to give high yields of the 4- and 3-sulfonic acids respectively,[48] also pentaethylbenzene gives the 6-sulfonic acid (89%).[48]

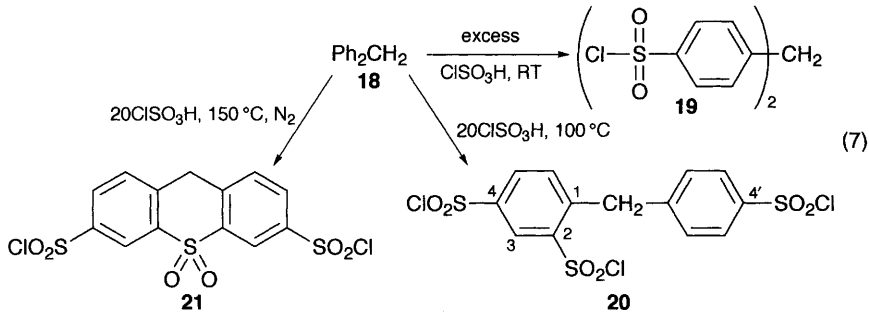
A general procedure for synthesis of alkylbenzenesulfonyl halides has been proposed[49] by heating an alkylbenzene with a halosulfonic acid or at room temperature in the presence of Lewis acids. For example, mesitylene, by stirring with fluorosulfonic acid and antimony pentafluoride at 25 °C (16 hours), gives 2,4,6-trimethylbenzene-1,3-disulfonyl fluoride (66%).

2.2 Polycyclic Aromatic Systems

2.2.1 Compounds not Containing Fused Aromatic Nuclei

2.2.1.1 Diarylalkanes. Early studies[1,2,50] showed that diphenylmethane **18** reacted with chlorosulfonic acid (one equivalent) at 0 °C to give the 4-sulfonic acid (82%) together with a small amount of the sulfone. Later workers[51] claimed that use of an excess of the reagent (4.2 equivalents) afforded the 4,4′-disulfonyl chloride **19** (Equation 7). However, repetition[52] of their procedure gave a gum which was difficult to extract into an organic solvent and the yield of **19** was only 45%. The optimum yield (60%) of the disulfonyl chloride **19** was obtained using slightly more chlorosulfonic acid (4.5 equivalents) for 48 hours with filtration of the reaction mixture before addition to ice.[52] The use of chlorosulfonic acid (two

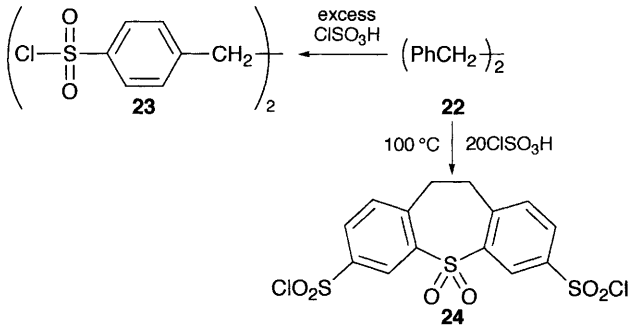
equivalents) in thionyl chloride as solvent gave a reasonable yield (53%), while reaction with chlorosulfonic acid (4.2 equivalents) for 3 weeks gave the purest product (51%).[52] Attempts to achieve further chlorosulfonation of diphenylmethane **18** by, for example, treatment with a large excess of chlorosulfonic acid (20 equivalents) at ambient temperature for 3 weeks were unsuccessful; only the disulfonyl chloride **19** was isolated. On the other hand, when the mixture was heated at 100 °C (3 hours), the 2,4,4′-trisulfonyl chloride **20** was isolated (67%) (Equation 7).



(7)

Under even more drastic conditions (150 °C, 4 hours), the same reaction mixture afforded the cyclic sulfone disulfonyl chloride **21** (45%).[53] Attempted chlorosulfonations of α-chloro and α,α′-dichlorodiphenylmethane by reaction with chlorosulfonic acid failed, possibly because the substitution of the α-hydrogens destroys the activating hyperconjugative effect on the phenyl rings.[52]

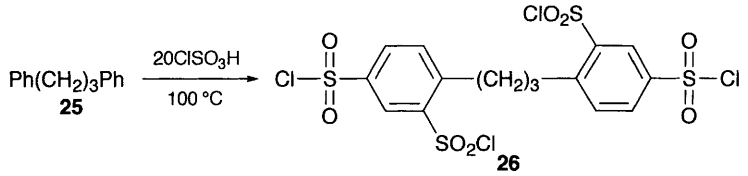
1,2-Diphenylethane (bibenzyl) **22** reacted with excess chlorosulfonic acid (4.5 equivalents) at room temperature (24 hours) to give the 4,4′-disulfonyl chloride **23** (79%) (Equation 8).[8,52]



(8)

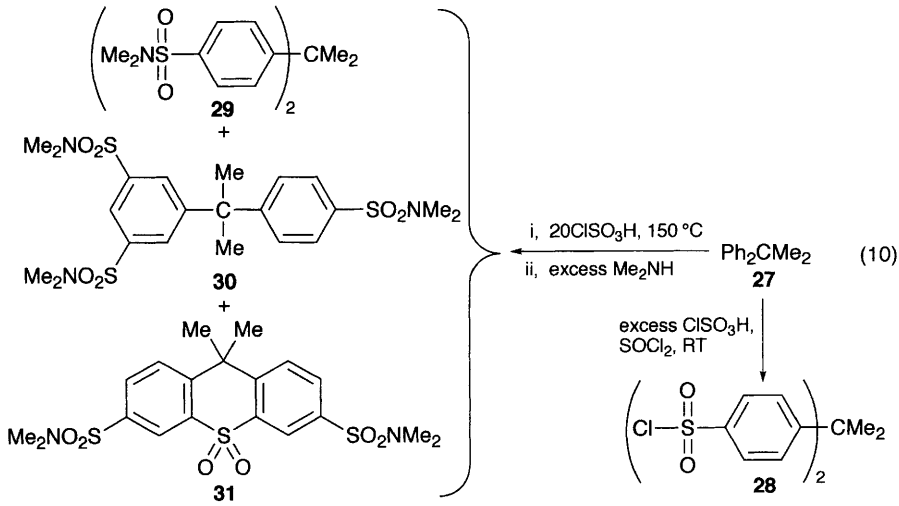
Diphenylethane **22** is more reactive towards chlorosulfonic acid than diphenylmethane **18**, probably as a result of increased hyperconjugative electron release from the ethylene bridge bond. When diphenylethane **22** was heated with a large excess of chlorosulfonic acid (20 equivalents) at 100 °C (4 hours), the cyclized product **24** was isolated in excellent (90%) yield (Equation 8).[53] The cyclization to the seven-membered ring sulfone **24** was more easily achieved than the analogous conversion of diphenylmethane **18** to the six-membered ring sulfone **21**

(Equation 7). This appeared rather surprising, since the two phenyl rings in 1,2-diphenylethane **22** are further apart than those in diphenylmethane **18**. However, examination of molecular models revealed that the methylene carbon atoms in the six-membered sulfone **21** appeared to be strained due to distortion of the normal tetrahedral sp^3 bond angle. In contrast, in the seven-membered ring sulfone **24**, the ethylene carbons appeared to have a more tetrahedral configuration and hence they are somewhat less sterically strained.[53] The reaction of 1,3-diphenylpropane **25** with hot excess chlorosulfonic acid was investigated in an attempt to synthesise the eight-membered ring sulfone analogous to compound **24**. However, diphenylpropane **25** with hot chlorosulfonic acid (20 equivalents) at 100 or 150 °C (4 hours) only gave the diphenylpropane tetrasulfonyl chloride **26** (Equation 9)[53] and no cyclization was observed.



(9)

2,2-Diphenylpropane **27** reacted with chlorosulfonic acid (three equivalents) in thionyl chloride at room temperature (7 days) to yield the 4,4′-disulfonyl chloride **28** (Equation 10). However, when **27** was heated with large excess of chlorosulfonic acid (20 equivalents) at 150 °C (4 hours) and subsequently treated with excess dimethylamine, the compounds **29–31** were isolated; the cyclized product **31** was only obtained in low yield[53] (Equation 10).

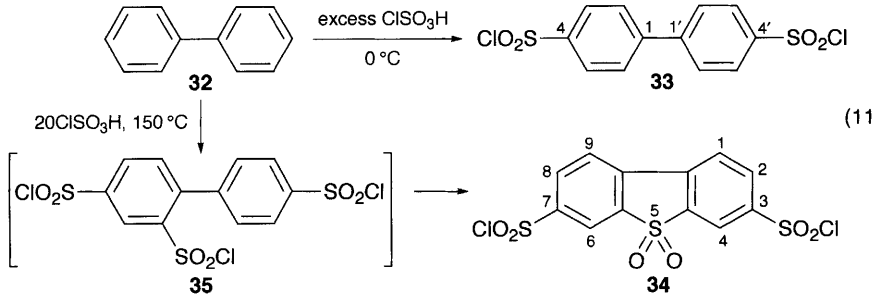


(10)

Attempted chlorosulfonation of stilbene (1,2-diphenylethene) or 1,4-diphenylbutadiene with chlorosulfonic acid failed to give identifiable products, probably as a result of acid-catalysed polymerization of the substrates in the highly acidic

media.[53] In contrast, early studies[2] suggested that stilbene reacts with oleum to give, probably the 4,4′-disulfonic acid, without effecting the double bond, but these results could not be reproduced with chlorosulfonic acid.

2.2.1.2 Biphenyl. Biphenyl **32** gives the 4-sulfonic acid by warming with chlorosulfonic acid (one equivalent) in tetrachloroethane and by treatment with an excess of the reagent at 0 °C, the 4,4′-disulfonyl chloride **33** is formed in 80% yield (Equation 11).[8,53a]

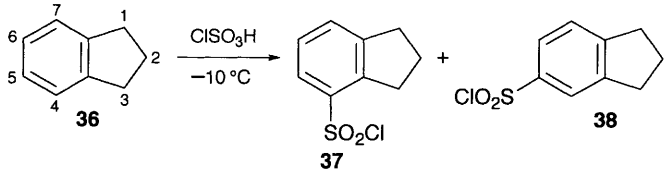


(11)

Pollak *et al.*[8] claimed that the reaction of biphenyl **32** with excess chlorosulfonic acid (six equivalents) at 18 °C affords dibenzothiophene-5,5-dioxide-3,7-disulfonyl chloride **34**, but more recent attempts[53,53a] to reproduce this result were unsuccessful and only the 4,4′-disulfonyl chloride **33** (80%) was isolated. However, the cyclized product **34** was obtained in good yield (72%) when biphenyl **32** was heated with a large excess of chlorosulfonic acid (20 equivalents) at 150 °C (4 hours) (Equation 11).[53] The reaction presumably involves the formation of the intermediate biphenyl-2,4,4′-trisulfonyl chloride, **35** which subsequently cyclizes with loss of hydrogen chloride to give the dibenzothiophene dioxide **34**. Further study[53] of the action of chlorosulfonic acid on biphenyl **32** showed that the optimum yield of the 4-sulfonyl chloride (43%) was derived from treatment of **32** with the reagent (1.5 equivalents) in thionyl chloride as solvent at 0 °C (1 week). The best yield (89%) of the 4,4′-disulfonyl chloride **33** was also achieved by treatment of the hydrocarbon **32** with chlorosulfonic acid (three equivalents) in thionyl chloride at room temperature (1 week).

2,2′,3,3′,4,4′,6,6′-Octamethylbiphenyl reacts with excess chlorosulfonic acid (12 equivalents) at 0 °C to give the 5,5′-disulfonyl chloride (77%).[54] Hexaphenylbenzene with hot excess chlorosulfonic acid gave hexa(chlorosulfonylphenyl)benzene; steric considerations suggested *para*-sulfonation.[54a]

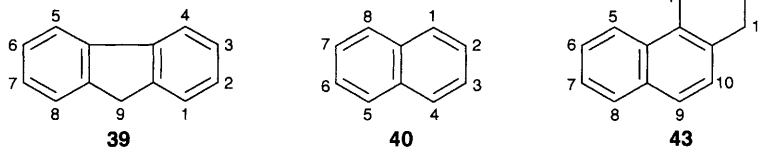
Indane **36** was added dropwise to excess chlorosulfonic acid (4.5 equivalents) at −10 °C (3 hours) and gave a mixture of the 4- and 5-sulfonyl chlorides **37** and **38** in 76% yield (Equation 12).[55] It was discovered[56] that with increasing temperature the relative amount of indane-5-sulfonic acid increases at the expense of the 4-isomer. This is presumably because the 5-sulfonic acid is relatively less sterically hindered than the 4-acid and consequently is the more thermodynamically stable isomer.



36 **37** **38** (12)

2.2.1.3 Fluorene. This is an example of a bridged biphenyl hydrocarbon. The action of chlorosulfonic acid and sulfuric acid on fluorene **39** results in substitution mainly at the 2- and 7-positions;[5,57–59] thus the action of chlorosulfonic acid (one equivalent) gives the 2-sulfonic acid while excess of the reagent affords 2,7-disulfonic acid.[2]

A similar orientation of sulfonation was found in the reaction of 9-alkylfluorenes[60] and 9,9′-spirofluorene;[61] these positions are *para* with respect to the bridge bond, so the substitution orientation is analogous to that of biphenyl itself.



39 **40** **43**

Cremlyn *et al.*[52] examined the reaction of fluorene **39** with excess chlorosulfonic acid (six or twelve equivalents) or less reagent (three equivalents) in thionyl chloride. In each case, the product appeared to be a 1:1 mixture of the 2-sulfonyl chloride and the 2,7-disulfonyl chloride. The latter compound was obtained as the major product when fluorene-9-carboxylic acid was treated with a large excess of chlorosulfonic acid (twelve equivalents) in boiling chloroform (2 hours).[52]

2.2.2 *Compounds Containing Fused Aromatic Nuclei*

2.2.2.1 Naphthalene. Early studies[1,2] showed that the action of slightly less than one equivalent of chlorosulfonic acid on a 10% solution of naphthalene **40** in carbon disulfide gives the 1-sulfonic acid and a little of the 1,5-disulfonic acid, but none of the 2-sulfonic acid was isolated.[6] Naphthalene has also been reacted with chlorosulfonic acid in nitrobenzene and in nitrotoluene at 20–35 °C.[62] With an equimolar quantity of the reagent, a mixture of the mono-sulfonic acids and dinaphthyl sulfones was formed;[63,64] at 6 °C, the 1,1-sulfone predominated, but at 170 °C, the 2,2′-isomer was the major product.[63] The reaction has also been extensively studied at low temperatures (−35 to 0 °C).[65]

In the disulfonation of naphthalene **40**, the two sulfonic acid groups are never *o*-, *p*- or *peri*-(1,8)- with respect to each other.[2] Naphthalene, by treatment with chlorosulfonic acid (two equivalents) at 15–45 °C, yields a mixture of the 1,5-disulfonic acid and the 1,5-disulfonyl chloride.[1,6,66]

When naphthalene was reacted with chlorosulfonic acid (two or four equiva-

lents) in carbon tetrachloride as diluent, a mixture of the sulfonyl chlorides and the 1- and 1,5-disulfonic acids was always formed; low temperatures favoured chlorosulfonation.[1] Gradual addition of naphthalene to chlorosulfonic acid at 5–10 °C, caused considerable evolution of hydrogen chloride and the mixture was heated at 50–55 °C for 12–14 hours to give naphthalene-1,5-disulfonyl chloride.

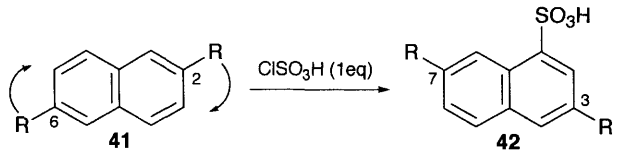
It was discovered that increasing the amount of the reagent speeded up the reaction and enhanced the yield of the product.[67] Dissolving naphthalene **40** in chlorosulfonic acid (10 equivalents) at 0 °C gives a reasonable yield of the 1,5-disulfonyl chloride (60%)[8] and provides the simplest route to this derivative. Potassium naphthalene-2-sulfonate, by heating with chlorosulfonic acid (three equivalents) at 100 °C, was converted into the 1,6-disulfonic acid;[1,2] this reaction must involve migration of the sulfonic acid group from the 2- to the 1-position. When naphthalene **40** was heated with excess chlorosulfonic acid under drastic conditions (180 °C, 10 hours), the product was tetrachlorophthalic anhydride.[68] In this reaction, chlorosulfonic acid functions as a chlorinating, oxidizing and dehydrating agent, since naphthalene is known to give phthalic acid on oxidation.

Naphthalene-1,5-disulfonyl chloride by treatment with a very large excess of chlorosulfonic acid afforded the 1,3,5-trisulfonyl chloride.[69] The powerful conditions required for this reaction are indicative of the strongly deactivating influence of the two sulfonyl groups on the substrate.

2.2.2.2 Alkylnaphthalenes. The presence of alkyl groups on the naphthalene ring facilitate sulfonation as a result of their (+I) electron donating effect. 1-Alkyl derivatives generally preferentially sulfonate in the 4-position of the naphthalene nucleus.[1,2] 1-Methylnaphthalene is more effectively sulfonated with chlorosulfonic acid than with concentrated sulfuric acid and reaction with chlorosulfonic acid in carbon tetrachloride (0 °C) gives a mixture of the 4- and 5-sulfonic acids (73%).[70,71] Reaction with an equimolar amount of the reagent at −7 to 0 °C, followed by treatment with potassium hydroxide, gave a high yield of potassium 1-methylnaphthalene-4-sulfonate (88%).[72]

2-Methylnaphthalene reacts with chlorosulfonic acid in nitrobenzene at 30–40 °C to yield the 8-sulfonic acid.[73] 1-Benzylnaphthalene with the reagent in nitrobenzene solution at room temperature affords the 4-sulfonic acid as the sole product[74] and 1,8-dibenzylnaphthalene with hot chlorosulfonic acid (100–110 °C) also probably gives the 4-sulfonic acid.[75]

Symmetrical 2,6-dialkylnaphthalenes (alkyl ≥ C4) **41** have been shown[76,77] to react with the reagent (one equivalent) to yield 3,7-dialkylnaphthalenesulfonic acids **42**, the reaction involves alkyl group migration since steric hindrance precludes sulfonation *ortho* to the alkyl group (Equation 13).



41 **42**

(arrows indicate alkyl group migration) (13)

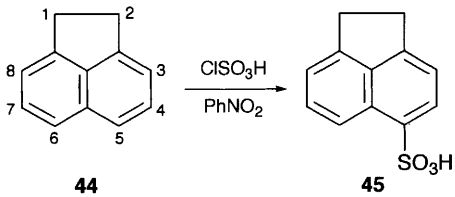
Similarly, 2,6-ditertiary butylnaphthalene (**41**; R = Bu^t), with excess chlorosulfonic acid (two equivalents), affords 3,7-ditertiary butylnaphthalene-1,5-disulfonic acid.[78]

Sulfonation of 1,2,3,4-tetrahydro-4-methylphenanthrene **43** (essentially a 1,2-dialkylnaphthalene derivative) with chlorosulfonic acid yields the 9-sulfonic acid.[79]

Tetralin (1,2,3,4-tetrahydronaphthalene) by reaction with excess chlorosulfonic acid (four equivalents) at −5 to −10 °C afforded a mixture of 5- and 6-sulfonyl chlorides (80% yield).[2]

2.2.2.3 Acenaphthene. Acenaphthene **44** is structurally related to the alkylnaphthalenes and consequently the preferred orientation of sulfonation should be in the 3- and 5-positions. However, the literature is confusing: with concentrated sulfuric acid at 100 °C, the product was first considered to be the 5-sulfonic acid,[80,81] but later it was argued that this assignment was erroneous and that the product was the 3-isomer.[1,5,82]

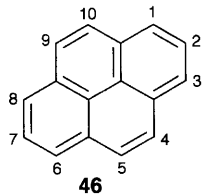
More recent studies[83] of the sulfonation of acenaphthene **44** by 95.2% sulfuric acid at 25 °C showed that the reaction afforded a mixture of the 3- and 5-sulfonic acids in approximate yields of 68% and 32% respectively. The preferred 3-sulfonation is explained in terms of an electrostatic, hyperconjugative proximity effect between the incoming sulfonic acid group and the adjacent methylene group. Sulfonation of acenaphthene by chlorosulfonic acid (one equivalent) in nitrobenzene at 0 °C was reported to yield the 3-sulfonic acid (75%),[82] and when acenaphthene **44** was heated with the reagent (0.5 equivalents) at 123–130 °C for 10 hours, the product was 3,3′-diacenaphthyl sulfone.[84] Repetition of the reaction of **44** with chlorosulfonic acid (one equivalent, 0 °C) was claimed to yield the 5-sulfonic acid (40%); while use of excess reagent (4.5 equivalents) in carbon tetrachloride (0–20 °C) afforded the 3,5-disulfonyl chloride.[85] In agreement, recent studies[85a] showed that the action of chlorosulfonic acid (one equivalent) on acenaphthene **44** at 0–20 °C gave an excellent yield of the 5-sulfonic acid (**45**, 76%) (Equation 14).



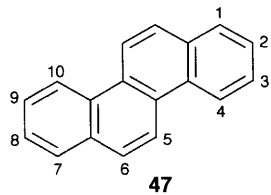
44 **45** (14)

The product (**45**), by warming with phosphorus pentachloride, afforded the corresponding sulfonyl chloride and the structures of both products were confirmed by NMR spectroscopy. Acenaphthene-5-sulfonyl chloride and the corresponding hydrazide are valuable fluorescence derivatization reagents for amines, amino acids and carbonyl compounds respectively in high performance liquid chromatography.[85a]

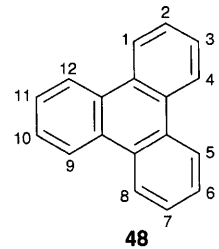
Pyrene **46** reacts with chlorosulfonic acid (two equivalents) in *sym*-tetrachloroethane (10–20 °C) for 15–20 hours to yield the 3-sulfonic acid (90–92%).[2,86,87]



46



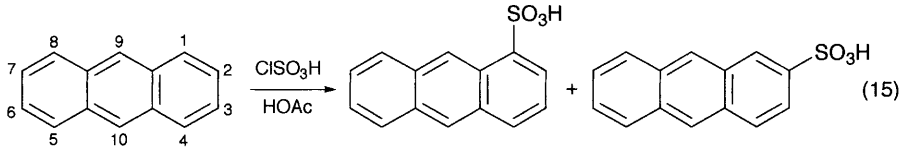
47



48

Chrysene **47** with chlorosulfonic acid at low temperature affords the 2-sulfonic acid which is useful as dye intermediate.[88] Triphenylene **48** reacts with chlorosulfonic acid in nitrobenzene to yield triphenylenesulfonic acid.[5,89]

2.2.2.4 Anthracene. Sulfonation of anthracene **49** with chlorosulfonic acid in acetic acid (95 °C) affords equal amounts of the 1- and 2-sulfonic acids (**50** and **51**) (Equation 15); increasing the temperature of the reaction favours the formation of the 2-isomer **51**.[90,91]



(15)

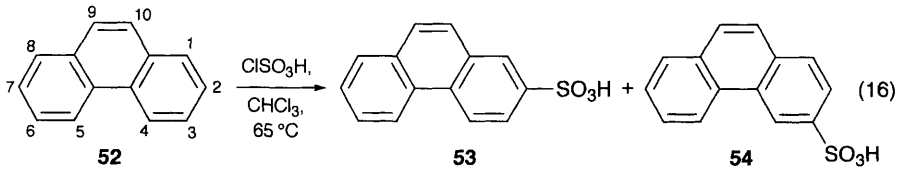
49 **50** **51**

Other products in the reaction of anthracene with chlorosulfonic acid include the 9-sulfonic acid, a mixture of anthracenedisulfonic acids, 9-chloroanthracene, 9,9-bianthryl and oligoanthracenes. The yield and formation of each product depended on the experimental conditions and the nature of the solvent used with the reagent, *e.g.* acetic acid, chloroform, dioxane or a mixture of pyridine and isoparaffin.[91] Under acidic conditions, anthracene does not sulfonate in the *meso* (9,10)-positions and the two rings react rather like naphthalene so that sulfonation, < 100 °C favours formation of the 1-sulfonic acid **50**, while higher temperatures tend to yield the 2-isomer **51**.

The absence of 9-sulfonation is remarkable since the predicted order of positional reactivity is $9 \gg 1 > 2$[5] and is due to steric hindrance, which causes protiodesulfonation to be very rapid in protic media. This argument is supported by the observation that sulfonation of anthracene **49** under aprotic conditions (sulfur trioxide–dioxane) yields the 1-, 2- and 9-sulfonic acids in 26, 8 and 60% yields respectively.[91]

The formation of oligoanthracenes was observed during mild sulfonation of **49** by chlorosulfonic acid (one equivalent) in nitrobenzene solution at 50 °C (3 hours). On the other hand, a similar reaction in acetic acid at 70 °C only afforded water-soluble sulfonic acids and the possible mechanisms of polymerization of anthracene were discussed.[92]

2.2.2.5 Phenanthrene. Studies in the sulfonation of phenanthrene **52** indicated a positional order of reactivity of $3 > 2 > 9 > 1$.[93] This is different from the theoretical order of $9 > 1 > 4 > 3 > 2$,[5] because of steric hindrance which accounts for the complete absence of the 4-isomer. Reaction of phenanthrene **52** with chlorosulfonic acid (one equivalent) in boiling chloroform affords the 2- and 3-sulfonic acids **53** and **54** (Equation 16) (85% yield of the mixture of isomers was isolated as the lead sulfonates).[94]



52 **53** **54** (16)

3 Aryl Halides

3.1 Halobenzenes

The (−I) inductive effect of the halogen atom means that halobenzenes are less easily sulfonated than benzene, and due to steric factors, the halogen atom tends to strongly direct the sulfonation to the *p*-position.[1,2] Huntress and Carten[95] introduced chlorosulfonic acid as a reagent for the identification of aryl halides either by reaction with neat excess chlorosulfonic acid or in the presence of chloroform as an inert solvent. In the majority of cases, the aryl halides were converted into the corresponding sulfonyl chlorides in good yields and these were subsequently treated with ammonium hydroxide to give the sulfonamides, the melting points of which were used in organic qualitative analysis to identify the original aryl halides.

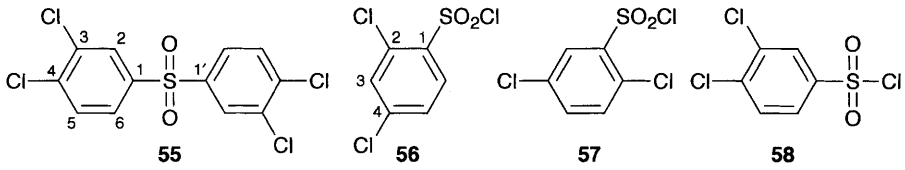
Some compounds gave abnormal results:[95] thus fluorobenzene with neat chlorosulfonic acid (40 °C) only gave 4,4′-difluorodiphenyl sulfone. On the other hand, treatment of fluorobenzene with the reagent in chloroform solution afforded some *p*-fluorobenzenesulfonyl chloride;[96] while *m*-difluorobenzene reacted with excess reagent (30–40 °C, 3 hours) to give 2,4-difluorobenzenesulfonyl chloride (98.6% yield).[97]

Chlorobenzene reacts with an equimolar amount of chlorosulfonic acid to give mainly the *p*-sulfonic acid together with a little of the sulfonyl chloride and the sulfone.[1] With an excess of the reagent good yields of *p*-chlorobenzenesulfonyl chloride are obtained.[2,95] The kinetics of the sulfonation of chlorobenzene with chlorosulfonic acid have been studied,[98] and the reaction has been reported in several patents.[99–103] These involved various modifications such as the use of excess reagent in hydrocarbon solvents containing alkali metal or ammonium salts, or a mixture of the reagent with thionyl chloride in the presence of sulfamic acid, sodium sulfate or dimethylformamide. In the reaction, the yield of 4,4′-dichlorodiphenyl sulfone can be increased under a variety of conditions;[104–106] the

sulfone is useful for treatment of leprosy and as a hardening agent for epoxide resins.

Chlorobenzene, by prolonged heating with excess chlorosulfonic acid, gives the 2,4-disulfonyl chloride.[8]

The reaction of bromobenzene with excess of the reagent at room temperature affords mainly the *p*-sulfonic acid with a little of the di(*p*-bromophenyl) sulfone.[86] However, under different conditions, the reaction is complex and appears to involve both bromination and appreciable sulfone formation; the former may arise from the relative weakness of the carbon–bromine bond.[1] Various attempts to sulfonate iodobenzene have given unsatisfactory results. With excess chlorosulfonic acid, with or without solvent, the only product was 4,4′-diiododiphenyl sulfone;[95] other conditions have afforded different products, *e.g.* *p*-diiodobenzene. As with bromobenzene, these problems appear to arise from the relative weakness of the carbon–halogen bond which can result in competing halogenation of the initially formed sulfonic acid derivative. The reactions of *o*-, *m*- and *p*-dichlorobenzenes with chlorosulfonic acid have been investigated.[107] *o*-Dichlorobenzene, by heating with the reagent at 100 °C, affords a good yield (85%) of 3,4,3′,4′-tetrachlorodiphenyl sulfone **55**, although the *m*- and *p*-dichlorobenzenes only gave the expected sulfonyl chlorides **56** and **57** respectively. The reason for the differences in behaviour arises from the lack of steric hindrance in the 4-position of *o*-dichlorobenzene which facilitates sulfone formation. This argument was confirmed by the observation[107] that 3,4-dichlorobenzenesulfonyl chloride **58** readily undergoes the Friedel–Crafts reaction with *o*-dichlorobenzene to give the sulfone **55** (60%). In contrast, *m*- and *p*-dichlorobenzenes did not condense with 2,4- or 2,5-dichlorobenzenesulfonyl chloride to give appreciable amounts of the corresponding sulfones. The reaction of *o*-dichlorobenzene with excess chlorosulfonic acid in chloroform solution at room temperature gives a low yield (15%) of 3,4-dichlorobenzenesulfonyl chloride **58**;[86] however repetition of the reaction in boiling chloroform resulted in a much improved yield of this compound[107] (81%). Patents[108,109] reported that the tetrachloro-sulfone **55** may be obtained by adding chlorosulfonic acid (2.8 equivalents) to *o*-dichlorobenzene at < 25 °C.



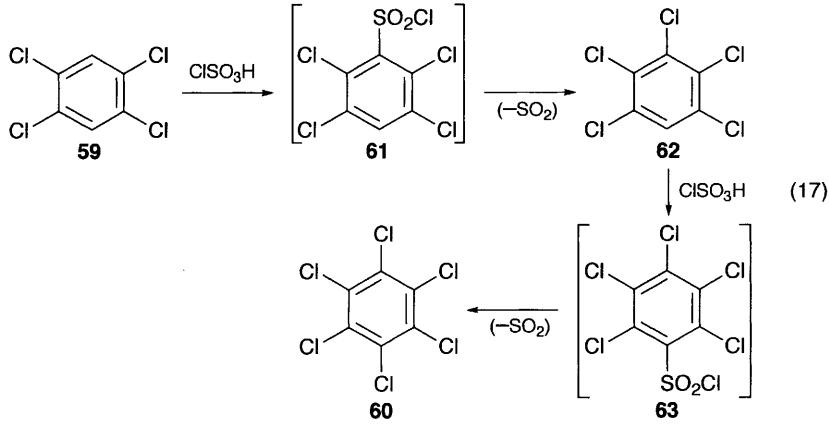
p-Dichlorobenzene is more difficult to sulfonate than the other isomers and the optimum yield (85%) of 2,5-dichlorobenzenesulfonyl chloride **57** was obtained by heating the substrate with excess chlorosulfonic acid at 150 °C for 1 hour[2,110] and more prolonged action (48 hours) has been claimed[1,111] to yield a mixture of 2,5-dichlorobenzene-1,3- and 1,4-disulfonyl chlorides.

p-Chlorobromobenzene by treatment with chlorosulfonic acid (seven equivalents) gave a mixture of 2-bromo-5-chloro- and 5-bromo-2-chloro-benzenesulfo-

nyl chlorides.[95] The former compound was the major product, possibly due to the weak (−I) inductive effect of the bromine atom. 1,2,4- and 1,3,5-Trichlorobenzene by reaction with excess chlorosulfonic acid were readily converted into the 2,4,5- and 2,4,6-trichlorobenzenesulfonyl chlorides respectively.[112–114] 1,2,3,4-Tetrachlorobenzene reacts with the reagent (three equivalents) under fairly forcing conditions (110 °C, 3 hours) to give 2,3,4,5-tetrachlorobenzenesulfonyl chloride.[115]

In contrast, attempts to chlorosulfonate 1,2,4,5-tetrachlorobenzene **59** with chlorosulfonic acid were unsuccessful: the reaction with excess reagent (150 °C, 18 hours) only afforded hexachlorobenzene **60**[115] in agreement with previous studies.[95]

A mechanism was proposed[116–119] for the conversion of **59**→**60** involving initial formation of the sulfonyl chloride **61** which subsequently suffered thermal decomposition with loss of sulfur dioxide and formation of pentachlorobenzene **62**. Finally repetition of these steps gave hexachlorobenzene **60**, as indicated in Equation 17. The mechanism is in agreement with the observation that several arylsulfonyl chlorides undergo thermal decomposition with concomitant chlorination.[118]



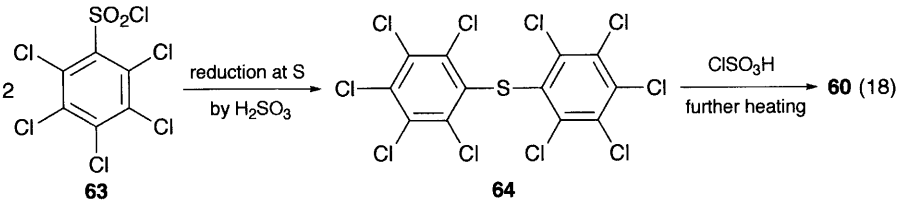
(17)

In particular, tetrachloropyridine-4-sulfonyl chloride on heating (120–140 °C) yields pentachloropyridine by a free-radical mechanism.[119] Attempts to chlorosulfonate pentachlorobenzene by reaction with chlorosulfonic acid failed, but the sulfonyl chloride was prepared indirectly by sulfonation of pentachlorobenzene with hot oleum followed by treatment with phosphorus pentachloride.[107] Pentachlorobenzenesulfonyl chloride **63**, on prolonged heating with chlorosulfonic acid formed hexachlorobenzene **60**. On the other hand, when the sulfonyl chloride **63** was heated in diphenyl ether, the product was bis(pentachlorophenyl) sulfide **64**. The latter compound was also obtained when 1,2,4,5-tetrachlorobenzene was boiled with chlorosulfonic acid for a comparatively short time and the sulfide **64** by longer boiling with the reagent was converted with hexachlorobenzene **60**.[117] The formation of the sulfide **64** would involve reduction of the sulfonyl chloride

63 which was probably achieved by sulfurous acid which may arise from homolytic decomposition of chlorosulfonic acid as indicated in Equation 18.

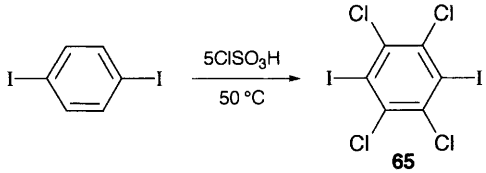
$$ClSO_3H \xrightarrow{\text{heat}} Cl^{\bullet} + \dot{S}O_3H$$

$$H^{\bullet} + \dot{S}O_3H \longrightarrow H_2SO_3$$



63 **64**

o-, *m*- and *p*-Dibromobenzenes react with excess chlorosulfonic acid in chloroform solution to give the corresponding sulfonyl chlorides.[95] *p*-Diiodobenzene by warming (50 °C) with excess chlorosulfonic acid (five equivalents) afforded tetrachlorodiiodobenzene **65**[95] (Equation 19).



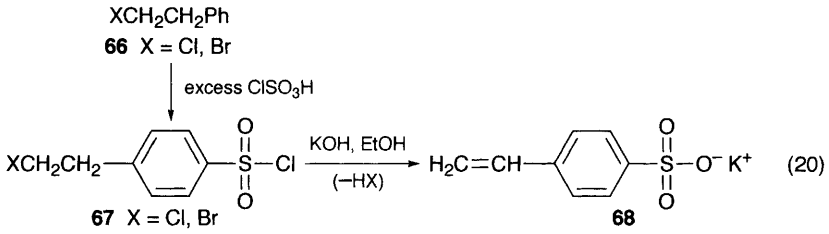
65 (19)

Chlorosulfonic acid is known[120] to function as a chlorinating agent for aromatic substrates at comparatively high temperatures; thus *p*-dichlorobenzene by heating with excess chlorosulfonic acid at 140 °C yields 1,2,4,5-tetrachlorobenzene and at 210–220 °C hexachlorobenzene is formed.[121] There are also several references[115–117,121] to the conversion of 1,2,4,5-tetrachlorobenzene to hexachlorobenzene by prolonged boiling with chlorosulfonic acid. However, the interesting feature of the anomalous reaction of *p*-diiodobenzene with chlorosulfonic acid (Equation 19) is that the chlorination is achieved under suprisingly mild conditions. Cremlyn and Cronje[107] considered that the facile chlorination occurring in this reaction may arise from the catalytic effect of traces of free iodine. Subsequent experiments confirmed this hypothesis and a mixture of chlorosulfonic acid and iodine has been demonstrated[107] to chlorinate several aromatic halides under mild conditions. In reaction with *p*-dichlorobenzene, the maximum yield (82%) of hexachlorobenzene was achieved by treatment with excess chlorosulfonic acid (five equivalents) and iodine (2.5 equivalents).[107] The proposed mechanism of chlorination involves iodine-catalysed homolytic decomposition of the intermediate arylsulfonyl chloride, followed by heterolytic chlorination effected by the evolved iodine monochloride.[97]

In 1-chloro-2-nitrobenzene, sulfonation by excess chlorosulfonic acid occurred *para* to the chlorine atom as would be anticipated[122–124] and with 1-chloro-4-nitrobenzene, the expected product, namely 2-chloro-5-nitrobenzenesulfonyl chloride, was also obtained.[124]

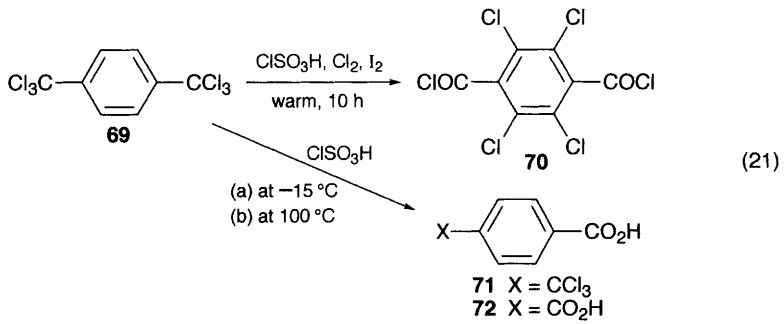
However, in the case of 1-chloro-3-nitrobenzene, it was claimed[124] that sulfonation occurred in the 4-position; this would involve the sulfonic acid group being adjacent to the bulky nitro group. This orientation appears unfavourable, as compared with sulfonation in the 6-position, *ortho* to the much less bulky chlorine atom. In the chlorosulfonation of all the chloronitrobenzenes, chloranil was isolated as a byproduct.[124] 3-(Trifluoromethyl)benzenesulfonyl chlorides are valuable intermediates for the synthesis of agrochemicals, drugs and dyes and are prepared by treating the corresponding benzotrifluorides with a mixture of fuming sulfuric acid and chlorosulfonic acid.[125]

β-Bromo-and β-chloro-ethylbenzene **66** reacted with excess chlorosulfonic acid to give the corresponding *p*-sulfonyl chlorides[126,127] **67**. β-Chloroethylbenzenesulfonyl chloride, (**67**; X = Cl) by treatment with alcoholic potassium hydroxide afforded potassium *p*-styrylsulfonate[126] **68** (Equation 20).



(20)

Perhalomethylbenzenes can be chlorinated by treatment with a mixture of excess chlorosulfonic acid, iodine and chlorine. For instance, hexachloro-*p*-xylene **69** reacts with chlorosulfonic acid (240 parts), iodine (2 parts) and chlorine (30 parts) at 5–10 °C (4 hours) to give a very high yield (96%) of the 2,5-dichloro derivative.[128] However, when hexachloro-*p*-xylene **69** was warmed with chlorosulfonic acid (30 °C, 10 hours) in the presence of excess chlorine and iodine catalyst, the product was tetrachloroterephthaloyl chloride (85%) **70**[129] (Equation 21).



(21)

In contrast, hexachloro-*p*-xylene reacted with chlorosulfonic acid alone at low temperature (–15 °C) to yield *p*-(trichloromethyl)benzoic acid **71**; while at 100 °C the product was terephthalic acid **72** (Equation 21).[130]

There has been much early work reported[1,2] on the sulfonation and chlorosulfonation of various alkylhalobenzene derivatives by chlorosulfonic acid. The results are interesting because they indicate the relative directive influence of simple

alkyl groups (*e.g.* methyl and ethyl) and halogen atoms. In alkylbenzenes, sulfonation occurs *ortho*/*para* to the alkyl group with a predominance of the *p*-sulfonic acid being formed. However, in halobenzenes sulfonation occurs almost exclusively in the *para*-position due to steric hindrance in the *ortho*-positions. Likewise, in alkylhalobenzenes the *para*-directive influence of the halogen atom appears to be greater than that of the alkyl group. However, if only *ortho*-positions are available then sulfonation *ortho* to the alkyl group appears to be favoured. For example sulfonation of 2-chlorotoluene yields the 5-sulfonic acid (*para* to the chlorine atom) and 4-chlorotoluene gives the 2-sulfonic acid (*ortho* to the methyl group) as the major products.[1] The results of the action of chlorosulfonic acid on alkylhalobenzenes are summarized in Table 1.

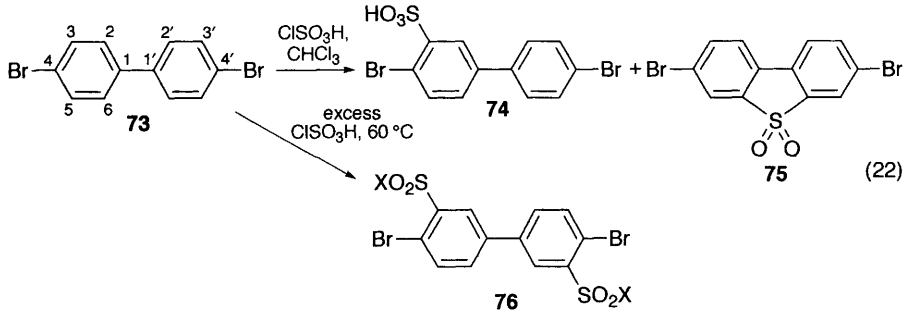
Table 1 *Sulfonation of alkylhalobenzenes by chlorosulfonic acid*

Benzene Derivative	*Structure and Comments*
2,4-dichloro-1,3-dimethyl-	6-SO_3H (*o*/*p* to methyl groups)[131]
2,4-dibromo-1,3-dimethyl-	6-SO_2Cl (excess reagent used)[132]
4,6-dichloro-1,3-dimethyl-	2-SO_3H (*o* to both methyl groups)[131]
2-bromo-1-methyl-4-isopropyl-	5-SO_3H + 5-SO_2Cl[133] (*p* to bromine atom), a rather surprising orientation of sulfonation because it is adjacent to the bulky isopropyl group
3-chloro-1-methyl-4-isopropyl-	6-SO_2Cl (excess reagent used) (*p* to the chlorine atom)[134,135]
3-bromo-1,2,4-trimethyl-	5-SO_2Cl[132,136](excess reagent at 100 °C) (*o*/*p* to both methyl groups)
5-bromo-1,2,4-trimethyl-	6-SO_3H[136] (due to the size of bromine, it is surprising that it was not the 3-SO_3H)
6-bromo-5-fluoro-1,2,4-trimethyl-	3-SO_3H[137]
6-chloro-5-fluoro-1,2,4-trimethyl-	3-SO_3H[137]
2-iodo-1,3,5-trimethyl-	$C_9H_9Cl_3$[138] (excess reagent for many days). Iodine-catalysed chlorination of the initial sulfonyl chloride
5,6-dibromo-1,2,4-trimethyl-	3-SO_3H[139] and other products, probably involving bromination of the sulfonic acid (reaction for 1–2 hours)
2-bromo-1,3-dimethyl-5-ethyl-	4-SO_3H + 4SO_2Cl (*o*/*p* to the methyl groups)[140]

It is important to add the caveat that these results were reported well before the advent of modern spectroscopic techniques for structural elucidation and accordingly the precise orientation of sulfonation in several cases remains uncertain. The results provide some evidence indicating that the combined directive effect of two alkyl groups appears to be greater than that of two similarly orientated halogen atoms. Thus in 2,4-dichloro-1,3-dimethylbenzene, sulfonation occurs in the 6-position which is *o*/*p* with respect to the methyl groups rather than the 5-position (*o*/*p* to the chlorine atoms).

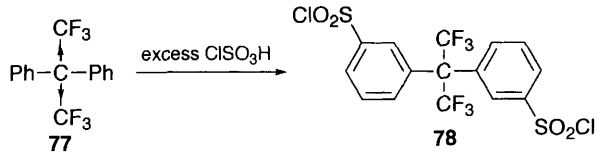
3.2 Halobiphenyls and Related Compounds

4,4′-Dibromobiphenyl **73** reacted with an equal weight of chlorosulfonic acid in chloroform solution (40 °C, 3 hours) to give a mixture of the 3-sulfonic acid (**74**, 32%) and the 2,2′-sulfone (**75**, 25%) (Equation 22). When the amount of chlorosulfonic acid was doubled, the yields of sulfonic acid and the sulfone were increased to 44% and 33% respectively.[141] On the other hand when 4,4′-dibromobiphenyl **73** was heated with excess chlorosulfonic acid (60 °C, 15 minutes) without solvent, the products were the 3,3′-disulfonic acid (**76**; X = OH, 41.5%), the 3,3′-disulfonyl chloride (**76**; X = Cl, 12.5%) and the 2,2′-sulfone (**75**, 42%) (Equation 22).[141]



(22)

1,1′-Bis(trifluoro)diphenylmethane **77** reacts with excess chlorosulfonic acid to give the 3,3′-disulfonyl chloride, **78** which is used as an intermediate in the synthesis of crosslinking agents for fluoro rubbers[142] (Equation 23). The 3,3′-orientation of sulfonation is presumably a reflection of the powerful electron-withdrawing (−I) effect of the trifluoromethyl groups.



(23)

3.3 Halonaphthalenes

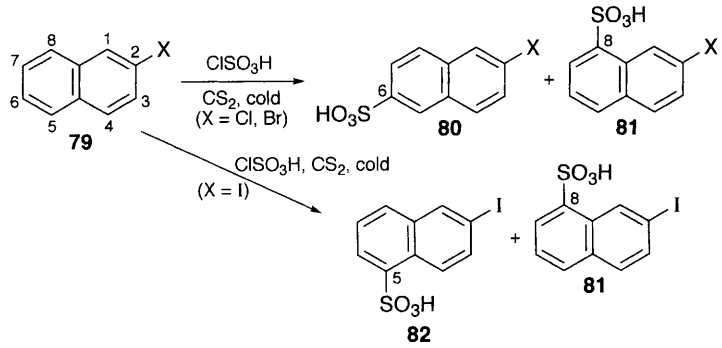
When 1-chloronaphthalene is treated with a cold 10% solution of chlorosulfonic acid in carbon disulfide containing slightly less than one equivalent of the reagent, the major product is 4-chloronaphthalenesulfonic acid.[1,143,144]

The action of excess chlorosulfonic acid in chloroform at 25 °C (20 minutes) on 1-chloronaphthalene afforded the corresponding sulfonyl chloride.[95]

1-Bromonaphthalene, by treatment with chlorosulfonic acid in carbon disulfide, gave a mixture of the 4-sulfonic acid and the sulfonyl chloride;[145] but with excess reagent in chloroform (25 °C) only the 4-sulfonyl chloride was obtained.[95]

1-Iodonaphthalene by reaction with chlorosulfonic acid in carbon disulfide similarly afforded mainly the 4-sulfonic acid with a little of the sulfonyl chloride.[146]

With the 2-halonaphthalenes **79**, the orientation of sulfonation depends on the nature of the halogen atom: when it is chlorine or bromine, reaction with chlorosulfonic acid (one equivalent) in cold carbon disulfide gives a mixture of the 6- and 8-sulfonic acids (**80**, **81**; X = Cl, Br) (Equation 24).



79 **80** **81** **82** **81** (24)

However, with 2-iodonaphthalene under similar conditions, the reaction yields the 5- and 8-sulfonic acids **82** and **81** (Equation 24). It has been suggested that possibly all the 2-halonaphthalenes on sulfonation initially yield the 5- and 8-sulfonic acids (α-sulfonation), but that when the halogen is chlorine or bromine, the former immediately rearranges to the 6-isomer. In contrast, for 2-iodonaphthalene-5-sulfonic acid, the rearrangement only occurs on heating (150 °C).

2-Chloronaphthalene (**79**; X = Cl) reacts with chlorosulfonic acid in carbon disulfide in the cold to yield mainly the 8-sulfonic acid (**81**; X = Cl), together with a little of the 6-sulfonic acid (**80**; X = Cl) (4%).[147] By treatment of (**79**; X = Cl) with excess reagent in chloroform, the 8-sulfonyl chloride was formed.[95]

2-Bromonaphthalene similarly reacted with chlorosulfonic acid in chloroform to give a mixture of the 6- and 8-sulfonic acids together with some sulfonyl chloride[147] and with excess reagent in chloroform the 8-sulfonyl chloride was again obtained.[95]

2-Iodonapthalene (**79**; X = I), by treatment with chlorosulfonic acid in carbon disulfide, gave a mixture of the 5- and 8-sulfonic acid;[148] the mixture of acids by heating (150 °C) was converted into the 6-sulfonic acid.[2]

Armstrong and Wynne[149] reacted all ten dichloronaphthalenes with slightly less than one equivalent of chlorosulfonic acid in carbon disulfide and the results are summarized in Table 2. In the 1,2-, 1,3-, 1,4- and 2,3-dichloronaphthalenes, the two chlorine atoms are contained in the same ring; this ring is therefore relatively deactivated as compared with the unsubstituted ring due to the electron-withdrawing (−I) inductive effect of the chlorine atoms, consequently sulfonation of these dichloronaphthalenes always occurs in the unsubstituted ring. It is also found that *peri* (1:8) sulfonation relative to the halogen atom is not favoured due to steric interaction. For instance, sulfonation of 1,3-dichloronaphthalene yields as one product the 7- rather than the 8-sulfonic acid, since the latter would contain the chlorine and sulfonic acid groups in the 1,8- or *peri* position. This argument also probably explains why sulfonation of 1,5-dichloronaphthalene does not yield the 4-sulfonic acid, whereas the α-orientation of sulfonation is favoured in the

Table 2 *Sulfonation of dichloronaphthalenes*

Naphthalene Derivative	*Structure and Comments*
1,2-dichloro-	5- + 6-SO_3H[149]
1,3-dichloro-	5- + 7-SO_3H[149]
1,4-dichloro-	6-SO_3H + traces of sulfonyl chloride and sulfone[149]
1,5-dichloro-	3-SO_3H + unknown product[149] (steric hindrance from the chlorine atoms probably inhibits sulfonation in the 4- and 8-positions)
1,6-dichloro-	4-SO_3H[149] (no chlorine atom to hinder 4-attack, hence expected α-sulfonation)
1,7-dichloro-	4-SO_3H[149,150]
1,8-dichloro-	4-SO_3H[149]
2,3-dichloro-	5- + 6-SO_3H[149]
2,6-dichloro-	4-SO_3H[149] expected α-sulfonation observed
2,7-dichloro-	3-SO_3H and unknown product[149] (a rather surprising orientation claimed here, 4-attack more likely)

1,6-, 1,7- and 1,8-dichloronaphthalenes as would be anticipated since this orientation is *para* to the chlorine atom.

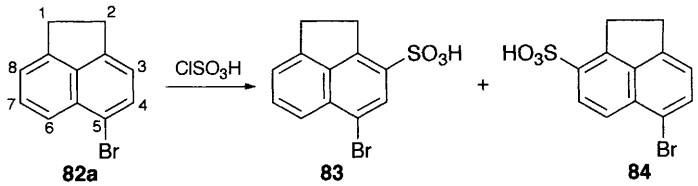
Sulfonation of 2,7-dichloronaphthalene is claimed[149] to yield the 3-sulfonic acid; however this orientation is rather unlikely due to steric hindrance and 4-sulfonation appears more favourable.

Heller[151] claimed that the action of chlorosulfonic acid in carbon disulfide solution on 1-chloro-4-bromonaphthalene affords mainly the sulfone and only a little of the sulfonic acid; this is a surprising result as this compound should yield the 6-sulfonic acid. 1,2,4-Trichloronaphthalene reacts with chlorosulfonic acid (100 °C, 1 hour) to yield a sulfonic acid of unknown orientation;[149] I would expect attack of this substrate to occur in the 6-position.

Generally in the sulfonation of halonaphthalenes low temperature tends to favour α-sulfonation as occurs with naphthalene itself.

3.4 Haloacenaphthenes

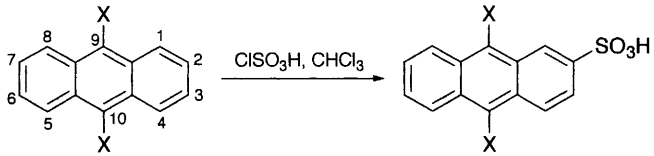
These may be conveniently considered here since they are closely related to the corresponding naphthalenes. 5-Bromoacenaphthene **82a** reacted with chlorosulfonic acid at room temperature to give a mixture of the 3- and 8-sulfonic acids **83** and **84** respectively[152,153] (Equation 25).



82a **83** **84** (25)

3.5 Haloanthracenes and Phenanthrenes

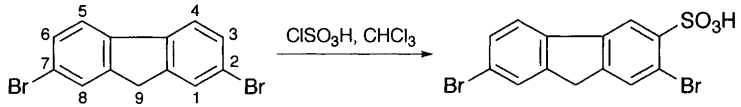
9,10-Dichloroanthracene (**85**; X = Cl) reacts with chlorosulfonic acid (0.5 parts) in warm chloroform (40 °C, 2 hours) to give the 2-sulfonic acid (**86**: X = Cl).[1,154] Similarly 9,10-dibromoanthracene (**85**; X = Br) reacts with the reagent (0.6 parts) in chloroform (room temperature) to yield the corresponding 2-sulfonic acid (**86**; X = Br)[1,154] (Equation 26). In these sulfonations, the presence of halogen atoms in the 9,10-positions inhibits substitution in the α-positions of the outside rings due to steric hindrance. 9-Bromooctahydroanthracene, by treatment with excess chlorosulfonic acid (three equivalents), affords a good yield (82%) of the 10-sulfonyl chloride.[155]



85 X = Cl, Br **86** (26)

3.6 Halofluorenes

2,7-Dibromofluorene **87**, by reaction with chlorosulfonic acid (one equivalent) in chloroform, yields a mono-sulfonic acid, probably the 3-acid **88**, although in this orientation the sulfonic acid group would be adjacent to the comparatively large bromine atom (Equation 27).[156]



87 **88** (27)

4 Aryl Nitro Compounds

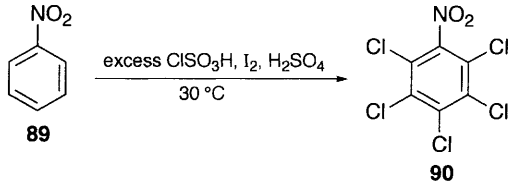
The sulfonation of aromatic nitro compounds is not of great synthetic importance because it is generally easier to nitrate an aromatic sulfonic acid.[1] However, in some cases, this may cause nitrodesulfonation[5] and also sulfonation, unlike nitration, often gives mainly one product rather than a mixture of isomers, consequently sulfonation of aromatic nitro compounds is sometimes a useful procedure.

In the aryl nitro compounds, the powerful electron-withdrawing (−I, −M) effect of the nitro group results in the sulfonation of nitrobenzene being more difficult than that of benzene. Early work[1] claimed that heating nitrobenzene with excess chlorosulfonic acid (two equivalents) afforded *m*-nitrobenzenesulfonyl chloride, but under drastic conditions (150 °C, 20 hours) the only product was reported[8] to be tetrachloro-*p*-benzoquinone (chloranil).

In more recent work,[156] nitrobenzene **89**, by heating with chlorosulfonic acid (four equivalents) at 100–120 °C (8 hours), afforded the *m*-sulfonyl chloride. The

yield of the product was claimed to be increased to 96.3% by carrying out the reaction with chlorosulfonic acid at 112 °C followed by cooling the mixture to 70 °C and the addition of thionyl chloride.[157]

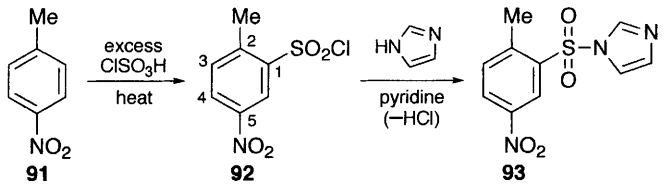
Nitrobenzene (**89**, 184.5 g) by reaction with a mixture of iodine (1.1 g) and 98% sulfuric acid (57 g) in chlorosulfonic acid at 30 °C afforded pentachloronitrobenzene **90** (87% yield)[158] (Equation 28). The product is useful as a soil fungicide and the synthesis provides another example of the use of a mixture of chlorosulfonic acid and iodine as a chlorinating reagent (see Section 3, p 50). The rate of chlorination of nitrobenzene **89** to pentachloronitrobenzene **90** by the chlorosulfonic acid–iodine mixture increased with the iodine concentration.[159] However, the rate was less than that observed in the presence of iodine chlorides. The most effective catalyst for chlorination was found to be a mixture of 0.75% iodine chlorides in chlorosulfonic acid which was stable for 3 days.[159]



89 **90** (28)

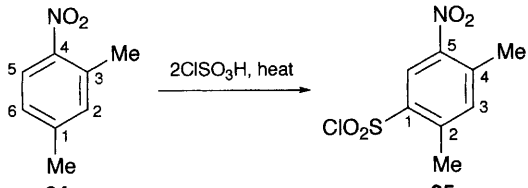
Chlorosulfonic acid in the presence of iodine catalyst at 85 °C converted nitrobenzene into a mixture of *m*-, *o*- and *p*-chloronitrobenzenes in a ratio of 80.6:13.9:5.5% with combined yield of 7% and in this reaction the intermediate was sulfuryl chloride (SO_2Cl_2).[160]

o-, *m*- and *p*-Nitrotoluenes have been sulfonated by treatment with chlorosulfonic acid (one equivalent) and *o*-nitrotoluene with excess of the reagent yields 3-nitro-4-methylbenzenesulfonyl chloride.[161] *p*-Nitrotoluene **91**, by heating with chlorosulfonic acid (two equivalents) first at 70–80 °C and finally at 120 °C, gives 2-methyl-5-nitrobenzenesulfonyl chloride[1] **92**. In both cases, sulfonation occurs respectively *p*- and *o*- to the electron-donating methyl group as would be expected. The chlorosulfonation of *p*-nitrotoluene **91** by chlorosulfonic acid is used in the synthesis of phenylsulfonylazoles as agricultural fungicides (Equation 29). For instance, 2-methyl-5-nitrobenzenesulfonyl chloride **92** by condensation with imidazole afforded the sulfonylimidazole **93**, which controlled *Phytophthora infestans*, an important fungal pathogen on tomato.[162]

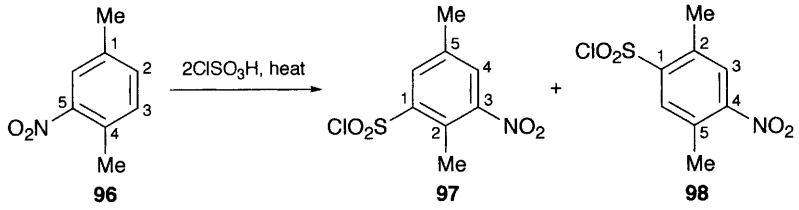


91 **92** **93** (29)

Heating 4-nitro-1,3-dimethylbenzene **94** with chlorosulfonic acid (two equivalents) yields the expected 5-nitro-2,4-dimethylbenzenesulfonyl chloride **95** in which sulfonation has occurred *o*/*p* with respect to the electron-donating methyl groups (Equation 30).[1]



(30)



(31)

5-Nitro-1,4-dimethylbenzene **96**, by heating with excess chlorosulfonic acid at 100 °C, is claimed[163] to yield a mixture of 3-nitro-2,5-dimethylbenzenesulfonyl chloride **97** and 4-nitro-2,5-dimethylbenzenesulfonyl chloride **98** (Equation 31). The former contains the sulfonyl moiety *o*- to the methyl and *m*- to the nitro group and is the major product in this chlorosulfonation.

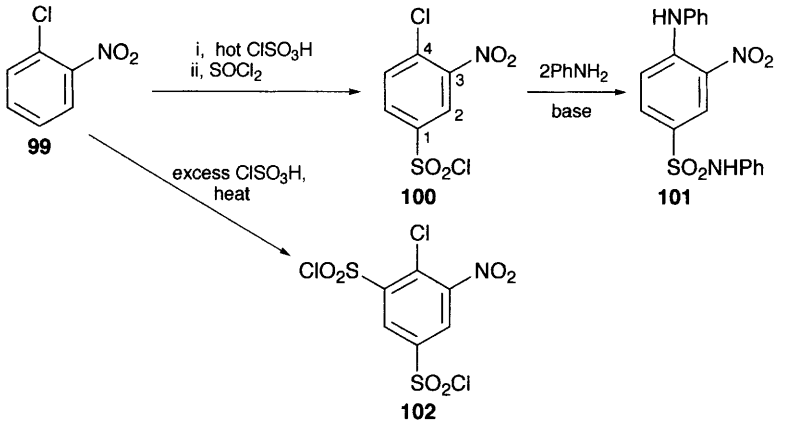
o-**99** and *p*-chloronitrobenzenes, by heating with excess chlorosulfonic acid (160–170 °C, 2 hours) or with oleum and chlorosulfonic acid or thionyl chloride,[164] gave respectively 4-chloro-3-nitro- and 2-chloro-5-nitro-benzenesulfonyl chloride[8] in which the orientation of the sulfonyl group is *p*- and *o*- to the chlorine atom as would be anticipated. 4-chloro-3-nitrobenzenesulfonyl chloride **100** has also been prepared by heating *o*-chloronitrobenzene **99** with chlorosulfonic acid at 100–110 °C followed by treatment with thionyl chloride at 70–80 °C.

The sulfonyl chloride **100** was then condensed with an aromatic amine to yield 2-nitro-4-sulfamoyldiphenylamine dyes; thus **100** by reaction with aniline yields CI Disperse Yellow 42 **101** (94% yield) (Equation 32).[165] In this sequence, the 4-chlorine atom in **100** is activated towards nucleophilic attack by the adjacent nitro group, so that on reaction with aniline both chlorine atoms are replaced by the amino group.

4-Chloro-3-nitrobenzenesulfonyl chloride **100**, by condensation with hydrazine and sodium azide in the cold, afforded the corresponding hydrazide and azide which possessed herbicidal and fungicidal activity.[166]

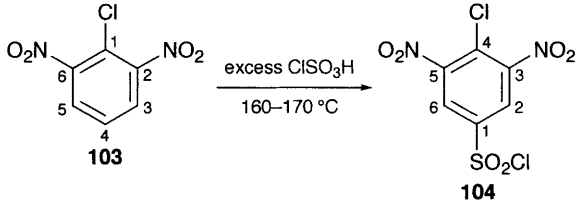
The chlorosulfonation of *o*-chloronitrobenzene **99** by chlorosulfonic acid has been optimized: the equilibrium constant for the synthesis of 4-chloro-3-nitrobenzenesulfonyl chloride **100** (Equation 32) was determined as well as the optimum molar ratio of the reactants.[167] *o*-Chloronitrobenzene **99**, by prolonged heating with a large excess of chlorosulfonic acid, is converted into the 1,3-disulfonyl chloride **102** (Equation 32).[8]

2,6-Dinitrochlorobenzene **103**, by heating with excess of the reagent (160–170 °C, 6 hours) gave 4-chloro-3,5-dinitrobenzenesulfonyl chloride **104** (Equation 33);[8] here sulfonation occurs in the expected position, namely *p* to the chlorine atom and *m* to the nitro groups.

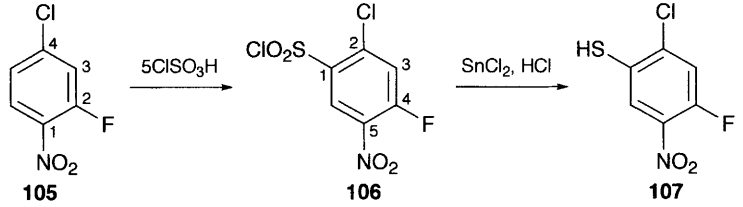


(32)

4-Chloro-2-fluoronitrobenzene **105** was treated with excess chlorosulfonic acid (five equivalents) at room temperature (30 minutes) and the mixture was then heated at 120–130 °C (3 hours) to give 2-chloro-4-fluoro-5-nitrobenzenesulfonyl chloride **106** (Equation 34). Sulfonation occurred in the expected position (*o*/*p* to the halogens and *m* to the nitro group). The sulfonyl chloride **106** could be reduced, by reaction with tin(II) chloride, to the corresponding thiol **107** which is used as a herbicide intermediate.[168]

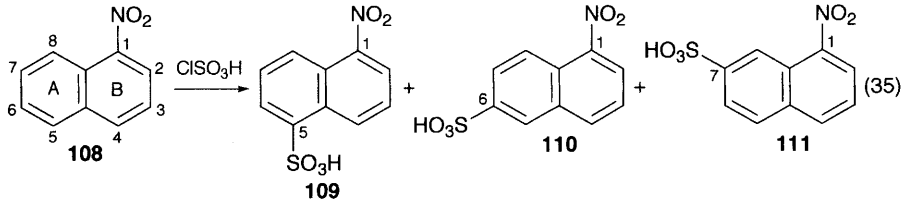


(33)



(34)

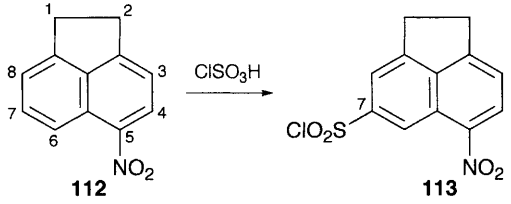
1-Nitronaphthalene **108** with chlorosulfonic acid (one equivalent) is reported[145] to give a mixture of the three isomeric naphthalenesulfonic acids **109–111** (Equation 35).



(35)

The 5-sulfonic acid **109** is much the largest component of the mixture as would be anticipated since sulfonation has occurred in the most reactive α-position of the naphthalene nucleus. In 1-nitronaphthalene **108**, the electron-withdrawing property of the nitro group will deactivate ring B relative to the unsubstituted ring A, so sulfonation will occur preferentially in ring A. It would be anticipated that the minor products **110** and **111** would probably contain the sulfonic acid group substituted in the less reactive β-positions of the naphthalene ring as shown in Equation 35. 8-Sulfonation would not be expected due to unfavourable *peri* (1,8-) steric interactions with the 1-nitro group.

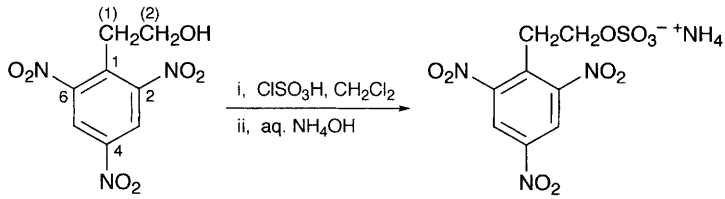
5-Nitroacenaphthene **112** reacts with excess chlorosulfonic acid to yield the 7-sulfonyl chloride **113**[169] (Equation 36). Acenaphthalene normally sulfonates with chlorosulfonic acid in the 5-position (see Section 2, p 45) so it is perhaps surprising that sulfonation of the 5-nitro derivative **112** did not occur in the equivalent 6-position. However, this would be hindered by *peri* interaction with the bulky 5-nitro group, so the SO_3H group migrates to the less hindered 7-position.



112 **113** (36)

The sequence **112**→**113** provides a synthetic route to obtain derivatives of acenaphthene-4-sulfonic acid which cannot be prepared by direct sulfonation of the hydrocarbon.[1]

The sulfonation of 1-(2-hydroxyethyl)-2,4,6-trinitrobenzene **114** by reaction with chlorosulfonic acid followed by treatment with aqueous ammonia yields novel energetic sulfonate salts **115**[170] (Equation 37). These salts can be used in conjunction with ammonium nitrate in explosive formulations. Studies[171] of the relative reactivity of nitrobenzene and *m*-chloronitrobenzene towards chlorination in chlorosulfonic acid showed that the former compound was 4.77 times more reactive.



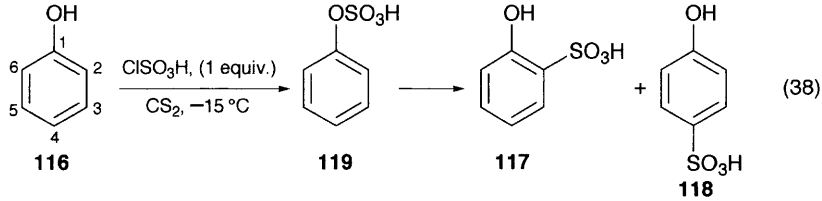
114 **115** (37)

5 Phenols

Phenols readily undergo sulfonation due to the electron-donating (+M, −I) property of the hydroxyl group and to the possible formation of intermediate sulfate esters which rapidly rearrange to the arylsulfonic acids.[1]

Phenols can either react with the sulfonating agent at the hydroxyl group by sulfation (*O*-sulfonation) or by sulfonation of the aromatic ring (*C*-sulfonation) or both. It is generally found[3,5] that sulfation is more easily achieved than sulfonation and in acidic reagents protonation of the hydroxyl moiety precedes sulfonation.[5] Sulfation (esterification) is favoured by electron-withdrawing substituents in the aryl ring, but is less common in *o*-substituted phenols due to steric hindrance.[172]

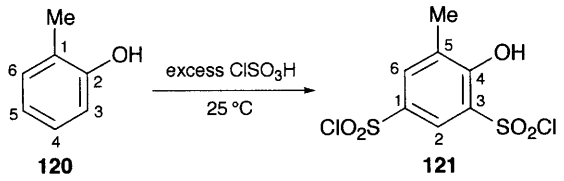
Chlorosulfonic acid is especially useful in the preparation of phenol sulfonyl chlorides because, in this case, the reaction of metal sulfonates with phosphorus pentachloride cannot be used.[1] Phenol **116**, by treatment with chlorosulfonic acid (one equivalent) in carbon disulfide at room temperature, yields a mixture of the *o*- and *p*-sulfonic acids **117** and **118** (mainly the *p*-isomer **118**), but at low temperature (−15 °C) the products were phenyl hydrogen sulfate **119** and the *p*-sulfonic acid **118**[173,180] (Equation 38). When the reaction time was increased the yield of the *p*-sulfonic acid **118** also increased and on standing the hydrogen sulfate **119** gradually rearranged to the sulfonic acids.[1,173,174] Later studies[175,176] found that the reaction in carbon disulfide or dichloroethane at −40 °C to 0 °C proceeds *via* the sulfate **119** and afforded almost equal amounts of the sulfonic acids **117** and **118** with traces of the 2,4-disulfonic acid. The relative rate of formation of the *o*-sulfonic acid **117** as compared with that of the *p*-isomer **118** increased with decreasing temperature and on heating the *o*-isomer **117** was converted into the *p*-isomer **118**.[175] Sulfation of phenols was also effected by treatment with chlorosulfonic acid in a tertiary amine, *e.g.* pyridine or *N,N*-dimethylaniline, as solvent. In this case, the effective reagent is probably the amine–sulfur trioxide complex.[177,178] As an example, *p*-nitrophenyl sulfate was prepared by reaction of *p*-nitrophenol with chlorosulfonic acid in carbon disulfide and dimethylaniline.[179]



116 **119** **117** **118** (38)

Phenol **116**, by treatment with excess chlorosulfonic acid, yields the 2,4-disulfonyl chloride and heating the substrate with a large excess of the reagent at 130–140 °C (4–5 hours) affords the 2,4,6-trisulfonyl chloride,[1,180] but no sulfonylide derivative was reported from this substrate.

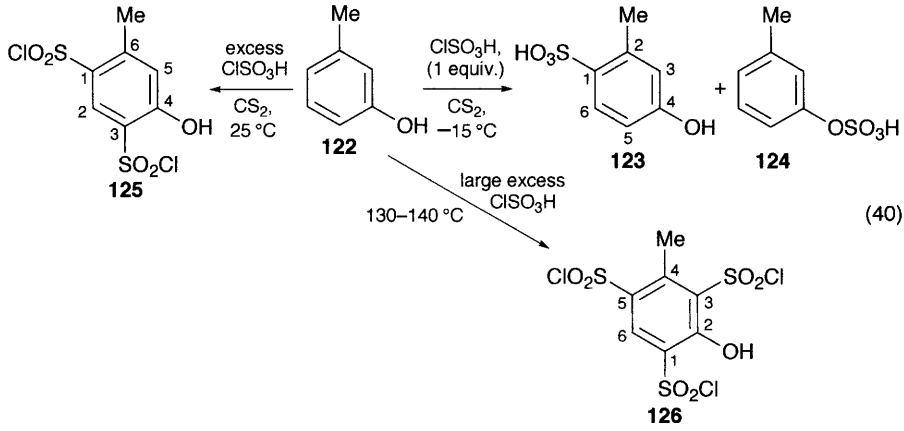
o-Cresol **120**, by reaction with excess chlorosulfonic acid at room temperature gave 4-hydroxy-5-methylbenzene-1,3-disulfonyl chloride **121**[1,7,180] (Equation 39). In the chlorosulfonation of *o*-cresol **120**, the sulfonyl groups enter *o*/*p* with respect to the hydroxyl group as would be anticipated.



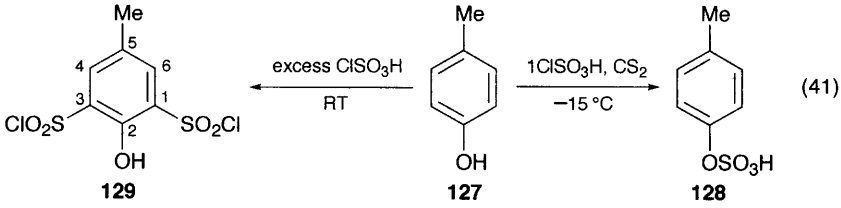
120 121 (39)

m-Cresol **122**, by treatment with chlorosulfonic acid (one equivalent) in carbon disulfide at −15 °C, gave a mixture of 4-hydroxy-2-methylbenzenesulfonic acid **123** and *m*-tolyl hydrogen sulfate **124**. Reaction of *m*-cresol with an excess of the reagent in carbon disulfide at 25 °C afforded the 1,3-disulfonyl chloride **125** while heating the mixture at 130–140 °C (6 hours) and pouring it onto concentrated hydrochloric acid gave 2-hydroxy-4-methylbenzene-1,3,5-trisulfonyl chloride **126**[1,7,180] (Equation 40).

Addition of chlorosulfonic acid (one equivalent) to a solution of *p*-cresol **127** in carbon disulfide at −15 °C, gave *p*-tolyl hydrogen sulfate **128**[173] (Equation 41). Reaction of *p*-cresol **127** with excess chlorosulfonic acid at room temperature yields 2-hydroxy-5-methylbenzene-1,3-disulfonyl chloride **129**. *o*-, *m*- and *p*-Cresols were sulfonated by the action of chlorosulfonic acid at 25–105 °C and the isomeric mixture of cresolsulfonic acids by treatment with formaldehyde (2:1) gave condensation products which were useful pharmaceuticals.[181]



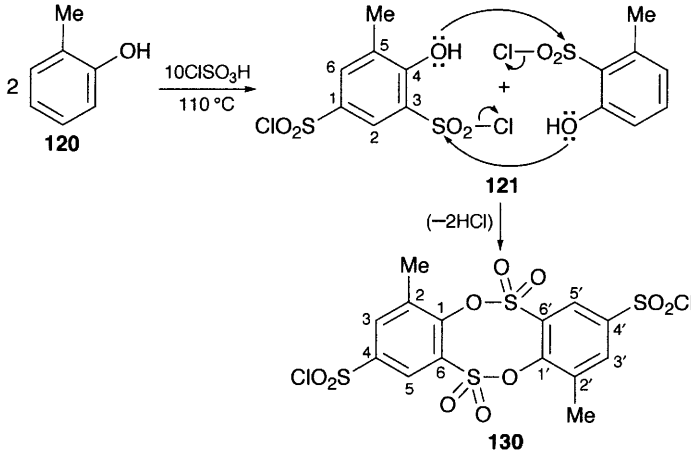
125 122 123 124 126 (40)



129 127 128 (41)

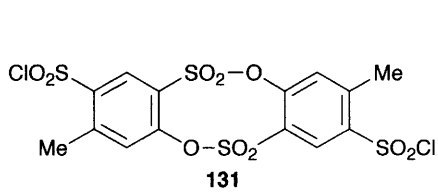
Early literature[1,7,180] claimed that the three isomeric cresols, on heating with a large excess of chlorosulfonic acid, afforded condensation products termed sulfonylides which probably possess the structures **130–132** containing an interesting eight-membered oxygen–sulfur heterocyclic ring. For example, *o*-

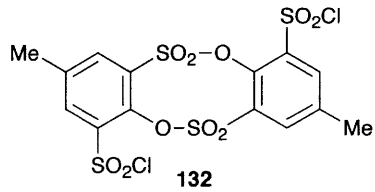
cresol **120**, on heating with chlorosulfonic acid (10 equivalents, 110 °C) for 3 hours, gave 4-hydroxy-5-methylbenzene-1,3-disulfonyl chloride **121** together with 2,2′-dimethyldiphenyl-1,6,1′,6′-sulfonylide-4,4′-disulfonyl chloride **130**; the latter presumably results from self-condensation of two moles of the disulfonyl chloride **121** as indicated (Equation 42).



(42)

Similarly *m*-cresol, by heating with excess chlorosulfonic acid (10 equivalents) at 110 °C ($1\frac{1}{4}$ hours), is reported[1,7,180] to yield *m*-cresolsulfonylide disulfonyl chloride **131**. Likewise under similar conditions, *p*-cresol **127** was converted into *p*-cresolsulfonylide disulfonyl chloride **132**.



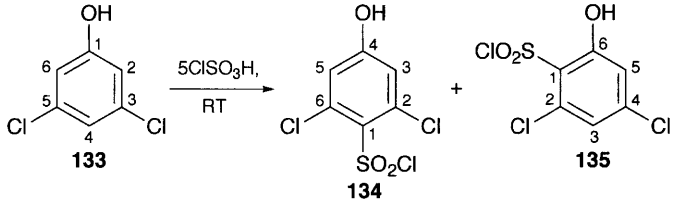


The sulfonylidedisulfonic acids are claimed[1,7,180] to be high melting point solids which are stable in boiling water and alcohol and may be crystallized from dilute hydrochloric acid. It is possible that *m*-cresoltrisulfonic acid **126** (Equation 40) may be formed *via* the sulfonylidedisulfonyl chloride **131** by further attack of the chlorosulfonic acid under the drastic conditions employed (130–140 °C, 6 hours). However, the structure of the sulfonylides remains in some doubt and their synthesis needs repetition so that the structures can be checked by modern techniques.

The action of excess chlorosulfonic acid at room temperature on 2,3-, 2,4-, 2,5-, 2,6-, 3,4- and 3,5-dichlorophenols afforded the following substituted benzenesulfonyl chlorides: 2,3-dichloro-4-hydroxy; 3,5-dichloro-2-hydroxy; 2,5-dichloro-4-hydroxy; 3,5-dichloro-4-hydroxy; 4,5-dichloro-2-hydroxy and 2,6-dichloro-2-hydroxy.[182] The orientation of sulfonation is controlled by the electron-releasing hydroxyl group, so that where possible, sulfonation occurs *para*

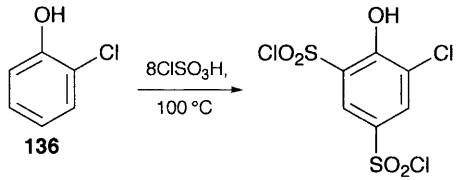
to this group; however if this position is blocked by a substitutent then sulfonation occurs *ortho* to the hydroxyl group.[3,182] The chlorosulfonation experiments demonstrated that the maximum yields of the dichlorohydroxybenzensulfonyl chlorides from the appropriate dichlorophenols required the use of a large excess of chlorosulfonic acid (about five equivalents) due to condensation of the phenolic hydroxyl group with the reagent.[182] 2,4-Dichlorophenol has been converted into 2-hydroxy-3,5-dichlorobenzenesulfonyl chloride by treatment with chlorosulfonic acid (four equivalents) in the presence of thionyl chloride (up to two equivalents); the sulfonyl chloride is used in the manufacture of 2-hydroxybenzenesulfonamide, a herbicide intermediate.[182a]

The orientation of chlorosulfonation of the 2,4- and 2,5-dichlorophenols was confirmed by NMR studies.[53a] However, in the case of 3,5-dichlorophenol **133**, it was shown that the reaction gave not only the previously reported[182] 2,6-dichloro-4-hydroxybenzenesulfonyl chloride **134**, but also the 2,4-dichloro-6-hydroxy isomer **135** in which chlorosulfonation has occurred *ortho* to the hydroxyl group (Equation 43).



133 **134** **135** (43)

The two isomeric sulfonyl chlorides **134** and **135** were obtained in approximately equal amounts and the additional *o*-sulfonation may occur by an intramolecular mechanism.[53a] The chlorosulfonation of 2,6-dihalophenols by chlorosulfonic acid and the subsequent condensation of the 4-sulfonyl chloride with secondary amines, *e.g.* *N*-methylaniline, yields sulfonamides, like 3,5-dibromo-4-hydroxy-*N*-methylphenylsulfonamide, which is an effective herbicide against wild oats.[183] The various dichlorohydroxybenzenesulfonyl chlorides were converted into sulfonamides, hydrazides and azides for screening as novel biocides.[182] *o*-Chlorophenol **136**, by heating with chlorosulfonic acid (eight equivalents) at 100 °C (1 hour), gave the 1,3-disulfonyl chloride **137** (59%) (Equation 44).



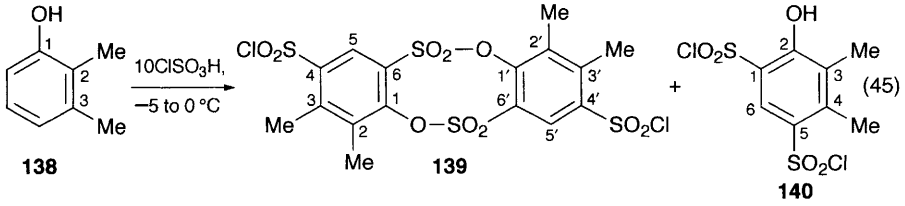
136 **137** (44)

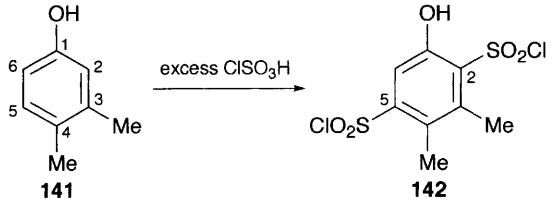
In *o*-chlorophenol **136**, both the *o*- and *p*-positions relative to the phenolic hydroxyl group are free for sulfonation.

The action of chlorosulfonic acid on five of the xylenols (dimethylphenols) has been examined in some detail.[1,184] It was found that sulfonylides are not formed

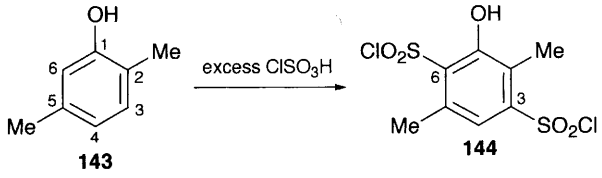
when the chlorosulfonyl group was between the hydroxyl and methyl groups in agreement with the condensation mechanism shown (Equation 42). Consequently, in reaction with an excess of the reagent, only the 2,3- and 2,4-dimethylphenols **138** and **148** afforded appreciable quantities of the corresponding sulfonylides **139** and **150**.[1,184]

o-Xylenol (2,3-dimethylphenol **138**) by treatment with chlorosulfonic acid (10 equivalents) at −5 to 0 °C (24 hours) gave a mixture of 2,3,2′,3′-tetramethyldiphenyl-1,6,1′,6′-sulfonylide-4,4′-disulfonyl chloride **139** and 2-hydroxy-3,4-dimethylbenzene-1,3-disulfonyl chloride **140** (Equation 45). However, if the low temperature reaction is only carried out for a shorter time (4 hours), only water-soluble products resulted; and when the mixture of 2,3-dimethylphenol **138** and chlorosulfonic acid (10 equivalents) was heated at 110 °C for 2 hours, the sulfonylide disulfonyl chloride **139** was isolated.[184] 3,4-dimethylphenol **141**, by reaction with chlorosulfonic acid (10 equivalents), is claimed[184] to give the 2,5-disulfonyl chloride **142**, while 2,5-dimethylphenol **143** yields the 3,6-disulfonyl chloride **144** (Equations 46 and 47).





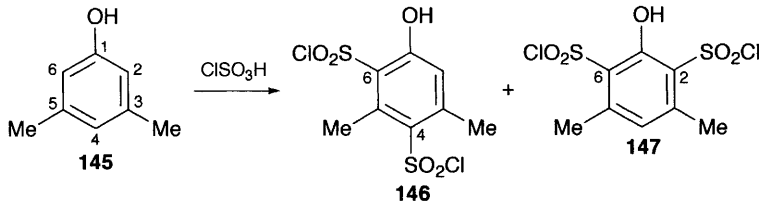
(46)



(47)

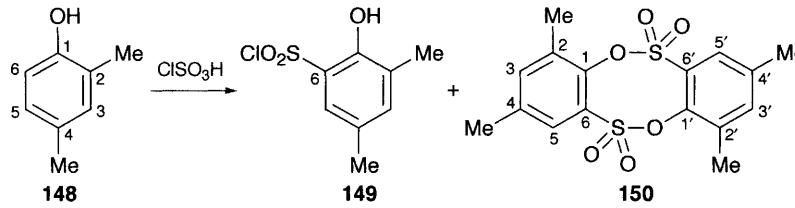
The proposed products **142** and **144** have an unexpected orientation of the sulfonyl groups; thus it would be anticipated that the compound **142** would actually be the 2,6-disulfonyl chloride (sulfonation *ortho* to the hydroxyl group), while **144** should be the 4,6-disulfonyl chloride (sulfonation *ortho*/*para* to the hydroxyl group). The evidence presented in favour of the structures **142** and **144** was based on the observation the sulfonic acids obtained by hydrolysis of the disulfonyl chlorides **142** and **144** coupled with diazotized *p*-nitroaniline to give orange-yellow dyes, indicative of vacant positions *o* or *p* to the hydroxyl group.[184]

3,5-Dimethylphenol **145** reacted with chlorosulfonic acid to give a mixture of the 4,6- and 2,6-disulfonyl chlorides **146** and **147** (Equation 48) containing the chlorosulfonyl group in the expected orientations with respect to the hydroxyl moiety; the relative amounts of these products depended on the reaction temperature.



(48)

2,4-Dimethylphenol **148** reacted with excess reagent to yield a mixture of 6-sulfonyl chloride **149** and the 2,4,2′,4′-tetramethyl-1,6,1′,6′-sulfonylide **150** (Equation 49).[184] In this example, the disulfonyl chloride was not formed, presumably because only one activated position (namely *ortho* to the hydroxyl group) is vacant. The chlorosulfonation of higher alkylphenols has been reported using chlorosulfonic and sulfuric acid.[185]

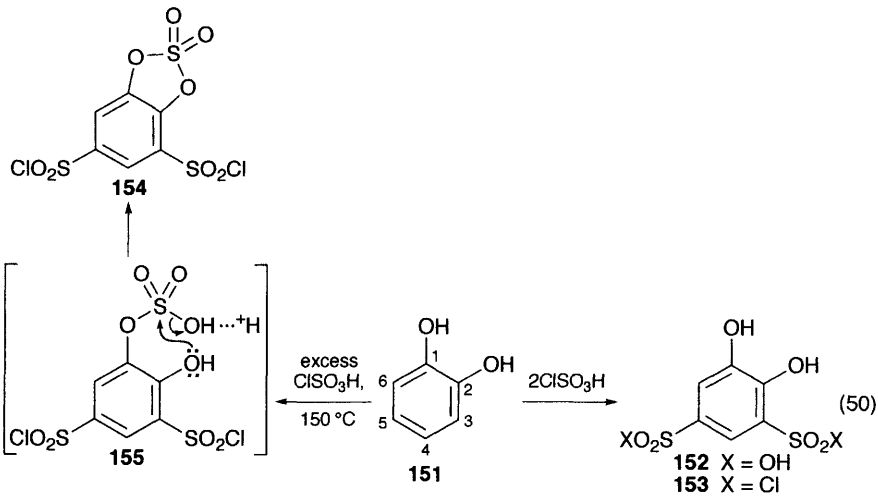


(49)

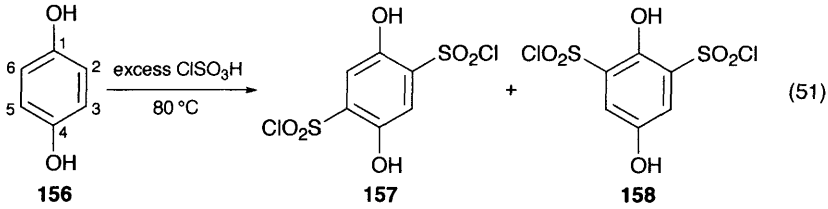
Substituted 2-(aminomethyl)phenyl hydrogen sulfates, useful as antihypertensive drugs, were synthesized by reacting the appropriate phenol with chlorosulfonic acid in pyridine.[186]

The sulfonation of 2-tert-butylphenol with chlorosulfonic acid has been studied kinetically: the reaction mixture was demonstrated to contain 13 acids (derivatives of phenol, 2-tert-butylphenol, 4-tert-butylphenol and 2,4-ditert-butylphenol).[187] The majority of the reactions gave first order rate constants and the operation of a two-phase reaction mechanism was discussed with reference to direct sulfonation, sulfate ester rearrangement and *ipso* sulfonation.

The action of chlorosulfonic acid on di- and polyhydric phenols has been examined.[1,5,7] Catechol (1,2-dihydroxybenzene, **151**) reacts with the reagent (two equivalents) at room temperature (24 hours) to yield the 3,5-disulfonic acid **152**.[188] On the other hand, heating catechol **151** with excess reagent (10 equivalents) at 110 °C afforded the corresponding disulfonyl chloride **153** (Equation 50). If the reaction mixture is heated at 150 °C (8 hours), the product was the cyclic sulfate of the 3,5-disulfonyl chloride **154** (Equation 50) which is probably formed by acid-catalysed dehydration of the initially formed hydrogen sulfate **155**.[188]

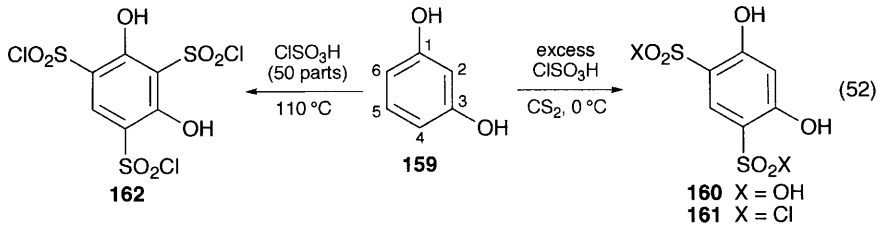


Quinol (1,4-dihydroxybenzene **156**) only gives water-soluble products by reaction with chlorosulfonic acid at room temperature, but on heating with excess of the reagent at 80 °C, quinol yields a mixture of the 2,5- and 2,6-disulfonyl chlorides **157** and **158** (Equation 51).[188,189]



More recently the chlorosulfonation of hydroquinone or *p*-quinol **156** has been reported by using a mixture of chlorosulfonic acid and thionyl chloride to yield 2,5-dihydroxybenzenesulfonyl chloride.[190] Quinol **156**, with excess chlorosulfonic acid under drastic reaction conditions (150–160 °C, 8 hours), yields chloranil (tetrachloro-*p*-benzoquinone), pentachlorophenol and other byproducts.[188] The formation of these products is indicative of the chlorinating and oxidising properties of chlorosulfonic acid.

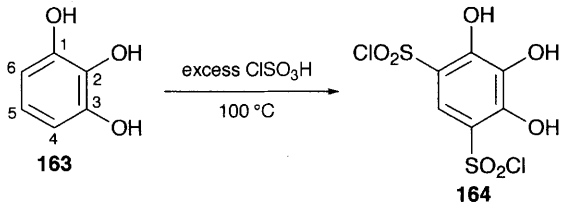
Resorcinol (1,3-dihydroxybenzene) **159** and chlorosulfonic acid (five parts) in carbon disulfide at 0 °C or room temperature gave the 4,6-disulfonic acid **160** while with a larger excess of the reagent (ten parts) at room temperature, the 4,6-disulfonyl chloride **161** was isolated (Equation 52).[191] When resorcinol **159** was heated with a very large excess of chlorosulfonic acid (50 parts) at 110 °C for 2 hours, the product was the 2,4,6-trisulfonyl chloride **162** and when the mixture was subjected to even more drastic reaction conditions (160–170 °C, 110 hours), the product was hexachlorobenzene.[191] The rapid addition of chlorosulfonic acid (two equivalents) to resorcinol **159** in nitrobenzene at 15–75 °C precipitates pure 2,4-dihydroxybenzenesulfonic acid in almost quantitative yield.[192]



(52)

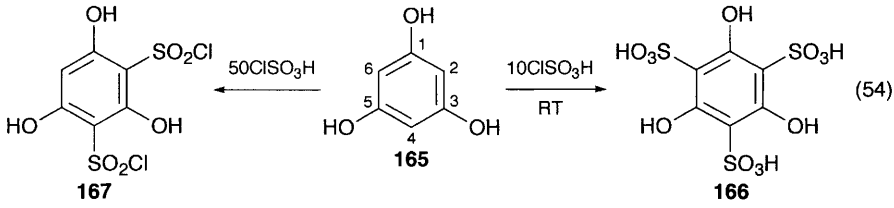
Recently,[192a] it has been shown that phenols are quantitatively sulfonated by treatment with chlorosulfonic acid in dialkyl carbonate solvents; thus resorcinol with the reagent in dimethyl carbonate gave 99% sulfonation.

Pyrogallol (1,2,3-trihydroxybenzene, **163**) reacted with excess chlorosulfonic acid (10 equivalents) at 100 °C (45 minutes) to give the 4,6-disulfonyl chloride **164** (Equation 53). When the reaction was heated to higher temperatures, a mixture of products resulted, including pentachlorophenol.



(53)

Phloroglucinol (1,3,5-trihydroxybenzene, **165**) reacted with excess chlorosulfonic acid (ten equivalents) at room temperature to yield the 2,4,6-trisulfonic acid **166**. In contrast, treatment of phloroglucinol **165** with a very large excess of the reagent (25–50 equivalents) for several days afforded the 2,4-disulfonyl chloride **167**.[193] (Equation 54).

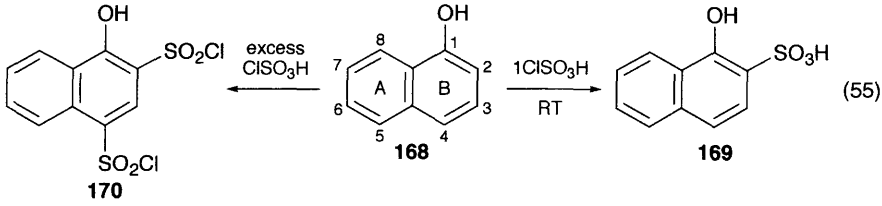


(54)

The latter compound **167** also resulted from treatment of the trisulfonic acid **166** with excess chlorosulfonic acid. It is surprising that these reactions did not yield the trisulfonyl chloride. However, it is possible that the sulfonic acid groups may be specially stabilized in this compound by intramolecular (-O–H···O-) hydrogen bonding between the hydroxyl and sulfonic acid groups. The reaction of phloroglucinol **165** and excess chlorosulfonic acid at 150–160 °C produced a mixture of pentachlorophenol and hexachlorobenzene, again indicative of the chlorinating properties of the reagent at higher temperatures.

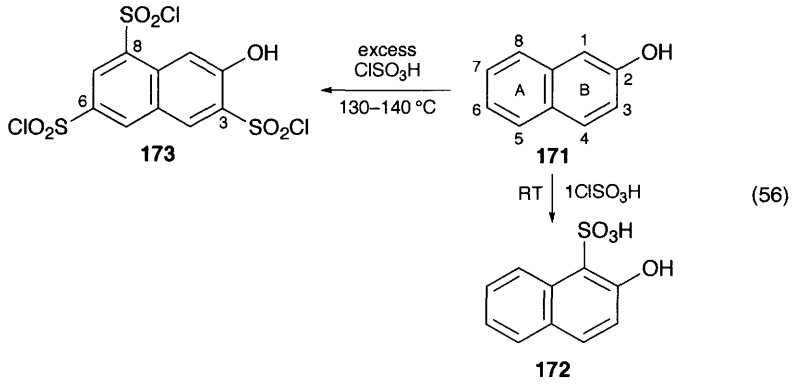
5.1 Naphthols

α- or 1-Naphthol **168** reacts with chlorosulfonic acid at room temperature to give the 2-sulfonic acid[1,7,194] **169** (Equation 55). The reaction of **168** with the reagent in an inert solvent at low temperature is claimed[195] to yield the 4-sulfonic acid, and this product also results from reaction at 100 °C in the absence of solvent.[194] 1-Naphthol **168** reacts with excess chlorosulfonic acid (five parts) at room temperature ($2\frac{1}{2}$ hours) to yield the 2,4-disulfonyl chloride **170** (Equation 55), while prolonged action (4–5 days) affords the 2,4,7-trisulfonyl chloride.[196]



(55)

β or 2-Naphthol **171** on reaction with chlorosulfonic acid (one equivalent) at room temperature gives the 1-sulfonic acid **172**[194] (Equation 56).



(56)

The latter compound **172** in 96–98% yield was manufactured by sulfonation of 2-naphthol **171** by a solution of chlorosulfonic acid in dichloroethane at 0–5 °C.[197] In the process, the evolved hydrogen chloride gas was removed from the reactor by dry air and separately treated with sulfur trioxide to obtain chlorosulfonic acid which was recycled.

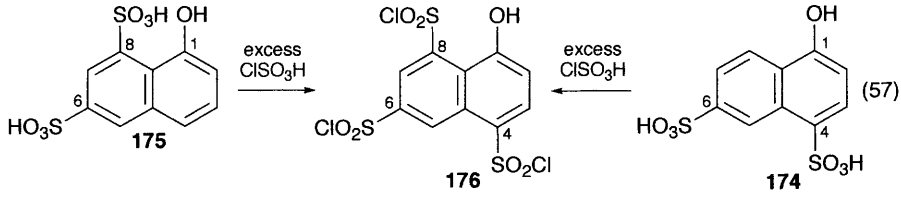
The sulfonation of 2-naphthol is of importance in the manufacture of 2-aminonaphthalene-1-sulfonic acid (Tobias acid), an important dyestuff intermediate. 2-Naphthol **171** was reacted with chlorosulfonic acid in nitrobenzene at 5–7 °C while passing dry air through the reaction mixture, which was sequentially treated with aqueous sodium hydroxide, ammonium hydroxide, and 50% sulfuric acid to give Tobias acid (83.5%).[198] 2-Naphthol **171** by reaction with excess chlorosulfonic acid at 0 °C yields the 1-sulfonyl chloride[1,194] and the reagent (one equivalent) in tetrachlorethane (130 °C) yields the 6-sulfonic acid.[194] The action of excess chlorosulfonic acid at room temperature affords a mixture of the 1,5-

and 1,6-disulfonyl chlorides.[196] However at 130–140 °C, the reaction yields the 3,6,8-trisulfonyl chloride **173** (Equation 56).

The latter compound **173** also results from heating the 1,5- or 1,6-disulfonic acids with excess chlorosulfonic acid, a reaction involving rearrangement of the 1-chlorosulfonyl group.[1]

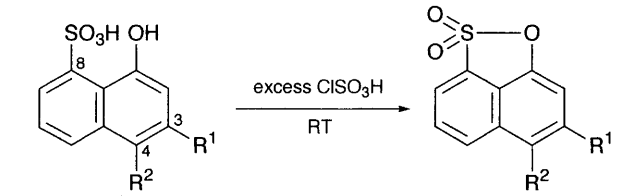
In the naphthols **168** and **171**, ring B is activated towards sulfonation by the attached hydroxyl group relative to the unsubstituted ring A: consequently initial sulfonation always preferentially occurs in ring B.

1-Naphthol-3-, 5-, 6- and 8-sulfonic acids react with excess chlorosulfonic acid to yield trisulfonyl chlorides;[1] 1-naphthol-4,6- and 6,8-disulfonic acids **174** and **175** on treatment with excess reagent afforded the same trisulfonyl chloride which is therefore identified as the 4,6,8-derivative **176**[1,199] (Equation 57). 1-Naphthol-5- and 6-sulfonic acids reacted with chlorosulfonic acid to give probably the 2,5,7- and 2,6,8-trisulfonyl chlorides respectively.



(57)

1-Naphthol-8-sulfonic acid **177** or the 3,8- or 4,8-disulfonic acids **178** and **179** reacted with chlorosulfonic acid (two equivalents) at room temperature to yield the corresponding naphthalenesultone **180** or the sulfonyl chlorides **181** and **182**[1,199] (Equation 58).

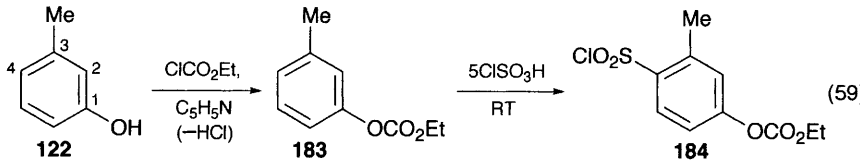


177 $R^1 = R^2 = H$
178 $R^1 = SO_3H$, $R^2 = H$
179 $R^1 = H$, $R^2 = SO_3H$

180 $R^1 = R^2 = H$
181 $R^1 = SO_2Cl$, $R^2 = H$
182 $R^1 = H$, $R^2 = SO_2Cl$

(58)

Phenols and their simple derivatives react with excess chlorosulfonic acid to give di- and trisulfonyl chlorides; consequently it is generally not feasible to prepare the mono-sulfonyl chlorides using this reagent. However, it has been discovered[200] that if the phenol is first converted into the carbethoxy ester, this can be subsequently reacted with excess chlorosulfonic acid, under controlled conditions, to give the mono-sulfonyl chloride. For instance, *m*-cresol **122** was condensed with ethyl chloroformate in the presence of a base (pyridine) to yield the carbethoxy ester **183**, which by treatment with excess chlorosulfonic acid afforded the 4-sulfonyl chloride **184** (Equation 59).



(59)

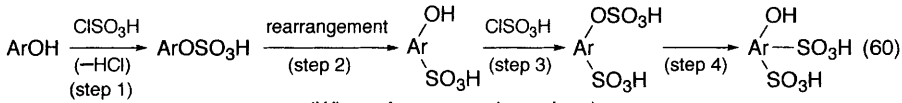
In the carbethoxy derivative **183**, the electron-donating power of the original hydroxyl group has been reduced by the attached carbethoxy group hence facilitating selective monochlorosulfonation, and research showed that other protective groups did not lead to the same selective monochlorosulfonation of phenols.[200]

Extensive literature[1,5,7,180,184,188,189,193,194] demonstrated that chlorosulfonic acid is an effective reagent for the conversion of phenols into phenolpolysulfonyl chlorides. The reagent caused four different types of reaction: sulfonation, chlorosulfonation, chlorination and oxidation.[199] In some instances, the phenolic hydroxyl group was esterified (sulfated) prior to sulfonation and in other cases condensation products, *e.g.* sulfonylides, were isolated. The predominance of any of the quoted reaction types depends on the experimental conditions, *e.g.* time, temperature, quantity of chlorosulfonic acid, solvent (if any) and the nature of the phenolic substrate.

With unsubstituted phenols, it has proved impossible to obtain the corresponding monosulfonyl chloride unless the phenol is first converted into the carbethoxy derivative.

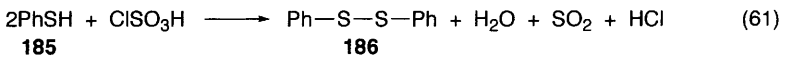
A reaction mechanism for the sulfonation of phenols was postulated[200] in which the first step is esterification (sulfation) of the hydroxyl group (step 1) followed by rearrangement of the sulfate ester into the arylsulfonic acid (step 2). In the presence of sufficient chlorosulfonic acid, the two-step sequence is repeated (steps 3 and 4) leading to the disulfonic acid (Equation 60). In the case of highly reactive phenols, the process can be repeated further yielding polysulfonated products.

Thiophenol **185** (two equivalents) reacts with chlorosulfonic acid to give diphenyl disulfide **186**[201] (Equation 61). In this reaction chlorosulfonic acid functions as a mild oxidizing reagent.



(60)

(Where Ar = aromatic nucleus)

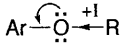


(61)

6 Aryl Ethers

This section includes both alkyl aryl ethers **187** and diaryl ethers **188**. In both cases, the oxygen atom causes an overall donation of electrons (+M, –I effect)

into the aromatic nucleus, which, as in the case of phenols (Section 5), facilitates sulfonation of the aromatic ring although with aromatic ethers *O*-sulfonation (sulfation) is not possible. In the alkyl aryl ethers **187** the electron donation is enhanced by the inductive (+I) electronic effect of the alkyl group.



187 R = alkyl radical

188 Ar = an aryl radical, Ar′ = the same or different aryl group

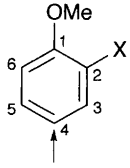
Huntress and Carten[201a] studied the action of chlorosulfonic acid on 42 aromatic ethers in order to determine the utility of the reagent for the characterization of aromatic ethers. 36 of the ethers were converted into their monosulfonyl chlorides and these were subsequently reacted with ammonium hydroxide to give the corresponding sulfonamides which were well-defined crystalline solids with sharp melting points suitable for identification of the original aryl ether. Six of the ethers examined failed to yield satisfactory monosulfonyl chlorides; namely: *o*- and *p*-methoxybiphenyl, diphenyl ether and the 4,4′-dibromo derivative as well as methyl and ethyl benzyl ethers.

In alkyl phenyl ethers, the preferred orientation of sulfonation is *para* with respect to the electron donating alkoxy group, but if this position is blocked by a substituent then sulfonation may occur *ortho* to the alkoxy group.[1,3,5]

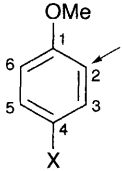
Anisole (methyl phenyl ether or methoxybenzene (**187**; Ar = Ph, R = Me)) reacts with chlorosulfonic acid (two equivalents) in chloroform at 0 °C to give 4-methoxybenzenesulfonyl chloride;[1,201a,202] the latter was also obtained by treatment of **187** with a mixture of chlorosulfonic acid and sulfuric acid at 10 °C.[203,204]

The chlorosulfonation of *o*- **189** and *p*- **190** substituted anisoles by chlorosulfonic acid was also achieved in high yields.[205] The *o*-isomers **189** generally only required mild conditions (*e.g.* a few minutes at 0 °C); the ease of chlorosulfonation is probably due to the lack of steric hindrance in the reactive 4-position.

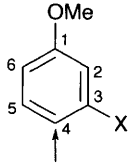
The *p*-isomers **190** required slightly stronger conditions (*e.g.* 1 hour at room temperature) as there is now slight steric shielding at the 2-position. The *m*-isomers **191** gave poor yields of the 4-sulfonyl chlorides at 0 °C, while at higher temperatures extensive decomposition occurred. With the *m*-acetamido derivative (**191**; X = NHCOMe), only the sulfonic acid was formed and with the strongly deactivating nitro substitutent, chlorosulfonation was only successful with the *ortho*-derivative (**189**; X = NO_2).[205]



189



190



191

(X = Br, Cl, NO_2, OMe, NHCOMe; arrows indicate positions of chlorosulfonation)

o-, *m*- and *p*-Methylanisoles (**189–191**; X = Me) were converted into their sulfonyl chlorides by treatment with chlorosulfonic acid (two equivalents) in cold chloroform. With the *m*-methyl derivative, a larger excess of the reagent afforded

the 4,6-disulfonyl chloride.[201a] On the other hand, treatment with an equimolar quantity of chlorosulfonic acid in carbon disulfide at −15 °C gave the 6-sulfonic acid, while with more reagent (two equivalents), the product was the 4,6-disulfonic acid.[174]

2,3,5-Trimethylanisole reacts with excess chlorosulfonic acid to give 4-methoxy-2,3,6-trimethylbenzenesulfonyl chloride;[206,207] this compound is used as a reagent for the protection of amino groups in peptide synthesis. Phenetole (ethyl phenyl ether, **187**; R = Et), by reaction with chlorosulfonic acid (two equivalents) in chloroform yields the 4-sulfonyl chloride[1,201a,208] which is used in the preparation of heat sensitive recording materials.[208]

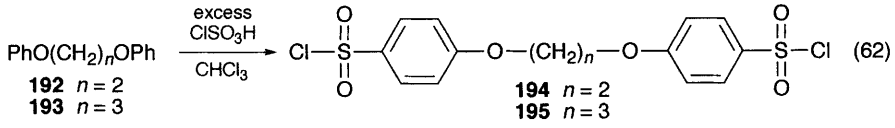
o-, *m*- and *p*-Methyl derivatives of phenetole with chlorosulfonic acid in chloroform yield the corresponding 4-,4- and 2-sulfonyl chlorides respectively.[201a] Likewise, n-butyl-2-methyl and n-propyl-4-methyl-phenyl ethers afford the 4- and 2-sulfonyl chlorides.[201a]

2,3-, 2,5-, 3,4- and 3,5-Dichloroanisoles were converted into their sulfonyl chlorides by treatment with chlorosulfonic acid.[209] *n*-Dodecyl phenyl ether (**187**; R = n-$C_{12}H_{25}$) reacts with excess of the reagent in dichloroethane at 5–10 °C to give the *p*-sulfonyl chloride, an intermediate in the synthesis of hydroxyalkoxybenzenesulfones used as levelling agents in dyeing polyamide fibres.[210] *p*-(Dodecyloxy) toluene, by treatment with a mixture of chlorosulfonic acid, phosphorus oxychloride and dimethylformamide in chloroform afforded 2-dodecyloxy-5-methylbenzenesulfonyl chloride, used in the preparation of silver halide photographic photosensitive materials.[211] Long chain fluorinated sulfamoyl alcohols, used as property enhancers for leather, paper and textiles, are obtained by reaction of monounsaturated fluorinated alkoxyphenyl ethers, *e.g.* $C_{10}H_{19}OF$, with chlorosulfonic acid (four equivalents) and thionyl chloride, followed by condensation of the resultant sulfonyl chloride with an appropriate amino alcohol.[212] Several polyhydric phenol methyl ethers have been chlorosulfonated by Huntress and Carten;[201a] thus catechol dimethyl ether (1,2-dimethoxybenzene) reacted with excess chlorosulfonic acid in chloroform to yield 3,4-dimethoxybenzenesulfonyl chloride. Similarly, resorcinol dimethyl ether (1,3-dimethoxybenzene) and quinol dimethyl ether (1,4-dimethoxybenzene) gave 2,4-dimethoxy- and 2,5-dimethoxy-benzenesulfonyl chlorides, while pyrogallol trimethyl ether (1,2,3-trimethoxybenzene) gave 2,3,4-trimethoxybenzenesulfonyl chloride.[201a]

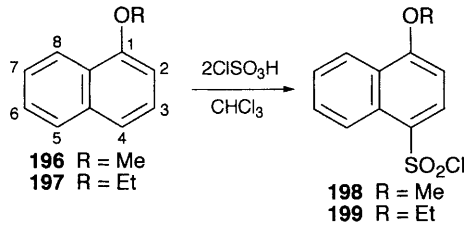
Ethylene- and trimethylene-glycol diphenyl ethers **192** and **193** reacted with excess chlorosulfonic acid in chloroform to give the 4,4′-disulfonyl chlorides **194** and **195** respectively[201a] (Equation 62).

1-Methoxy- and 1-ethoxy-naphthalene **196** and **197** reacted with the reagent in chloroform to give the 4-sulfonyl chlorides **198** and **199** (Equation 62);[1,201a] the sulfonation occurs in the predicted 4-position. The corresponding 2-alkoxynaphthalenes **200** and **201**, according to early workers,[1,213–215] reacted with the reagent (one equivalent) in carbon disulfide to give a mixture of the 6- and 8-sulfonic acids **202** and **203** (X = OH),[213] whereas in chloroform, at low temperature, the ethoxy derivative **201** yields the expected 1-sulfonic acid (kinetically controlled product), which on standing at room temperature rearranges to give a mixture of the ethoxy-6- and 8-sulfonic acids **202** and **203**; X = OH (Equation

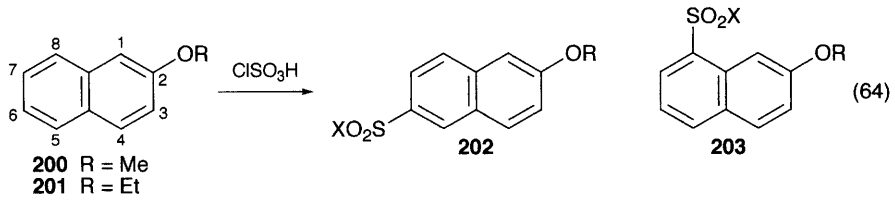
64).[214] This mixture was obtained directly by reaction of **201** with the reagent in carbon disulfide at room temperature.[215] According to Huntress and Carten,[201a] the 2-alkoxynaphthalenes **200** and **201** both reacted with excess chlorosulfonic acid (two equivalents) in chloroform to give the 8-sulfonyl chlorides, (**203**; X = Cl) whereas use of a larger excess of the reagent is claimed by Lapworth[214] to give the 1,6-disulfonic acid.



(62)



(63)

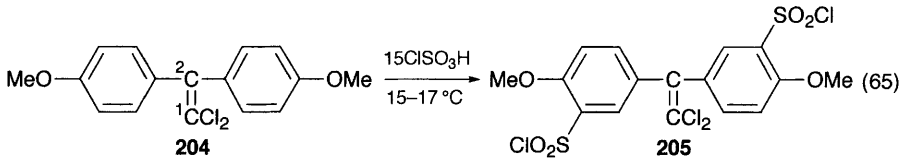


(64)

In the sulfonation of 2-substituted naphthalene derivatives, the energetically predicted point of attack is the 1-position, but the observed sulfonation of 2-methyl and 2-ethoxynaphthalene is mainly at the 6- and 8-positions of the naphthalene ring.[5]

6.1 Diphenyl Ether and Derivatives

Diphenyl ether (phenoxybenzene **206**), by reaction with excess chlorosulfonic acid at room temperature, afforded phenoxybenzene-4,4′-disulfonyl chloride.[216–218] This product was also obtained by reaction with the reagent at temperatures > 40 °C in the presence of nitrogen-containing compounds (*e.g.* urea or its salts);[219] fatty acids (*e.g.* acetic acid);[220] or alkali metal salts (*e.g.* potassium sulfate).[221] Chlorosulfonated bisalkoxyphenyl derivatives are biologically active, fire resistant materials, which are manufactured by reaction of the corresponding bisalkoxyphenyls with a large excess of chlorosulfonic acid at 10–30 °C; thus 1,1-dichloro-2,2-bis (4-methoxyphenyl) ethylene **204** with the reagent (15 equivalents, 4 hours) afforded the corresponding 3,3′-disulfonyl chloride **205**, 70%[221a] (Equation 65).

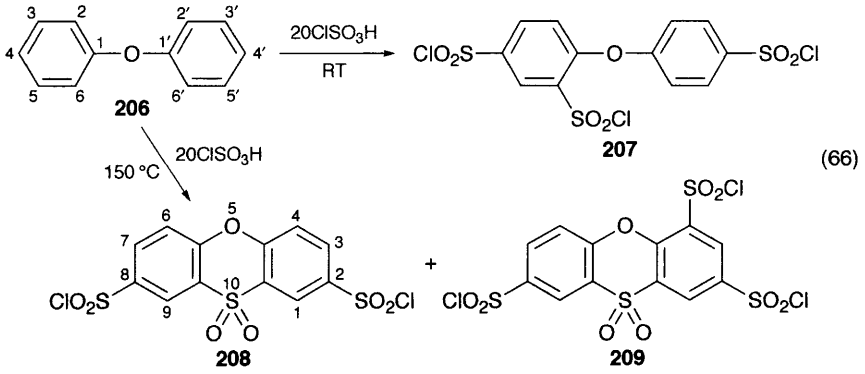


4,4′-Di(acylamido) diphenyl ethers are similarly chlorosulfonated by treatment with excess reagent in cold carbon tetrachloride; thus 4,4′-diacetamidodiphenyl ether afforded the 3,3′-disulfonyl chloride (85%).[222]

2′-Chloro- and 2′,6′-dichloro-4-nitrodiphenyl ethers were converted into the corresponding 4′-sulfonyl chlorides by reaction with excess chlorosulfonic acid (five equivalents).[223,224] The comparatively poor yields of the sulfonyl chlorides obtained may be due to their susceptibility towards hydrolysis, as a result of the presence of the electron-withdrawing groups. Several sulfonyl derivatives of diphenyl ethers, *e.g.* azides, hydrazides and hydrazones showed pronounced algaecidal activity.[225]

When diphenyl ether **206** was treated with a very large excess of chlorosulfonic acid (20 equivalents) at room temperature (4 weeks), a low yield (15%) of the 2,4,4′-trisulfonyl chloride **207** was isolated.[53]

When the same reaction mixture was heated at 100 °C (4 hours), a much improved yield of the trisulfonyl chloride **207** (82%) was obtained. Even more drastic conditions, namely heating the mixture at 150 °C for 4 hours, afforded a mixture of phenoxathiin-10,10-dioxa-2,8-disulfonyl chloride **208** and the corresponding 2,4,8-trisulfonyl chloride **209** (Equation 66).



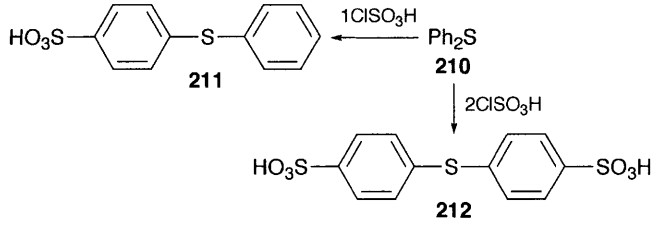
The cyclization of diphenyl ether **206** to the cyclic sulfone derivatives **208** and **209** achieved by prolonged heating with a large excess of the reagent is analogous to similar reactions observed with biphenyl and the diphenyl alkanes (see Section 2, pp 42 and 40). 4-Bromodiphenyl ether by treatment with excess chlorosulfonic acid (two equivalents) at 25–30 °C afforded the 4-sulfonyl chloride[201a,215] (45%). In this molecule, the other reactive 4-position is blocked by the bromine atom. In contrast, with diphenyl ether **206** all attempts to obtain the monosulfonyl chloride by reaction with chlorosulfonic acid failed, and the only isolated product was the 4,4′-disulfonyl chloride.[53] In the case of 4,4′-dibromodiphenyl ether, in which

both the 4 and 4′-positions are blocked, chlorosulfonation by treatment with excess reagent (eight equivalents, 100 °C) yields the 2,2′-disulfonyl chloride (72%). However, when the experiment was repeated using only an equimolar amount of the reagent in boiling carbon tetrachloride, the product was the 2-sulfonic acid, isolated in the form of the sodium salt.[201a,226]

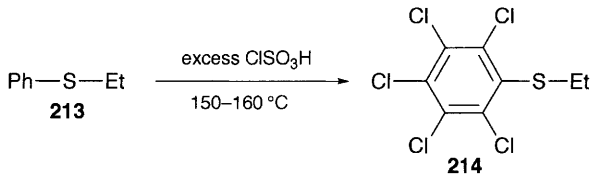
Early work[227] claimed that 4,4′-diethoxybiphenyl apparently reacted with chlorosulfonic acid to give a mixture of the 3-sulfonic acid, 3,3′-disulfonic acid and an unknown compound containing sulfur and chlorine, probably a sulfonyl chloride. With this substrate, it would be anticipated that treatment with excess chlorosulfonic acid would yield the 3,3′-disulfonyl chloride.

6.2 Diphenyl Sulfide

Diphenyl sulfide **210** by reaction with an equimolar quantity of chlorosulfonic acid afforded 4-(phenylthio) benzenesulfonic acid **211**, while the use of an excess of the reagent gave the 4,4′-disulfonic acid **212**[228,229] (Equation 67). The same two products **211** and **212** were obtained by reaction of diphenyl sulfide with concentrated sulfuric acid.[229]



(67)



(68)

A recent patent[230] described the synthesis of 99% pure 4-(phenylthio) benzenesulfonic acid **211** (81% yield) by treating diphenyl sulfide **210** with chlorosulfonic acid in dichloromethane at 0 °C (2 hours).

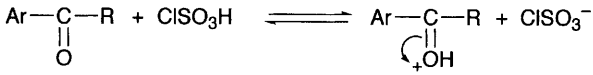
Thiophenetole (ethyl phenyl sulfide, **213**) by prolonged heating with chlorosulfonic acid at 150–160 °C gave ethyl pentachlorophenyl sulfide **214**[8] (Equation 68).

This reaction provides another example of chlorination by chlorosulfonic acid when used under forcing conditions (see also Section 3, p 50).

7 Aromatic Carbonyl Compounds

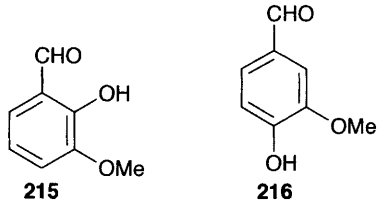
Aromatic carbonyl compounds are protonated in strongly acidic media, like sulfuric and chlorosulfonic acid (Equation 69).[5] As a consequence, the carbonyl group exerts a powerful electron-withdrawing effect on the attached aromatic

nucleus; the sulfonation of aromatic carbonyl compounds is therefore more difficult to achieve than for the parent aromatic hydrocarbons. Comparatively little work has been reported[1,3] on the sulfonation of aryl aldehydes and none of these studies involved the use of chlorosulfonic acid.



(69)

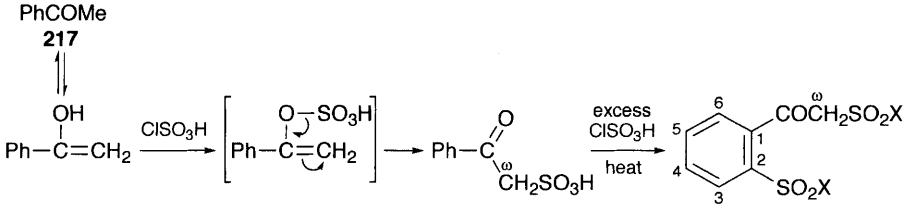
More recent attempts to chlorosulfonate *o*-vanillin **215**, vanillin **216** and 2,5-dimethoxybenzaldehyde with chlorosulfonic acid, under various conditions, were unsuccessful and the reactions only afforded charred products.[231] In contrast, aromatic ketones of both the alkyl aryl and diaryl type have been successfully reacted with chlorosulfonic acid.[1,3,5]



215 **216**

7.1 Acetophenone

Acetophenone **217**, by mixing the excess chlorosulfonic acid in the cold followed by heating the mixture at 110 °C (1 hour), gave a disulfonyl chloride which was originally considered to be the 3,5-derivative.[232] However, subsequent work by Suter and Weston[233] in which acetophenone **217** was treated with the reagent (10 equivalents) in carbon tetrachloride at 0 °C and heated at 110 °C (45 minutes) showed that the product was the 2,ω-disulfonic acid **218** (X = OH); the reaction probably involves initial sulfation of the enolic form of the ketone **217** which then rearranges to form the ω-sulfonic acid **219** (Scheme 1).



219 **218**

Scheme 1

In support, acetophenone-ω-sulfonic acid **219** reacts with excess chlorosulfonic acid to give the disulfonyl chloride (**218**, X = Cl, 15%). In his book, Cerfontain[5] provides further mechanistic details of the conversion of **217** to **218**. Later studies[234] showed that the sulfonation of acetophenone **217** with chlorosulfonic acid may occur at either the *o*- or *m*-positions depending on the reaction conditions. Thus, when the reactants are mixed together in the cold (0 °C) and

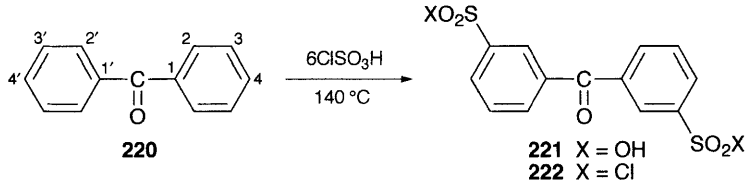
then heated (110 °C), a substantial amount of *o*-sulfonation is observed.[233] On the other hand, when acetophenone **217** is gradually added to excess chlorosulfonic acid (six equivalents) at 110 °C, mainly *m*-sulfonation occurred yielding the 3,ω-disulfonic acid.[234]

In acetophenone therefore, sulfonation occurs both in the aromatic ring and in the side chain; however, in the case of 4-substituted acetophenones both reactions do not necessarily occur.[3] For instance, the 4-methyl-,[235] 4-hydroxy-[236] and 4-methoxy-[237] acetophenones all reacted with excess chlorosulfonic acid to give the corresponding 3-sulfonyl chlorides. Chapman claimed[237a] that acetophenone reacted with chlorosulfonic acid at 120 °C to give 3-chlorobenzothiophene-1,1-dioxide-2-sulfonyl chloride.

7.2 Benzophenone

Benzophenone (diphenyl ketone, **220**) was first converted into the 3,3′-disulfonic acid **221** by heating the ketone with 15% oleum.[238] Lapworth claimed that the substrate was scarcely affected by chlorosulfonic acid and the only product of the reaction was a small quantity of benzophenone-2,2′-disulfone.[238]

However, Cremlyn and co-workers,[224] discovered that benzophenone **220**, by heating with excess of the reagent (six equivalents) at 140 °C (3 hours), afforded a low yield (15%) of the 3,3′-disulfonyl chloride **222** and the 3,3′-disulfonic acid (**221**, 60%) (Equation 70). Later workers[239] claimed that using a larger excess of chlorosulfonic acid (10 equivalents) at 150 °C resulted in an improved yield (50%) of the disulfonyl chloride **222**; repetition of the experiment largely confirmed their results, but gave a slightly lower yield of the product (40%).[240]



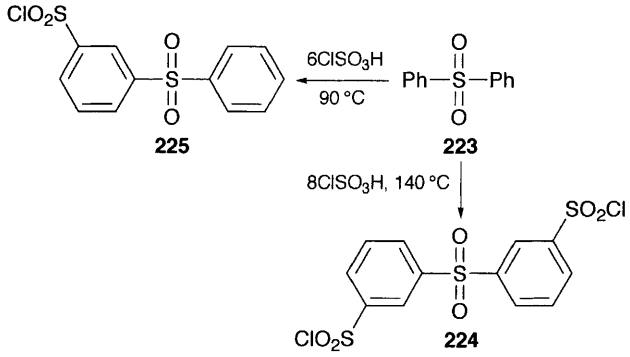
220 **221** X = OH **222** X = Cl (70)

4-Methoxybenzophenone was found to react with chlorosulfonic acid (four equivalents) at 50 °C (10 hours) to give the 3-sulfonyl chloride.[240] The greater ease of reaction and the orientation of chlorosulfonation of this substrate is due to the presence of the strongly electron-donating methoxy group.

Alkoxyhydroxybenzophenonesulfonic acids are used in the manufacture of cosmetic sunscreen additives; they are synthesized by sulfonation of the parent alkoxyhydroxybenzophenones with chlorosulfonic acid at temperatures in the range (−20 to 100 °C) using an aliphatic or aromatic ester solvent.[241,242] For instance, 2-hydroxy-4-methoxybenzophenone reacts with chlorosulfonic acid (2.6 equivalents) in ethyl acetate at 0–5 °C (30 minutes), then at room temperature (12 hours) to yield 4-hydroxy-2-methoxybenzophenonesulfonic acid (80%).[242] The sulfonation may also be effected in excellent yield (95.3%), by reacting the substrate with an equimolar amount of chlorosulfonic acid in dimethyl carbonate at 10–35 °C (1 hour).[242a] In this example, of course, the sulfonation is greatly

facilitated by the presence of the two electron-donating substitutents and occurs, as expected, *o*/*p* with respect to the activating methoxy and hydroxy groups.

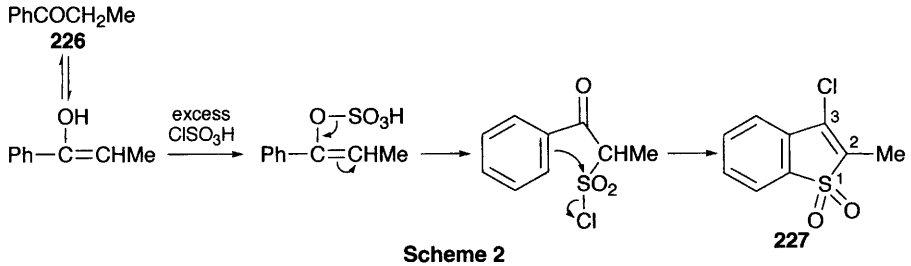
The sulfonyl, like the carbonyl group, is a strongly electron-withdrawing moiety and consequently the chlorosulfonation of diphenyl sulfone, like benzophenone, demands forcing conditions. Diphenyl sulfone **223** was reported[243] to react with chlorosulfonic acid (two equivalents) at 90 °C to give a mixture of the 3-sulfonic acid and the 3,3′-disulfonic acid. Later work by Cremlyn *et al.*[224] found that diphenyl sulfone **223**, by heating with a large excess of the reagent (eight equivalents) at 140 °C (4 hours), gave a good yield of the 3,3′-disulfonyl chloride (**224**, 77%) (Equation 71). This was a much better yield of the disulfonyl chloride than was obtained from benzophenone under comparable conditions, suggesting that the carbonyl group exerts a more powerful electron-withdrawing effect than the more bulky sulfonyl moiety.



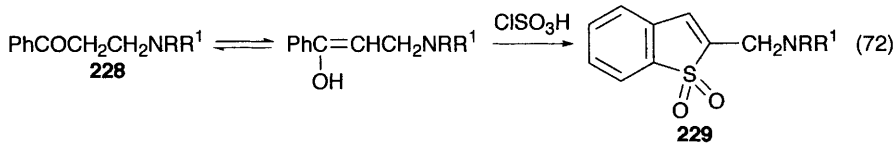
(71)

It was also discovered that diphenyl sulfone **223**, by prolonged heating with chlorosulfonic acid (six equivalents) at 90 °C, gave a low yield of the 3-sulfonyl chloride **225** (Equation 71).[224] Treatment of ethyl phenylsulfone and its *p*-chloro derivative with the reagent both yield the corresponding 3-sulfonyl chlorides[5,8] so that sulfonation occurs, as expected, in the *meta* position relative to the sulfonyl group. Di-*p*-xylylsulfone reacts with chlorosulfonic acid (10 parts, 150–160 °C) to yield the 3,3′-disulfonyl chloride.[8]

An improved procedure for the chlorosulfonation of substituted diaryl sulfones involves heating the appropriate 4,4′-dialkyl or dihalodiaryl sulfone with chlorosulfonic acid (2–4 equivalents) at 140–150 °C and subsequent treatment with thionyl chloride (6–10 equivalents).[244] The action of chlorosulfonic acid on propiophenone (ethyl phenyl ketone **226**) results in a novel cyclization reaction yielding 3-chloro-2-methylbenzothiophene-1,1-dioxide **227**[245] (Scheme 2). The reagent similarly caused smooth cyclization of Mannich bases **228**, the reaction again proceeding *via* the enolic sulfonic acid to yield the cyclic sulfone **229** (Equation 72).[245]

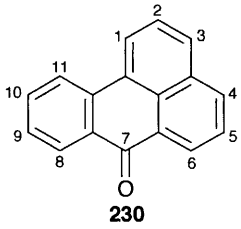


Scheme 2



(72)

7-Benzanthrone **230** reacts with chlorosulfonic acid (one equivalent) in tetrachloroethane to give mainly the 3-sulfonic acid while further sulfonation yields the 3,9-disulfonic acid.[246]

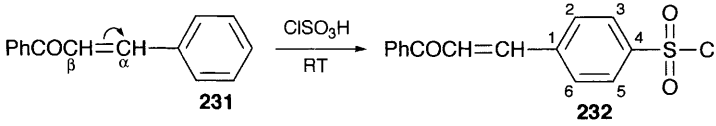


230

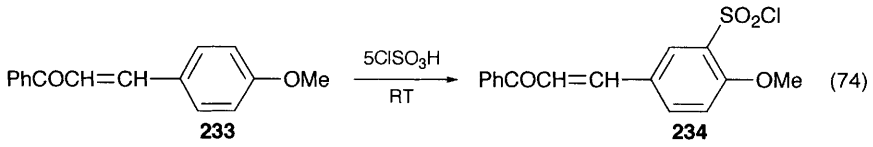
7.3 Chalcones

The reaction of chalcone **231** with chlorosulfonic acid was studied under different conditions: treatment with the reagent (three equivalents) at 0 °C (5 hours) or at 50 °C (3 hours) gave no reaction, while at 100 °C, the product was benzoic acid. However, reaction with excess chlorosulfonic acid (six equivalents) at room temperature for 1 or 3 weeks gave the 4-sulfonyl chloride **232** in yields of 27 or 75% respectively.[247] (Equation 73).

In chalcone **231**, sulfonation is facilitated by the activating influence of the α, β-alkenic double bond which causes an overall donation of electrons into the aromatic ring. 4-Methoxychalcone **233** reacted with chlorosulfonic acid (five equivalents) for 1 week to give the 3-sulfonyl chloride (**234**, 63%) (Equation 74).



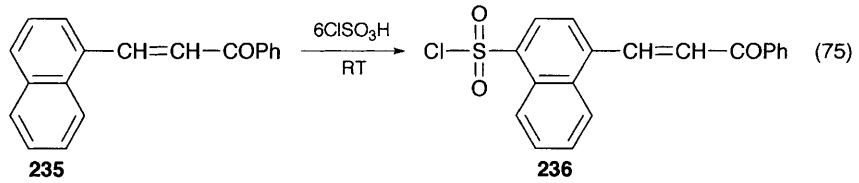
(73)



(74)

The increased yield in the chlorosulfonation of 3-methoxychalcone (63%) as compared with chalcone (27%), under comparable conditions, is a reflection of the activating effect of the methoxy group which also directs the orientation of sulfonation into the 3-position.

α-Naphthylchalcone **235** reacts with chlorosulfonic acid (six equivalents) for 1 day to give the 4-sulfonyl chloride (**236**, 76%) (Equation 75).[248]



(75)

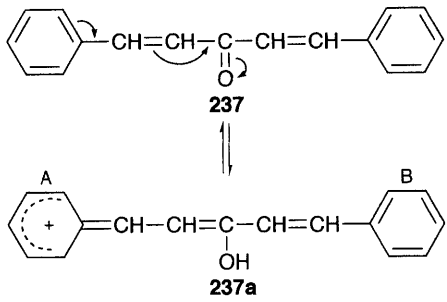
The relative ease of sulfonation of **235** in comparison with chalcone **231** is due to the greater reactivity of the naphthalene nucleus towards electrophilic substitution and the orientation of sulfonation occurs in the predicted 4-position of the naphthalene ring in view of the electron-donating character of the alkenic double bond.[248] 2-, 3-, and 4-Methoxy, 3,4-dimethoxy- and 4-phenyl-chalcone, together with the 2-thienyl and cinnamylidene analogues reacted with chlorosulfonic acid (six equivalents or three equivalents in thionyl chloride) at room temperature to give the corresponding sulfonyl chlorides.[249] The orientation of sulfonation was discussed in terms of stereoelectronic factors and was confirmed by NMR spectral analysis.

In 3-methoxychalcone, both the 4- and 6-positions are activated towards sulfonation by the combined effects of the alkenic double bond and the methoxy group, consequently reaction can occur in either position. 3-Methoxychalcone with chlorosulfonic acid (six equivalents) for 3 hours gave the 6-sulfonyl chloride (60%), while treatment with chlorosulfonic acid (six equivalents) in excess thionyl chloride afforded the 4,6-disulfonyl chloride (88%).[249]

Generally the chlorosulfonation of diphenyl derivatives in which the two aryl rings are not in conjugation, *e.g.* benzophenone and diphenyl ether does not lead to selective monochlorosulfonation.

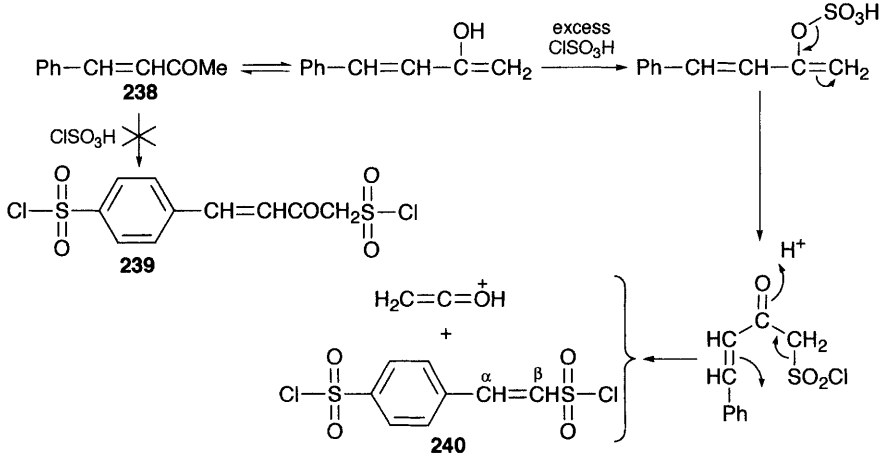
7.4 Diarylideneketones

Dibenzylideneacetone **237**, on the other hand, by prolonged reaction (5 days) with chlorosulfonic acid (five equivalents) gave the 4-sulfonyl chloride (84%).

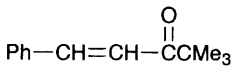


Reaction with a larger quantity of the reagent (ten equivalents) for 8 days afforded the 4,4′-disulfonyl chloride.[53a] The selectivity has been ascribed to the formation of a fully conjugated cation **237a** in the strongly acidic medium, namely chlorosulfonic acid, and this is indicated by the deep red colour produced. In the cationic form of dibenzylideneacetone **237a**, ring B is clearly more susceptible to sulfonation than ring A, so extended conjugation explains the observed selective monochlorosulfonation of this substrate.[53a]

The action of excess chlorosulfonic acid (10 equivalents in chloroform, 1 week) on benzylideneacetone **238**, by analogy with the chlorosulfonation of acetophenone, was expected to yield the 4,ω-disulfonyl chloride **239**, but actually it undergoes a novel reaction to form styrene-4,β-disulfonyl chloride (**240**, 94%).[250] Repetition[251] gave a lower yield (56%) which appears very sensitive to the purity of the starting material and the work-up procedure. The mechanism for the conversion of **238** into **240** is depicted in Scheme 3 and involves enolization, chlorosulfonation, rearrangement to the ω-sulfonyl chloride and elimination of ketene. Later work[251] demonstrated that benzylidenepinacolone **241**, which cannot undergo enolization, similarly reacts with excess chlorosulfonic acid to give styrene-4,β-disulfonyl chloride (**240**, 68%). It was expected that this substrate would yield benzylidenepinacolone-4-sulfonyl chloride.



Scheme 3



241

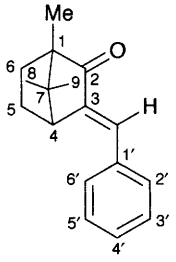
The formation of disulfonyl chloride **240** was rationalised in terms of attack by chlorosulfonic acid at the carbonyl oxygen atom which is analogous to attack on the enol in case of benzylideneacetone, the remainder of the mechanism resembles that already given (Scheme 3) for the conversion of acetophenone into acetophenone-2,ω-disulfonyl chloride (p 77).

Several other arylidene derivatives of ketones have been chlorosulfonated by treatment with chlorosulfonic acid; this general area has been widely exploited by Cremlyn and co-workers at the University of Hertfordshire. It is useful because the arylidene moiety provides an active site for the chlorosulfonation of a wide range of substrates.[3]

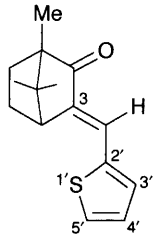
3-Benzylidenecamphor **242** reacts with excess chlorosulfonic acid (six equivalents) at room temperature (1 week) followed by treatment with thionyl chloride (1 day) to yield the *p*-sulfonyl chloride (65%).[252] These reaction conditions afforded the optimum yield of the product which was estimated from the yield of the dimethylamide derivative. In this reaction, there was surprisingly no apparent attack by the reagent on the camphor ring (see p 161).

Application of an essentially similar procedure effected the chlorosulfonation of 3-(*o*- and *p*-methoxybenzylidene) camphors in the expected 5′- and 3′-positions.

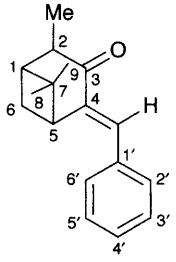
The orientation of sulfonation is in agreement with previous results observed in the chlorosulfonation of *o*- and *p*-methoxychalcones.[249] The orientation is controlled by the powerful electron-releasing properties of the methoxy group; this effect is clearly demonstrated in the chlorosulfonation of 3-(*m*-methoxybenzylidine) camphor which affords the 4′,6′-disulfonyl chloride.



242



243

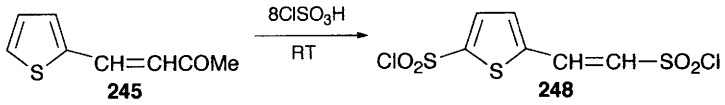


244

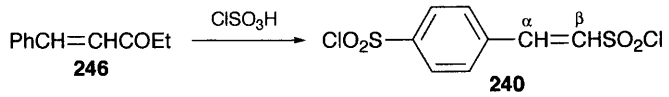
In the case of 3-(2′-thienylidene) camphor **243** chlorosulfonation, under similar conditions, gave the 5′-sulfonyl chloride[252] (sulfonation adjacent to the electron-donating heterosulfur atom). 4-Benzylidenepinocamphorone **244** reacted with excess chlorosulfonic acid (six equivalents) at room temperature (1 week), followed by treatment with thionyl chloride–DMF catalyst, to give the *p*-sulfonyl chloride, characterized by formation of sulfonamide derivatives.[253]

2-Thienylideneacetone **245**, together with the benzylidene derivatives of ethyl methyl ketone **246** and diethyl ketone **247**, by treatment with excess chlorosul-

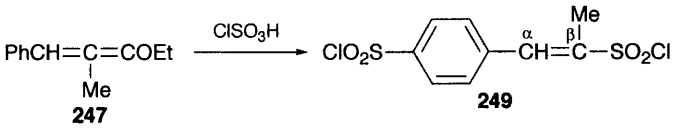
fonic acid (10 equivalents) in chloroform (1 week), afforded the thienylidene 5,β-disulfonyl chloride **248** and the styrene disulfonyl chlorides **240** and **249** (Equations 76–78).



(76)



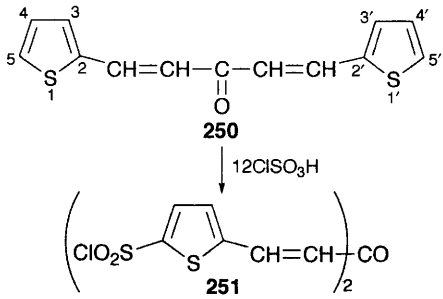
(77)



(78)

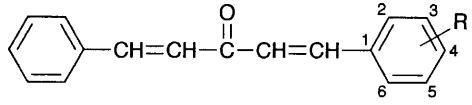
It is interesting that the action of excess chlorosulfonic acid on the benzylidene derivative of ethyl methyl ketone **246** afforded styrene-4,β-disulfonyl chloride **240** (Equation 77), the identical compound to that obtained by similar treatment of benzylideneacetone **238** (see p 82). On the other hand, the benzylidene derivative of diethyl ketone **247**, under the same conditions, afforded the β-methylstyrenedisulfonyl chloride **249** (Equation 78). The formation of both products **240** and **249** can be rationalized in terms of the mechanism proposed for the analogous reaction of benzylideneacetone as shown in Scheme 3.

Di-(2-thienylidene) acetone **250** reacted with excess chlorosulfonic acid (12 equivalents) at room temperature (1 week) to give the 5,5′-disulfonyl chloride (**251**, 85%).[254] (Equation 79)



(79)

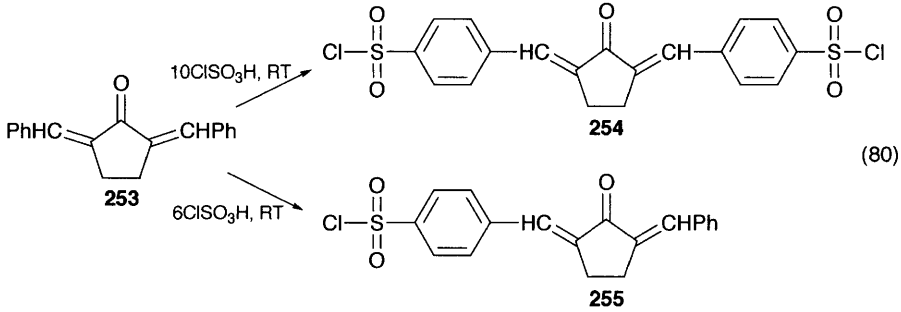
All attempts to prepare the 5-sulfonyl chloride by reaction of **250** with the reagent under a variety of conditions failed. This result is different from the analogous chlorosulfonation of dibenzylideneacetone **237** when selective mono-chlorosulfonation was possible and may be due to the greater reactivity of the thiophene nucleus towards electrophilic attack. Benzylideneacetone **238** was condensed with aromatic aldehydes to yield the corresponding 1,5-diaryl-1,4-dien-3-ones **252**.



252 R = 4-Cl; 2,4-Cl_2; 3,4-Cl_2; 3-NO_2

Attempted chlorosulfonation of (**252**; R = 4-Cl, 3,4-Cl_2) with chlorosulfonic acid (10 equivalents, room temperature, 1 week) failed to give pure products.[254]

A series of diarylidene and heteroarylidene ketones of varying ring sizes have been synthesized and treated with chlorosulfonic acid.[255] 2,5-Dibenzylidenecyclopentanone **253** reacted with chlorosulfonic acid (10 equivalents, 1 week) at room temperature to give the 4,4′-disulfonyl chloride (**254**, 73%) (Equation 80). Reaction using less reagent (six equivalents) afforded the 4-sulfonyl chloride (**255**, 47%).



(80)

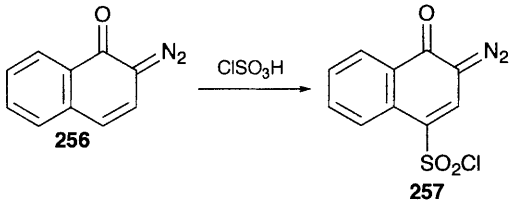
With 2,6-dibenzylidenecyclohexanone, the action of excess chlorosulfonic acid similarly gave the 4,4′-disulfonyl chloride (84%). The reaction was discovered to be very sensitive to impurities in the starting material and was only successful when it had been freshly recrystallized. The action of excess chlorosulfonic acid on the dibenzylidene derivatives of cycloheptanone and octanone also gave excellent yields of the corresponding 4,4′-disulfonyl chlorides (81 and 85% respectively). However, attempts to obtain the corresponding monosulfonyl chlorides were unsuccessful, as were those with 2,6-dibenzylidenecyclohexanone. This result contasts with the behaviour of dibenzylidenecyclopentanone **253**, where both the mono- (**255**) and di- (**254**) sulfonyl chlorides can be isolated. (Equation 80).

The essentially planar nature of the cyclopentanone ring allows the dibenzylidene derivative **253** in chlorosulfonic acid to form a fully conjugated cationic intermediate, similar to that obtained with dibenzylideneacetone **237a**, which permits selective monochlorosulfonation.

Attempted chlorosulfonation of 2,4-dibenzylidenecyclobutanone gave a mixture of products which could not be characterized. The problems experienced with this substrate are probably due to the sensitivity of the four-membered cyclobutane ring to ring-opening reactions.[255]

2-Diazo-1,2-naphthaquinone **256** reacts with chlorosulfonic acid to yield the 4-sulfonyl chloride **257** (Equation 81).[256–258] The conversion may be effected by using excess reagent (6–10 equivalents) in the presence of thionyl chloride (2–5

equivalents) at 35–60 °C optionally in a solvent and with rigid exclusion of light.[257] Other workers[258] claimed that the highest yields of the product **257** (50%) were obtained by reaction with chlorosulfonic acid at 63 °C for 80 minutes.



256 **257** (81)

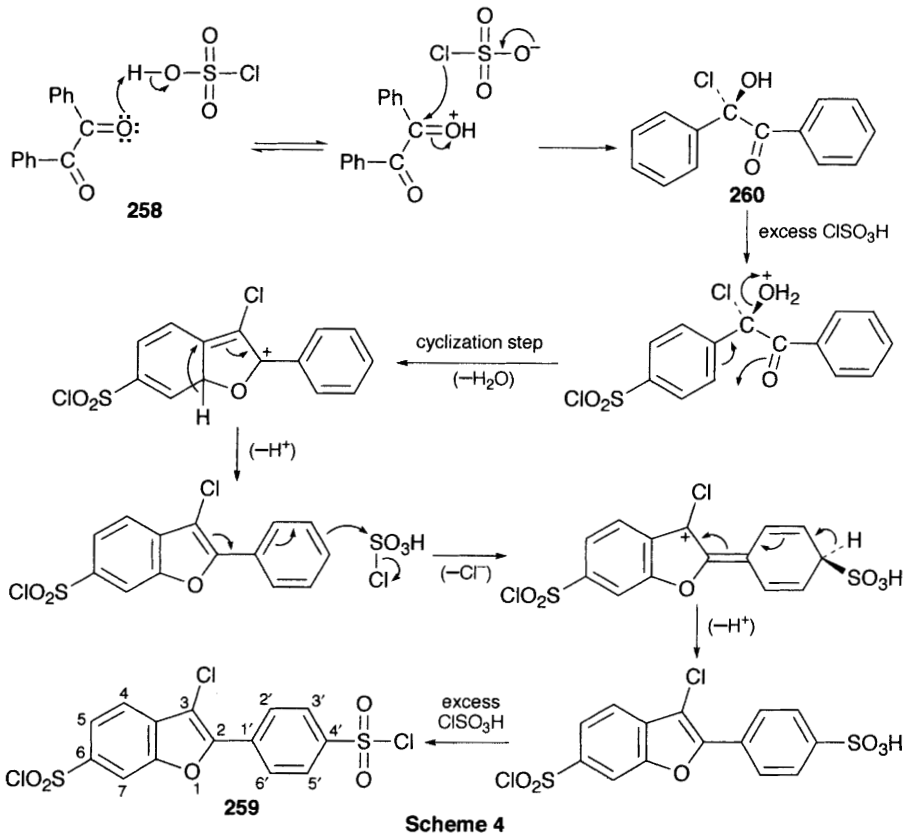
The pure sulfonyl chloride (**257**) was recently obtained by reaction of the diazo compound **256** with chlorosulfonic acid, followed by treatment with thionyl chloride and/or phosphorus pentachloride.[258a]

7.5 Benzils and other Diketones

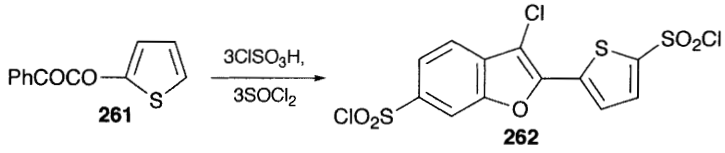
Benzil **258** undergoes a novel cyclization reaction on treatment with chlorosulfonic acid (six equivalents) at 40 °C (2 hours) to yield 3-chloro-2-phenylbenzofuran-6,4′-disulfonyl chloride (**259**, 60%).[259] The mechanism originally proposed for the reaction involved cyclization to the benzofuran ring system prior to sulfonation. However, this mechanism is probably incorrect and has been modified so that sulfonation occurs *before* cyclization as shown in Scheme 4.

In the modified reaction mechanism,[260] the chlorohydrin intermediate **260** is sulfonated and in this molecule the deactivation of the phenyl nucleus towards electrophilic attack is significantly reduced. The chlorohydrin moiety provides the appropriate reactivity, directs the orientation of chlorosulfonation and allows the reaction to proceed under comparatively mild conditions.

It was originally anticipated that the chlorosulfonation of benzil **258** would demand forcing conditions, rather similar to those required for chlorosulfonation of benzophenone, namely prolonged reaction with a large excess of reagent at 150 °C (see p 78). In the cyclization of benzil, TLC showed that some unreacted sulfonic acid remained and in an effort to increase the yield of the benzofuran disulfonyl chloride **259**, a greater quantity of the reagent (12 equivalents) was used; however under these conditions, the product was 3-chloro-2-phenylbenzofuran-4,6,4′-trisulfonyl chloride. On the other hand, heating benzil **258** with less chlorosulfonic acid (three equivalents) in thionyl chloride for 1 hour afforded an excellent yield of the benzofuran disulfonyl chloride (> 90%).[261] The cyclization reaction with chlorosulfonic acid has been successfully extended to several symmetrical and unsymmetrical benzils and heterocyclic analogues, which gave the corresponding substituted benzofurans.[260,261] The ring closure is dependent on the electronic character of the substituent groups and can be controlled by electron-withdrawing groups. Reaction of 2-thienylbenzil **261** with chlorosulfonic acid (three equivalents) in boiling thionyl chloride gave the benzofuran derivative **262** (Equation 82).



Scheme 4



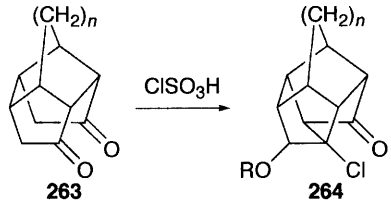
(82)

In contrast, 3-thienylbenzil with chlorosulfonic acid–thionyl chloride, gave a mixture of isomers; these results are in accord with the predicted reaction mechanism.[261]

1,4-Diaminoanthraquinone was treated with chlorosulfonic acid (1.03 equivalents) in *o*-dichlorobenzene over 1 hour at 30 °C. The mixture was heated at 70 °C and more of the reagent (1.1 equivalents) was added. After further heating at 115–120 °C (10 hours), the reaction afforded, as expected, the 2-sulfonic acid (95% yield).[262]

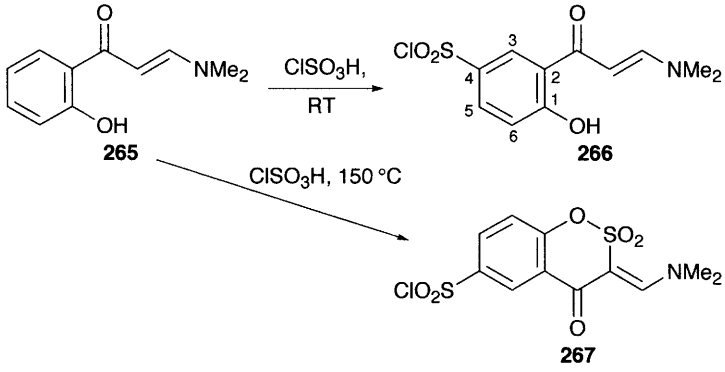
1,5-Di (2-methoxyanilino) anthraqinone, by treatment with a large excess of chlorosulfonic acid (17 equivalents) at 40–45 °C (1 hour), gave the 5-chlorosulfonyl derivative.[263]

The diketones (**263**; $n = 1, 2$) by treatment with chlorosulfonic acid rearranged to form the chlorosulfite **264** (64% yield) (Equation 83).[264]



(83)

Reaction of the enaminoketone **265** with chlorosulfonic acid at room temperature gave the 4-sulfonyl chloride **266**, in which chlorosulfonation occurred, as expected, *para* to the phenolic hydroxyl group (Equation 84).

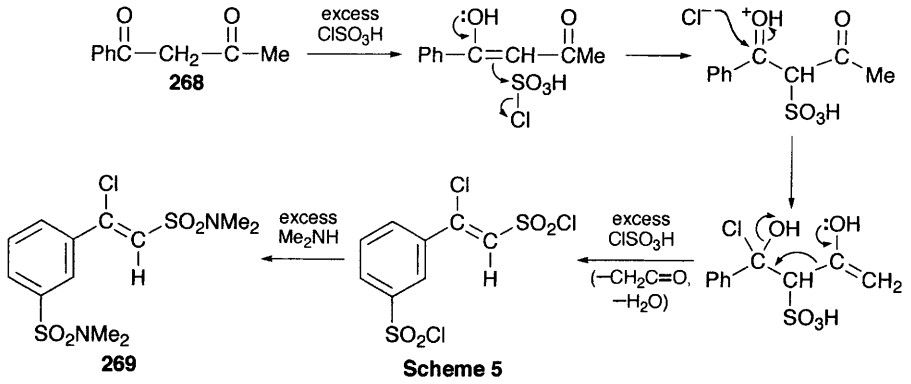


(84)

In contrast, when the reaction was carried out at 150 °C, the enaminoketone **265** cyclized to form the benzoxathianesulfonyl chloride **267** (Equation 84).[265]

Benzoylacetone (**268**) reacts with excess chlorosulfonic acid (10 equivalents) at room temperature (three hours), followed by treatment with dimethylamine to give the bisdimethylamide (**269**, 33%) (Scheme 5).[265a] In this sequence, direct sulfonation occurs on the methylene carbon atom of the enolic form and subsequent reaction is *via* the chlorohydrin intermediate and involves expulsion of ketene as has previously been observed in the chlorosulfonation of benzylideneacetone (see p 82). In the reaction, sulfonation of the phenyl ring occurs in the position *meta* to the electron-withdrawing carbonyl moiety as would be anticipated.

Attempts to obtain benzoylacetone monosulfonyl chloride by reaction with chlorosulfonic acid (three equivalents) in thionyl chloride were unsuccessful.[265a]



268 **269**

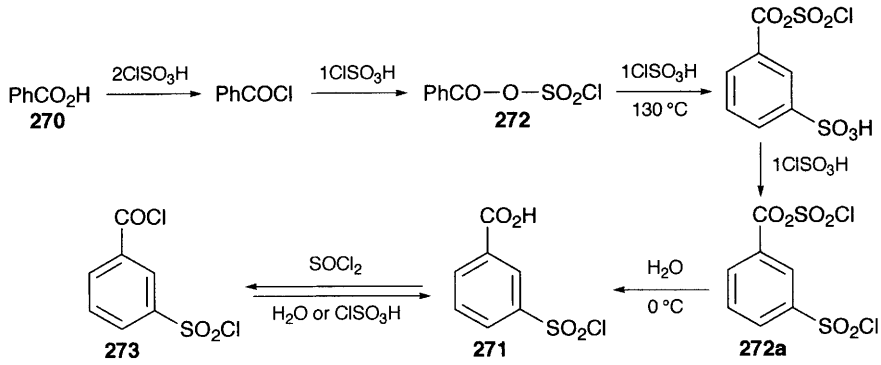
Scheme 5

8 Aromatic Carboxylic Acids and Amides

In aromatic carboxylic acids, the carboxylic acid group (CO_2H) is an electron-withdrawing moiety (−I, −M effects), hence it reduces the reactivity of the attached aromatic nucleus towards electrophilic substitution. So like aromatic carbonyl compounds (Section 7), aromatic carboxylic acids are more resistant towards sulfonation than the parent aromatic hydrocarbons. The reaction therefore generally requires rather forcing conditions, *e.g.* the use of a large excess of chlorosulfonic acid at temperatures of more that 120 °C.[3] The reactions of benzoic, cinnamic and phenylacetic acid with chlorosulfonic acid were reported by Suter.[1]

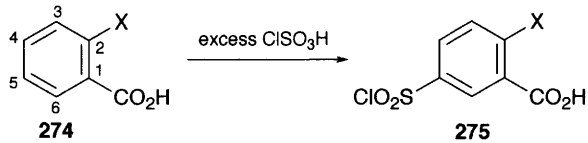
8.1 Benzoic Acid and Derivatives

Smiles and Stewart[266] first demonstrated that the action of excess chlorosulfonic acid on benzoic acid **270** yields 3-chlorosulfonylbenzoic acid **271** (Scheme 6). Later work by Cremlyn[267] showed that a large excess of the reagent (at least five equivalents) at 130 °C (1 hour) was needed to obtain the optimum yield (82%) of the sulfonyl chloride **271**. The postulated reaction mechanism for the chlorosulfonation of benzoic acid involves the mixed anhydride intermediate **272**, which accounts for the large excess of reagent required (Scheme 6). In agreement, it was found that the use of the carboxylic acid amide often permitted a high yield of the corresponding *m*-chlorosulfonyl derivative to be obtained using less chlorosulfonic acid (three to four equivalents).[267] On addition of the crude reaction product to crushed ice, the intermediate **272a** is rapidly cleaved to regenerate the carboxylic acid group, whereas the chlorosulfonyl group is relatively unaffected. Attempts to convert benzoic anhydride into the corresponding 3,3′-disulfonyl chloride by treatment with excess chlorosulfonic acid were unsuccessful. The only isolatable product was 3-chlorosulfonylbenzoic acid **271** which probably arises from initial protonation of benzoic anhydride in the strongly acidic medium.[267]



Scheme 6

In the reaction of benzoic acid with a large excess of chlorosulfonic acid, the dichloride **273** may be an intermediate. 3-Chlorosulfonylbenzoyl chloride **273** was easily prepared by treatment of 3-chlorosulfonylbenzoic acid **271** with thionyl chloride and was shown to reform the 3-sulfonyl chloride **271** by reaction with either water or chlorosulfonic acid (Scheme 6). Stewart[110] successfully reacted cinnamic, salicylic and phenylacetic acid with excess chlorosulfonic acid to obtain the corresponding sulfonyl chlorides. Several *ortho*-substituted benzoic acids (**274**; X = Me,[267] OMe,[268] OH,[110,268–271] Cl,[267] Br[267]) have been treated with excess chlorosulfonic acid (four to six equivalents). When X is an electron-donating group, chlorosulfonation occurred under relatively mild conditions (40–60 °C, 1–2 hours) to give the 5-sulfonyl chloride **275** in yields of 70–90% (Equation 85).



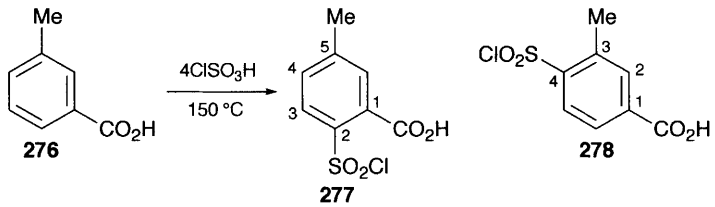
(85)

The observed orientation of sulfonation in the 5-position which is *para* to the electron donor group (X) and *meta* to the carboxylic acid group is in agreement with predicted stereoelectronic effects. When X is an electron-withdrawing group (*e.g.* chlorine or bromine), the chlorosulfonation demanded rather more forcing conditions, *e.g.* heating with excess reagent at 120–130 °C for 2–3 hours. In the chlorosulfonation of *p*-substituted benzoic acids containing powerful electron-donating groups such as hydroxy[270] or methoxy,[272] the reaction required heating with the reagent (five equivalents) at 60–65 °C to give the 3-sulfonyl chloride in lower yields (50–60%). However, with less powerful electron-donor groups, the chlorosulfonation demanded higher temperatures; thus with *p*-toluic acid, the reaction was carried out at 120–150 °C[267,273] (3 hours).

When moderately powerful electron-withdrawing groups (*e.g.* chlorine[267,273] or fluorine[273]) are present, the reaction required forcing conditions (*e.g.* 120–130 °C, 3–8 hours).

2,4-Dichlorobenzoic acid reacted with chlorosulfonic acid (140 °C, 8 hours) to yield the 5-sulfonyl chloride (60%).[273] With benzoic acids substituted with

strongly deactivating groups for instance, *m*-nitrobenzoic acid and phthalic acid (benzene-1,2-dicarboxylic acid), attempted chlorosulfonation by prolonged treatment with excess chlorosulfonic acid (four to six equivalents) at 150 °C was unsuccessful.[267] *m*-Nitrobenzoic acid was unchanged after 15 hours and phthalic acid after 48 hours only gave phthalic anhydride (dehydration product). However, it is interesting that the action of excess chlorosulfonic acid on 4-hydroxybenzene-1,3-dicarboxylic acid yields the 5-sulfonyl chloride.[1] The chlorosulfonation of this substrate presumably succeeds as a result of the strongly activating influence of the hydroxy group. Salicylic acid (*o*-hydroxybenzoic acid) (**274**; X = OH) reacts smoothly with excess chlorosulfonic acid (three to five equivalents) at 50–60 °C (1 hour) to yield the 5-sulfonyl chloride (60%).[110,267] 5-Alkylsulfonylsalicylanilides used as antiseptics were synthesized *via* the chlorosulfonation of salicylic acid.[274] When salicylic acid was treated with chlorosulfonic acid under rather more drastic conditions, namely a large excess of the reagent (10 equivalents) at 130–140 °C for $1\frac{1}{2}$ hours, the 3,5-disulfonyl chloride was isolated.[188] The 5-bromo- and 5-chloro derivatives of salicylic acid by heating with excess chlorosulfonic acid afforded the corresponding 3-sulfonyl chlorides which have been converted into a range of sulfonyl derivatives.[53a,269,275,276] The action of chlorosulfonic acid on *m*-toluic acid **276** may give either the 2-sulfonyl chloride **277** or the 4-sulfonyl chloride **278** (Equation 86).

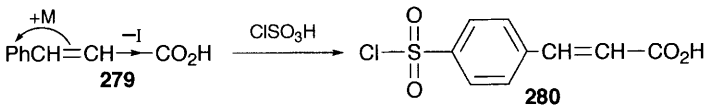


(86)

So that sulfonation may occur either *o* or *p* with respect to the electron-donating methyl group. When the substrate **276** was treated with excess reagent (four equivalents, 150 °C, $2\frac{1}{2}$ hours), the product was a sulfonyl chloride (76%) which on the basis of NMR spectroscopic evidence was concluded[267] to be the 2-sulfonyl chloride **277** rather than the 4-isomer **278**. The formation of **277** may be favoured by stabilization due to intramolecular hydrogen bonding which is not possible in the alternative structure **278**.

8.2 Cinnamic Acid

The reaction of cinnamic acid **279** with 18% oleum at 90 °C yields a mixture of the *p*-sulfonic acid (72%), the *m*-isomer (27%) and less than 1% of the *o*-isomer.[277] In contrast, when cinnamic acid **279** was warmed with chlorosulfonic acid (four equivalents, 50–60 °C) for $3\frac{1}{2}$ hours apparently the only product was the *p*-sulfonyl chloride **280** (60%)[110,267] (Equation 87).

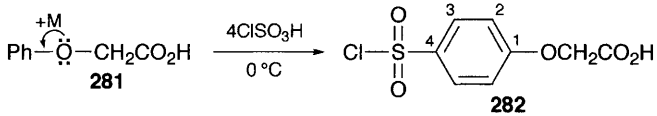


(87)

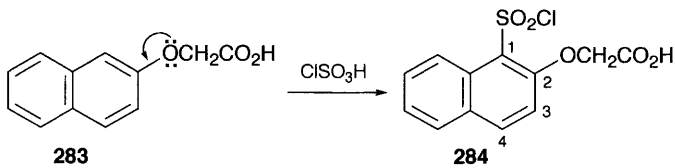
In cinnamic acid **279**, the electron donation from the alkenic double bond (+M effect) apparently predominates over the electron-withdrawing (−I effect) due to the carboxylic acid group which is transferred to the phenyl ring *via* the double bond. The latter effect probably accounts for the appreciable amount of the *m*-isomer isolated from the oleum sulfonation reaction.

8.3 Phenoxyacetic Acid and Related Acids

Phenoxyacetic acid **281** is a more reactive substrate than cinnamic acid due to the powerful electron-donating (+M) effect of the lone pair of electrons on the oxygen atom and treatment with excess chlorosulfonic acid (four equivalents) for 40 minutes at 0 °C afforded the *p*-sulfonyl chloride (**282**, 56%)[267] (Equation 88). The reaction was repeated with *o*-chlorophenoxyacetic acid, but only gave a very low yield of the sulfonyl chloride.[267] However, the chlorosulfonation of ethyl-2-chlorophenoxyacetate by chlorosulfonic acid (four equivalents) at 25 °C is reported[278] to yield ethyl-4-chlorosulfonylphenoxyacetate in almost quantitive yield. Ethyl 3- and 4-chlorophenoxyacetates were similarly chlorosulfonated to yield the corresponding 4- and 2-sulfonyl chlorides respectively. The chlorosulfonation of ethyl 2,4-dichloro-, 2,5-dichloro- and 2,3,5-trichlorophenoxyacetates by the reagent demanded slightly higher reaction temperatures of 30, 55 and 60 °C respectively and gave the corresponding 6-, 4- and 4-chlorosulfonyl derivatives.[278] *β*-Naphthoxyacetic acid **283** by reaction with chlorosulfonic acid afforded the 1-sulfonyl chloride **284**[279] (Equation 89).



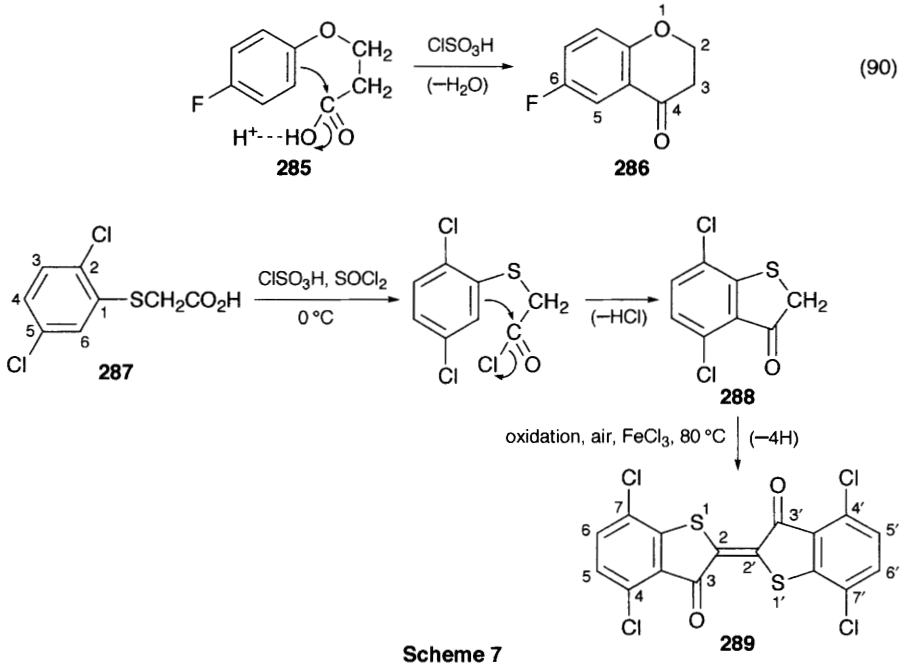
(88)



(89)

Treatment of the appropriate phenoxypropionic acid with chlorosulfonic acid yields 4-chromanones, useful as synthetic intermediates for the manufacture of agrochemicals, drugs and photosensitizers.[280] For instance, *p*-fluorophenoxypropionic acid **285** by dropwise addition to chlorosulfonic acid at 3–5 °C, and subsequent reaction at room temperature (30 minutes) gave 6-fluoro-4-chromanone (**286**, 82%) (Equation 90).[280] In this cyclization reaction, chlorosulfonic acid is acting as an acidic dehydrating agent. A rather similar cyclization reaction has

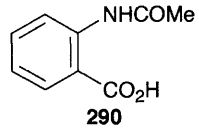
been reported[281] when arylthioglycollic acids react with chlorosulfonic acid in the presence of an inorganic halide, *e.g.* thionyl chloride, sulfuryl chloride or phosphorus trichloride. The initial cyclized product could subsequently be oxidized to yield thioindigos, valuable as dyes and pigments.[281] For instance, 2,5-dichlorophenylthioglycollic acid **287** reacted with chlorosulfonic acid in thionyl chloride at 0 °C (5 hours) to give the cyclic product **288**, which was oxidized to 4,4′,7,7′-tetrachlorothioindigo **289** (82%) (Scheme 7).



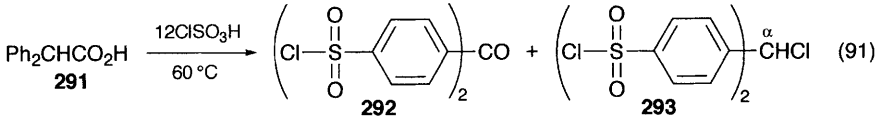
Scheme 7

8.4 Phenyl and Diphenylacetic Acid

Stewart[110] claimed that rapid treatment of phenylacetic acid with chlorosulfonic acid (five equivalents) in the cold afforded the *p*-sulfonyl chloride (35%). However, later attempts[267] to repeat the chlorosulfonation of phenylacetic acid using excess reagent (three to five equivalents) at 0 °C were unsuccessful and only afforded the unchanged acid. Attempted chlorosulfonation of *N*-acetylanthranilic acid **290** by heating with chlorosulfonic acid (five to seven equivalents) at 65–85 °C was also unsuccessful.[282] There was no reaction under these conditions and at higher temperatures (120–130 °C), extensive decomposition occurred. The failure of this reaction may be due to the bulky carboxylic acid group inhibiting the mesomeric activation of the benzene ring by the acetamido group. Diphenylacetic acid **291** reacted with excess chlorosulfonic acid (12 equivalents) at 60 °C (1 hour) to give a mixture of 4,4′-dichlorosulfonylbenzophenone **292** and α-chlorodiphenylmethane-4,4′-disulfonyl chloride **293** (Equation 91).[52]



290

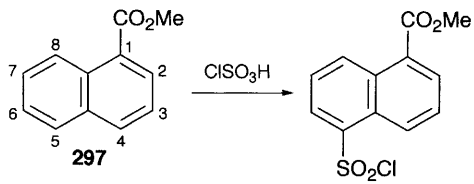


In this reaction, it is likely that rapid sulfonation of the phenyl rings occurs prior to loss of carbon monoxide.[52]

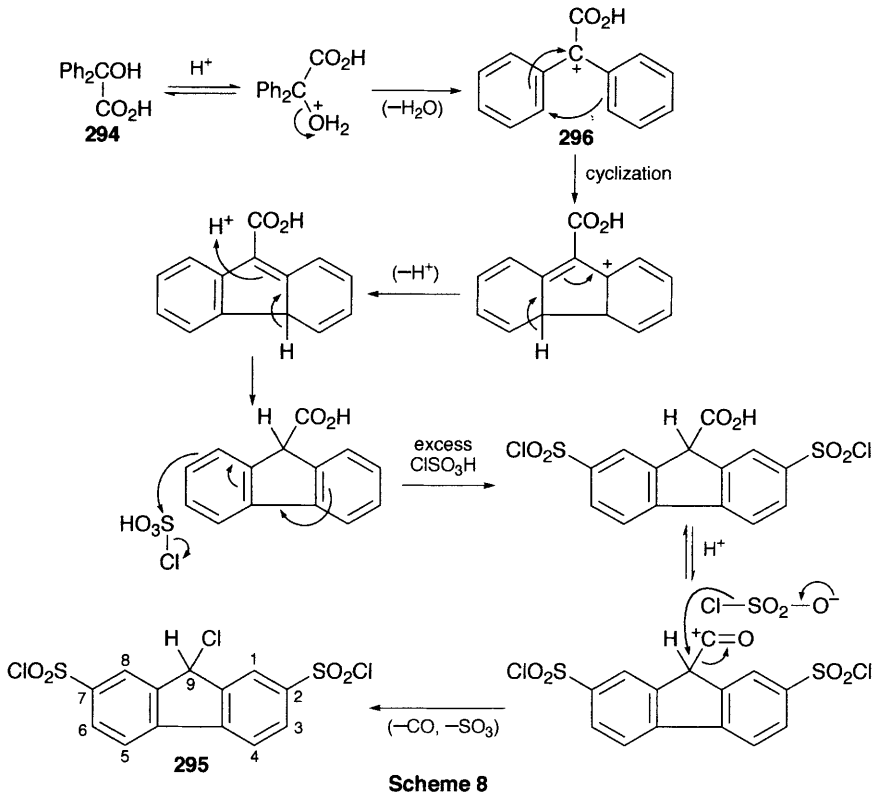
8.5 Benzilic Acid

Benzilic acid **294** was claimed[3] to react with chlorosulfonic acid (12 equivalents) in boiling chloroform to give 4,4′-dichlorosulfonylbenzophenone **292**, however repetition of the reaction afforded 9-chlorofluorene-2,7-disulfonyl chloride **295** (38%).[52] The proposed mechanism for this conversion is shown in Scheme 8 and involves protonation of the alcoholic hydroxyl group followed by loss of water. The carbocation **296** is formed *before cyclization* to fluorene-9-carboxylic acid, so that subsequent sulfonation should occur in the 2,7-positions.[52]

Benzoyl chloride and benzoic anhydride, by heating with excess chlorosulfonic acid followed by addition of the crude reaction mixture to crushed ice, both afforded 3-chlorosulfonylbenzoic acid.[267] These carboxylic acid derivatives (acid chlorides and anhydrides) are easily hydrolysed to the carboxylic acid group in the work-up procedure, so they behave similarly to the parent arylcarboxylic acid. On the other hand, arylcarboxylic acid esters may be chlorosulfonated without loss of the ester group; thus methyl-1-naphthalenecarboxylate **297** by treatment with excess chlorosulfonic acid gave the corresponding 5-sulfonyl chloride **298**[283] (Equation 92). Similar results were reported[278] in the chlorosulfonation of ethyl chlorophenoxyacetates in which the ester grouping was retained.



297 298 (92)

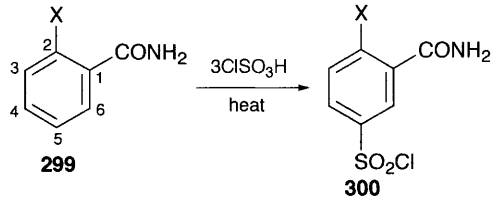


Scheme 8

8.6 Carboxylic Acid Amides

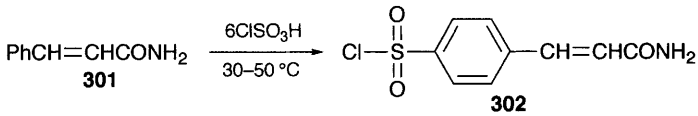
Aromatic carboxamides react with excess chlorosulfonic acid with little effect on the amido ($CONH_2$) group, as compared with the analogous reaction with carboxylic acids.[3,267] Consequently, the chlorosulfonation of aromatic carboxamides can be achieved in high yields using less reagent (three equivalents). The reaction also occurs more easily than it does with the corresponding carboxylic acid, because the carboxamido moiety is a less powerful electron-withdrawing group due to the greater electron donor (+M) effect of the amino group.

Carboxamides substituted in the 2-position by electron-donor groups (**299**; X = Me, OMe, OH) react easily with chlorosulfonic acid (three equivalents) at 50–70 °C for between 30 minutes and 2 hours to give excellent yields (85–98%) of the corresponding 5-sulfonyl chlorides **300** (Equation 93).[284]



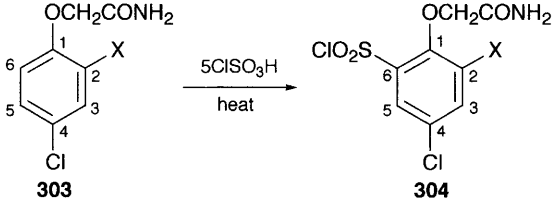
(93)

With 2-acetoxybenzamide (**299**; X = CO_2Me), chlorosulfonation afforded a mixture of the 5-sulfonyl chloride (**300**; X = CO_2Me) together with the corresponding hydroxy derivative (**300**; X = OH) the latter arising from partial hydrolysis of the initial reaction product during the work-up procedure. Chlorosulfonation of the analogous 4-substituted benzamides demanded a longer reaction period due to steric hindrance by the 4-substituent. For instance, 4-methoxybenzamide required warming with chlorosulfonic acid for more than 4 hours to obtain 5-amido-2-methoxybenzenesulfonyl chloride.[3] Cinnamide **301** reacted smoothly with chlorosulfonic acid (six equivalents) at 30–50 °C (1 hour) to yield the *p*-sulfonyl chloride (**302**, 65%) (Equation 94).



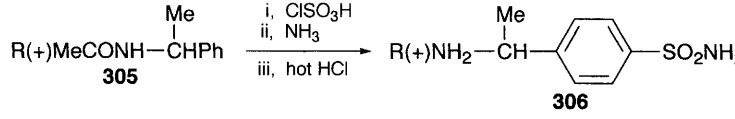
(94)

As in the case of cinnamic acid (p 91), the reaction is facilitated by the electron-donating effect of the π-electrons of the α,β-alkenic double bond.[285] Substituted cinnamides, *e.g.* the dimethylamide and morpholidate, were similarly chlorosulfonated;[286] the former by treatment with excess of the reagent (six equivalents) at room temperature (1 week), and the latter by heating at 70 °C for 3 hours to give the corresponding *p*-sulfonyl chlorides in yields of 60 and 72% respectively.[286] Phenoxyacetamide reacted with excess chlorosulfonic acid (five equivalents) at room temperature ($1\frac{1}{2}$ hours) followed by heating at 70 °C (30 minutes) to give the *p*-sulfonyl chloride (80%).[287] 2,4-Dichloro- (**303**; X = Cl) and 4-chloro-2-methylphenoxyacetamide (**303**; X = Me) also reacted with the reagent (five equivalents) at 80–90 °C or at 70–72 °C for $1\frac{1}{2}$ hours to give the corresponding 6-sulfonyl chlorides (**304**; X = Cl or Me) in moderate yields (44 and 35% respectively)[287] (Equation 95).



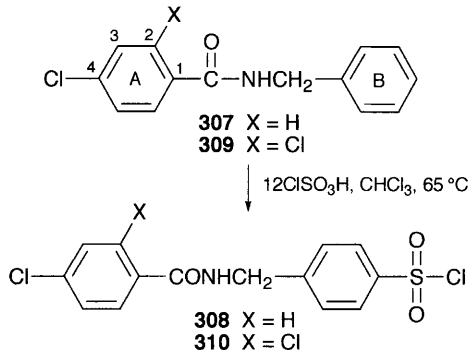
(95)

The yields obtained were substantially lower than those achieved in the chlorosulfonation of phenoxyacetamide, probably because steric interaction from the 2-substituent reduces the mesomeric activation of the aromatic nucleus by the phenoxy group. Phenylmethylacetamide **305** reacted sequentially with chlorosulfonic acid and ammonia to give a low yield of the *p*-sulfonamide **306** (Equation 96).[288]



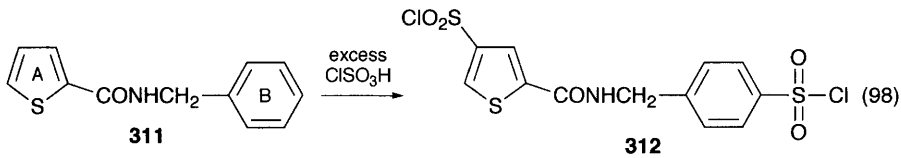
(96)

The latter compound is reported to possess antidiabetic properties.[288] *N*-Benzylcarboxamides are chlorosulfonated by chlorosulfonic acid. For instance, *N*-benzyl *p*-chlorobenzamide **307** reacted with excess chlorosulfonic acid (12 equivalents) in boiling chloroform (3 hours) to give an excellent yield (84%) of the *p*-sulfonyl chloride **308** (Equation 97).[289]



(97)

N-Benzyl 2,4-dichlorobenzamide **309** reacted similarly with the reagent to give the corresponding *p*-sulfonyl chloride (**310**, 74%).[289] In both cases, sulfonation occurred selectively in ring B, since ring A is deactivated towards electrophilic attack by the adjacent carbonyl group. The chlorosulfonation of *N*-benzylthiophene-2-carboxamide **311** with the reagent was examined under various conditions. With a very large excess of chlorosulfonic acid (16 equivalents) in boiling chloroform (4 hours), the disulfonyl chloride **312** was obtained (54%) (Equation 98). However, the optimum chlorosulfonation conditions were discovered to be prolonged reaction (31 days) with the reagent (16.5 equivalents) which afforded the product **312** in almost quantitative yield (90%).



(98)

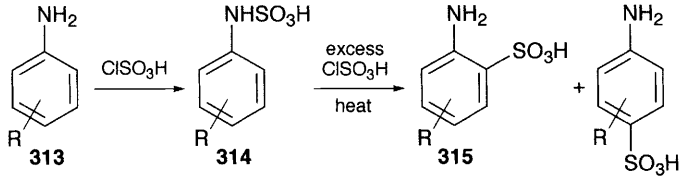
In the *N*-benzylthiophene derivative **311**, in contrast to the *N*-benzylbenzamides **307** and **309**, selective monochlorosulfonation was not observed indicating that the aromatic rings A and B in compound **311** must be of comparable reactivity towards sulfonation.

9 Aromatic Amines and Related Compounds

9.1 Anilines

Aromatic amines are often protected before treatment with chlorosulfonic acid to avoid decomposition; the protection may be achieved by acetylation (see p 102). However, in several instances unprotected amines have been successfully chlorosulfonated with the reagent.[1] In aromatic amines, the amino group exerts a

powerful electron-donor (+M, −I) effect on the attached aromatic nucleus so it would be anticipated that sulfonation would preferentially occur in the *o-/p-* positions of the aromatic ring. On the other hand, in strongly acidic media such as sulfuric acid and chlorosulfonic acid, the amino group is extensively protonated so the electron-donor effect is reduced and an appreciable quantity of *m-* sulfonation may occur. Indeed, when many amines are treated with oleum at low temperature, Suter[1] claimed that the *m*-sulfonic acids were formed. The sulfonation of amines is complicated by the effects of *N*-protonation, possible complex formation between the amine and the reagent, and *N*-sulfonation (sulfamation).[5,172] The relative thermodynamic stability of the various products is an important factor in the sulfonation reaction. The protonated amine and the complex will be less reactive towards electrophilic substitution than the free amine, hence a substantial amount of the product may arise from sulfonation of the free amine in spite of its relatively low concentration. The kinetics of the sulfonation of aromatic amines by chlorosulfonic acid in *o*-dichlorobenzene has been examined (see Chapter 2, p 14). It was found that aromatic primary amines generally reacted with a large excess of hot chlorosulfonic acid to give the *o-/p-* sulfonyl chlorides.[290–296] In these reactions, the amine **313** is probably first converted into the *N*-sulfonic acid **314** (sulfamation), which on heating undergoes ring substitution yielding the *o/p*-aminoarylsulfonic acids **315** and **316**[297] (Scheme 9). The sulfonic acids **315** and **316** in the presence of excess chlorosulfonic acid yield the corresponding sulfonyl chlorides.

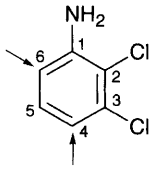


Scheme 9

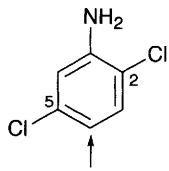
In the reaction of aniline with chlorosulfonic acid, only a trace of *o*-sulfonation occurred[298] and for amines in which the *p*-position is vacant, the *p*-sulfonic acid is probably the major product.[1] When an aromatic amine reacts with chlorosulfonic acid at low temperature (0–10 °C), the initial product is the *N*-sulfonic acid. However, this is only formed if the amine is sufficiently basic to form the amine salt with both the *N*-sulfonic acid and the evolved hydrochloric acid[299,300] which is in agreement with the known instability of aromatic sulfamic acids in neutral and acidic media.[5]

The 2,3-, 2,5-, 3,4- and 3,5-dichloroanilines **317–320** reacted with hot excess chlorosulfonic acid to yield the sulfonyl chlorides with the orientations indicated by the arrows.

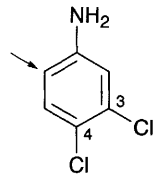
2,5-Dichloroaniline **318** did not undergo chlorosulfonation *ortho* to the amino group, presumably as a result of steric hindrance by the 5-chlorine atom; it gave a high yield of the 4-sulfonyl chloride by heating with chlorosulfonic acid in *o*-dichlorobenzene.[301] Neither the 2,5- or 3,4- dichloroanilines gave disulfonyl chlorides with chlorosulfonic acid, even at the boiling point.



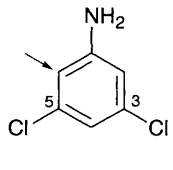
317



318

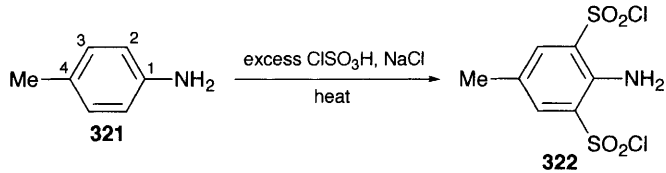


319

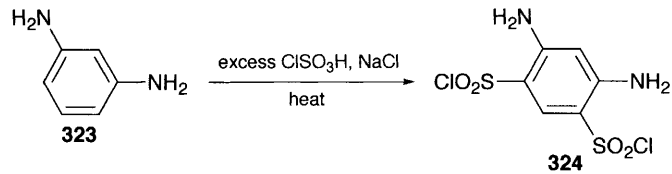


320

Aniline is easily disulfonated by treatment with chlorosulfonic acid[1] and by heating with a large excess of the reagent in the presence of sodium chloride at 150–160 °C (2 hours) aniline-2,4,6-trisulfonyl chloride is formed.[7,290] On the other hand, in the absence of sodium chloride, the major product was the corresponding trisulfonic acid. Aniline-2,4,6-trisulfonyl chloride has also been prepared from the 2,4-disulfonic acid by reaction with chlorosulfonic acid and thionyl chloride.[302] *p*-Toluidine **321**, by heating with excess chlorosulfonic acid–sodium chloride, was converted into the 2,6-disulfonyl chloride **322** (Equation 99) and *m*-phenylenediamine **323** afforded the 4,6-disulfonyl chloride **324** (Equation 100). In both these cases chlorosulfonation occurred, as expected, in *o*/*p*-orientation with respect to the amino group; however it has been reported[303] that *p*-toluidine may also be sulfonated in the *m*-position to give 3-amino-6-methylbenzenesulfonic acid. *m*-Methoxyaniline by warming with excess chlorosulfonic acid afforded 6-amino-4-methoxybenzene-1,3-disulfonyl chloride (sulfonation *o*/*p*- to the methoxy and amino groups).[296]

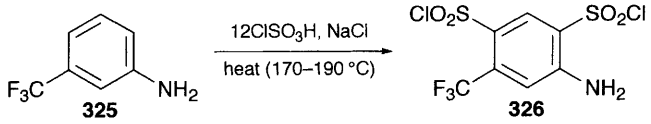


321 **322** (99)



323 **324** (100)

m-Trifluoromethylaniline **325** with a large excess of chlorosulfonic acid (12 equivalents) and sodium chloride (two equivalents) at 160–170 °C (2 hours) gave the disulfonyl chloride **326** (Equation 101).[293]



325 **326** (101)

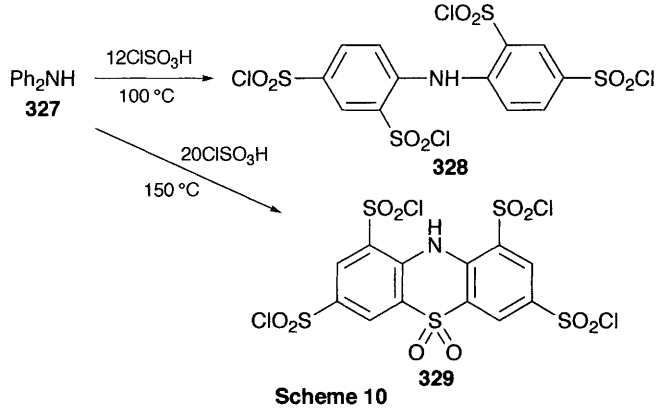
The forcing conditions for the chlorosulfonation are required because of the deactivating influence of the electron-withdrawing (–I) effect of the trifluoromethyl group. The product **326** is an important intermediate in the synthesis of

benzothiadiazine diuretics, used as antihypertensive drugs. In contrast *m*-trifluoromethylaniline **325** also reacts with chlorosulfonic acid in *o*-dichlorobenzene to yield the 6-sulfonic acid (95%).[294] *m*-Trifluoromethyl *N*-ethylaniline was reacted with chlorosulfonic acid to give 4-trifluoromethyl-2-(*N*-ethylamino)benzenesulfonyl chloride[304] and *m*-pentafluoroethylaniline afforded 4-amino-6-pentafluoroethylbenzene-1,3-disulfonyl chloride.[305]

2-Amino-5-methylpyridine was heated with chlorosulfonic acid (five equivalents) at 125 °C (2 hours) to give 2-amino-5-methylpyridine-3-sulfonyl chloride.[306]

Diphenylamine **327** reacts with chlorosulfonic acid in nitrobenzene < 90 °C; the initial product is the amine chlorosulfate which at higher temperatures decomposes to yield the 4-sulfonic acid and/or 4,4′- disulfonic acid depending on the ratio of reagent to substrate used.[297] However, attempts to prepare diphenylamine-4,4′-disulfonyl chloride by reaction of diphenylamine with excess chlorosulfonic acid (five equivalents) in thionyl chloride were unsuccessful.[53] The product appeared to be a complex mixture of polychloro derivatives of phenothiazine. On the other hand, reaction of diphenylamine **327** with a large excess of the reagent (12 equivalents) at 100 °C (1 hour) gave the 2,2′,4,4′-tetrasulfonylchloride (**328**, 72%) (Scheme 10).

When the substrate **327** was heated with a very large excess of chlorosulfonic acid (20 equivalents) at 150 °C (4 hours) the cyclic sulfone tetrasulfonyl chloride (**329**, 45%) was isolated (Scheme 10).[53]

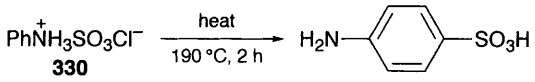


Scheme 10

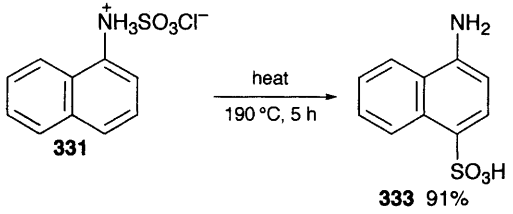
The latter conversion provides another example of the cyclization of diaryl compounds by treatment with a very large excess of chlorosulfonic acid under reflux. Analogous cyclizations occurred with biphenyl and diphenylmethane (see Section 2, p 40).

Primary aromatic amines, *e.g.* aniline or α-naphthylamine, by treatment with chlorosulfonic acid (one equivalent) in an inert organic solvent, *e.g.* chloroform, at 0 °C gave the corresponding chlorosulfates **330** and **331** as crystalline solids. The latter on strong heating (190 °C) afforded high yields of sulfanilic **332** and naphthionic acid **333** respectively (Equations 102 and 103).[307] These reactions are similar to the normal baking process which involves heating an aromatic amine

hydrogen sulfate[5] and yields the most thermodynamically stable *p*-aminoarylsulfonic acid.[307]



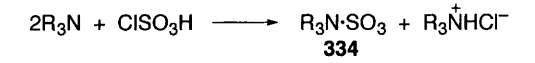
330 **332** 89% (102)



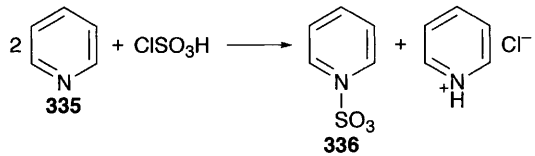
331 **333** 91% (103)

9.2 Tertiary Amines

It is well known[5,308] that chlorosulfonic acid reacts with alphatic and aromatic tertiary amines (R_3N) to yield the corresponding amine–sulfur trioxide complexes **334** (Equation 104). For instance, pyridine **335** reacts with the reagent to form the complex **336** (Equation 105). The complexes **334** are prepared by dropwise addition of chlorosulfonic acid to a slight excess (approx. two equivalents) of the appropriate tertiary amine dissolved in an inert organic solvent, *e.g.* dichloroethane, at low temperature.[309,310]

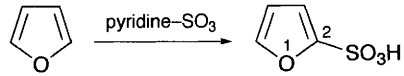


334 (104)

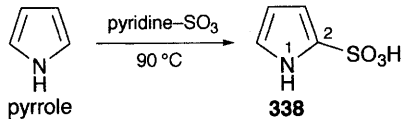


335 **336** (105)

The amine–sulfur trioxide complexes **334** are valuable sulfonating agents for alcohols and polysaccharides;[310] they may also be used for the sulfonation of the acid-sensitive heterocycles (furan and pyrrole) to the 2-sulfonic acids **337** and **338** (Equations 106 and 107). With these substrates, strongly acidic sulfonating agents, such as sulfuric and chlorosulfonic acid, cannot be used because they result in polymerization of the heterocycles.



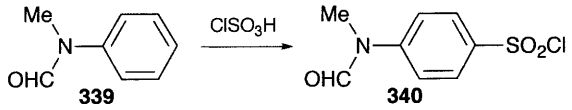
furan **337** (106)



(107)

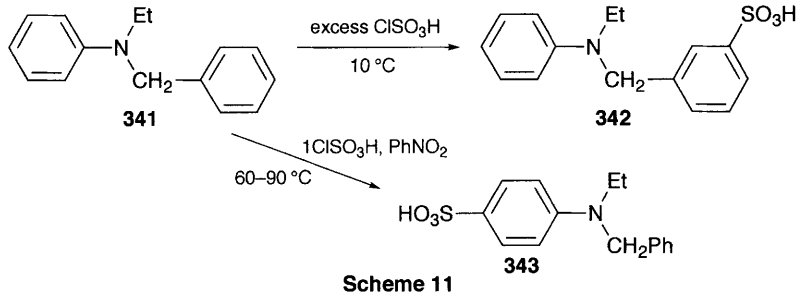
The amino–sulfur trioxide complexes are involved in various synthetic transformations involving aromatic tertiary amines. For instance, when *N,N*-dimethylaminobenzene is added to an equimolar quantity of chlorosulfonic acid, the major product is the amino–sulfur trioxide complex.

However, reversal of the order of addition produces mainly *p*-(dimethylamino)-benzenesulfonic acid[311] indictive of the sulfonating action of the complex. Similarly, sulfonation of *N*-methylformanilide **339** with chlorosulfonic acid afforded the *p*-sulfonyl chloride **340** (Equation 108).[312]



(108)

Sulfonation of *N*-ethyl-*N*-benzylaniline **341** by reaction with an excess of chlorosulfonic acid at 10 °C yields the *m*-sulfonic acid **342**[313] (Scheme 11).



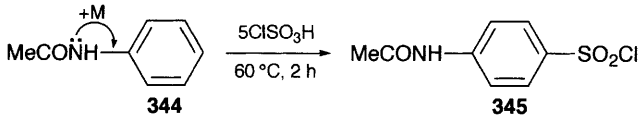
Scheme 11

On the other hand, when the substrate **341** was treated with an equimolar amount of the reagent in hot nitrobenzene (60–90 °C) sulfonation of the phenyl ring occurred yielding the *p*-sulfonic acid **343**[313] (Scheme 11). The latter reaction probably involves rearrangement of the initially formed ethylbenzylaniline–sulfur trioxide complex.[5]

9.3 Acetanilides (*N*-Acetylarylamines)

Aromatic amines are often protected by acetylation before chlorosulfonation because reaction of the resultant acetanilides reduces decomposition of the product. An important example is the chlorosulfonation of acetanilide (*N*-phenylacetamide, **344**) to form 4-(acetamido)benzenesulfonyl chloride (*N*-acetylsulfanilyl chloride, **345**) (Equation 109). Smiles and Stewart[314] reported that the synthesis went in excellent yield (80%) by treatment of acetanilide **344** with the reagent (five equivalents) at 60 °C for 2 hours. The reaction is of considerable

commercial importance because *N*-acetylsulfanilyl chloride **345** is the precursor of a range of sulfonamide antibacterial and other drugs.[315]



344 **345** (109)

In the chlorosulfonation **344** to **345** (Equation 109), the large steric size of the acetamido group effectively precludes *o*-sulfonation, so the *p*-sulfonyl chloride is essentially the sole product isolated. Studies of the chlorosulfonation of acetanilide **344** with excess chlorosulfonic acid (five equivalents) in the temperature range 0 to 100 °C indicated that the optimium temperature for the production of the monosulfonyl chloride **345** was 55–60 °C. Some disulfonation occurred > 40 °C, polysulfonation > 70 °C and even at 100 °C (2 hours), the reaction gave no sulfone.[316]

Improvements in the manufacture of acetylsulfanilyl chloride **345**, involved the recovery of sulfuric acid;[317] use of more reagent (six equivalents) at 40 °C (3 hours) and subsequent treatment with dilute sulfuric acid afforded 84% yield.[318]

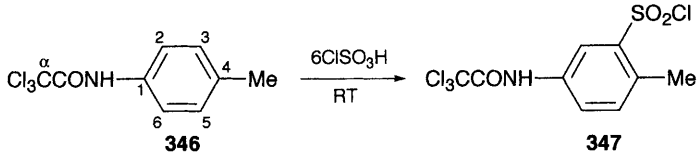
The quantity of chlorosulfonic acid employed may be reduced to 2.3–3.1 equivalents of reagent to substrate reacted at 30–32 °C for 40–60 minutes followed by addition of further reagent to give a reagent:substrate ratio of 4.87:1 followed by stirring the reaction mixture at 40–42 °C.[319] Reaction of acetanilide with chlorosulfonic acid in the presence of benzene < 95 °C afforded a mixture of the desired sulfanilyl chloride **345** and benzenesulfonic acid.[320] The chlorosulfonation of acetanilide by excess chlorosulfonic acid occurs in two stages and the kinetics have been determined.[321] In the reaction, the product yield was found to be inversely proportional to the concentration of the byproducts hydrogen chloride and sulfuric acid.[322] The use of a mixture of chlorosulfonic acid and excess sulfur trioxide enhanced the yield of product by formation of pyrosulfuryl chloride which reacted with the byproducts to form chlorosulfonic acid.[322]

Recent studies[322a] showed that in the chlorosulfonation of acetanilide, the molar excess of the reagent could be reduced to 3.48 without effecting the quality or yield (> 77.4%) of the product. Acetanilide has also been reacted with chlorosulfonic acid (4.8 equivalents) at 50 ± 2 °C, followed by hydrolysis, extraction and crystallization to yield dry N^4-acetylsulfanilyl chloride. The various factors effecting the yield of the dry product were discussed.[322b] A novel molten liquid chlorosulfonation of acetanilide by chlorosulfonic acid–thionyl chloride has been used as the first step in an improved six-stage synthesis of 2-(4-aminophenylsulfonyl)ethyl sulfate.[322c]

Several substituted acetanilides have also been treated with chlorosulfonic acid:[3] thus 2- and 3-chloro; 2,5- and 2,6-dichloroacetanilides reacted with excess reagent to give the corresponding 4-sulfonyl chlorides.[323]

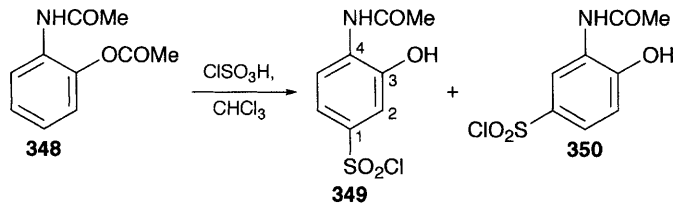
With 3-chloroacetanilide, the crude sulfonyl chloride could be characterized as the hydrazide,[323] or purified by recrystallization from benzene giving 18% yield.[324] The 2- and 3-chloroacetanilides reacted with reagent (four to five equivalents) at 60–80 °C (4 hours) to give low yields of the sulfonyl chlorides, but chlorosulfona-

tion of the 2,5-dichloro analogue demanded prolonged reaction at 80 °C (8 hours), while the 2,6-derivative needed even longer reaction time (14 hours). Surprisingly, all attempts to chlorosulfonate 2,3-dichloroacetanilide failed, possibly due to a 'buttressing effect' of the bulky acetamido group on the 2-chlorine atom.[323] Side chain substituted α-mono-, α,α,di- and α,α,α-trichloroacetanilides reacted smoothly with excess chlorosulfonic acid (five equivalents) at 60 °C to give excellent yields of the corresponding *p*-sulfonyl chlorides.[325] α-Bromoacetanilide-*p*-sulfonyl chloride is used as an amide-linking agent.[326] *p*-Methyl-α,α,α-trichloroacetanilide **346** reacted with excess reagent (six equivalents) at room temperature (8 hours) to give the sulfonyl chloride (**347**, 50%) (Equation 110).[325]



(110)

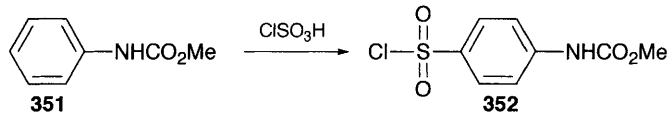
In this reaction, chlorosulfonation occurs *ortho* to the methyl group, since the relatively large size of the trichloroacetamido group precludes attack in the 2-position. The introduction of the powerful electron-donating methoxy group into acetanilide greatly facilitates chlorosulfonation. 2- and 4-Methoxyacetanilide both reacted easily with chlorosulfonic acid to give excellent yields of the corresponding 5- and 3-sulfonyl chlorides. Sulfonation has occurred respectively *p*- and *o*- to the methoxy group which clearly controls the orientation of sulfonation. In contrast, chlorosulfonation of 3-methoxyacetanilide afforded only a moderate yield of the 4-sulfonyl chloride.[327] 2-Methyl-, 2-methoxy- and 4-methylacetanilide all reacted with chlorosulfonic acid in boiling chloroform to give good yields of the corresponding sulfonyl chlorides. Several of the derived sulfonyl hydrazides showed antibacterial activity.[328] 2,5-Dimethoxyacetanilide reacted with chlorosulfonic acid (three equivalents) at 60 °C (1½ hours) to yield the 4-sulfonyl chloride (53%).[323] Later, other workers[329] discovered that a much improved yield (93%) of the product (used in the dye industry) was obtained by prolonged treatment of 2,5-dimethoxyacetanilide with a mixture of chlorosulfonic acid and thionyl chloride. 2-Acetoxyacetanilide **348**, by warming with the reagent (five equivalents) in chloroform at 50–60 °C (2 hours), suffered *O*-deacetylation yielding a mixture of the sulfonyl chlorides **349** and **350** (79%) (Equation 111).[282] NMR spectroscopy showed that the major product was 4-acetamido-3-hydroxybenzenesulfonyl chloride **349**, indicating that the acetamido moiety was the predominant



(111)

directive influence on the orientation of sulfonation rather than the hydroxyl group. This result may be explained in terms of hydrogen bonding between the carbonyl and hydroxyl groups.[282] 4-Acetoxyacetanilide with chlorosulfonic acid (five equivalents) at 60–70 °C (2 hours) afforded 5-acetamido-2-hydroxybenzenesulfonyl chloride (50%).[282] In this example, sulfonation occurs in the 3-position (*ortho* to the hydroxyl group) since the large acetamido group inhibits 2-sulfonation. Attempted chlorosulfonation of 3-acetoxyacetanilide failed; the reaction only gave black tars.[282] 2,4-Dimethylacetanilide reacted with chlorosulfonic acid to give 5-acetamido-2,4-dimethylbenzenesulfonyl chloride (69%).[330] Sulfonation occurred, as expected, *o*-/*p*- with respect to the methyl groups since the position *para* to the acetamido group is blocked. 3,5-Dimethylacetanilide reacted with excess reagent (four equivalents) at 90 °C (3 hours) to give 4-acetamido-2,6-dimethylbenzenesulfonyl chloride which is used in the preparation of aldose reductase inhibitors.[331,341]

N-Carbomethoxyaniline **351** reacts with chlorosulfonic acid to yield *N*-carbomethoxysulfanilyl chloride **352** (Equation 112).[332] The chlorosulfonation was examined under various conditions in order to optimise the yield of the product **352**. In experiments with reagent:substrate ratios of 3 to 8, a 5:1 ratio was found to be the most cost effective, affording the sulfanilyl chloride **352** in high yield (77.8%).[332] The chlorosulfonation of *N*-carbomethoxyaniline **351** (Equation 112) has also been performed by treatment with a mixture of chlorosulfonic acid (1.0–1.05 equivalents) and thionyl chloride (3–10 equivalents) in dimethylformamide (1.01–0.1 mol) at 20–85 °C for 1–10 hours.[333]



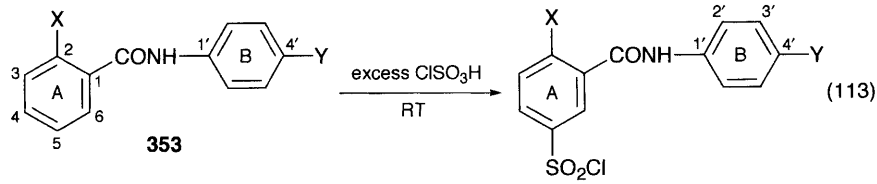
351 **352** (112)

1-Acetamidonaphthalene reacts with chlorosulfonic acid (three equivalents) at 60–65 °C for 2 hours to yield 4-acetamidonaphthalenesulfonyl chloride (45%).[334] Previous workers,[335] by performing the chlorosulfonation at 80 °C (1 hour), obtained a lower yield of the product (31%).

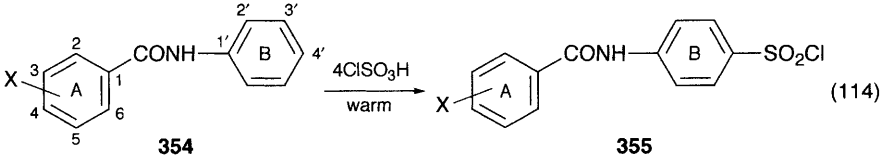
9.4 Anilides (*N*-Benzoylarylamines)

In benzoic acid anilide (benzanilide, **353**; X = Y = H), the phenyl ring A is relatively deactivated towards electrophilic substitution by the attached carbonyl group as compared with ring B, which is activated by the amino moiety, so sulfonation of benzanilide occurs selectively in ring B.

Several *o*-substituted carboxylic acid anilides (**353**; X = OH, OMe, Y = H; or X = OH, Y = Cl) reacted with excess chlorosulfonic acid (4–10 equivalents) at room temperature to give high yields of the corresponding 4-sulfonyl chlorides **354** (Equation 113).[270]

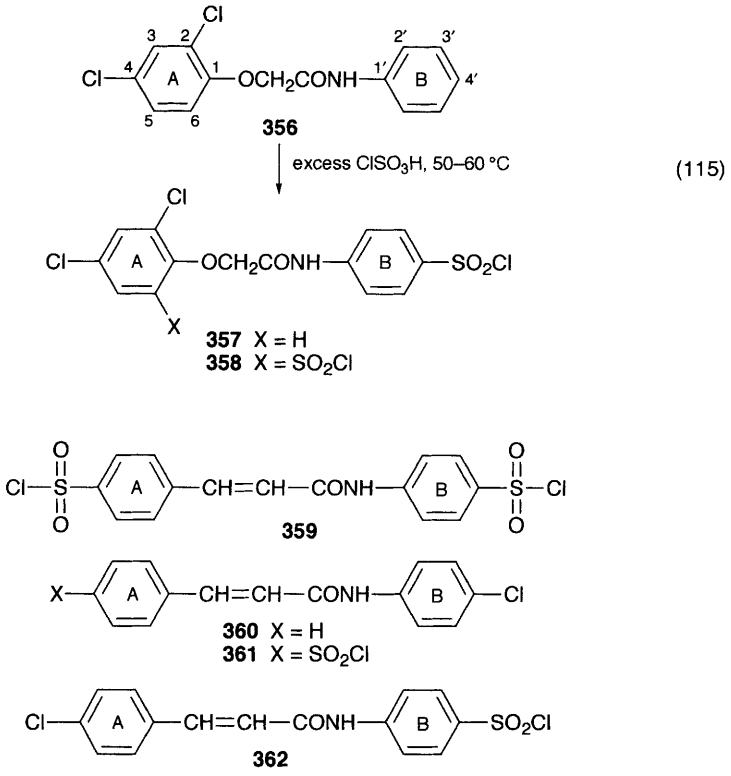


Sulfonation of these substrates has occurred selectively in ring A, because the introduction of the powerful electron donating hydroxy and methoxy groups has shifted the balance of reactivity in favour of ring A. On the other hand, when salicylanilide (**353**; X = OH, Y = H) and the *O*-methyl derivative (**353**; X = OMe, Y = H) were treated with a large excess of chlorosulfonic acid (eight equivalents), the reaction gave high yields (85%) of the corresponding 5,4′-disulfonyl chlorides,[270] in which sulfonation has occurred in both aromatic rings. Benzanilide (**353**; X = Y = H), together with the 4-chloro, 3-nitro and 2,4,2,5- and 3,4-dichloro derivatives **354** reacted with warm chlorosulfonic acid (four equivalents) to give the corresponding 4′-sulfonyl chlorides **355**[336] (Equation 114).

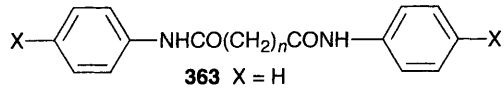


With these electron-withdrawing substituents in ring A, there is now exclusive sulfonation in ring B due to the electron-donating amino group attached to this ring. Nicotinic and isonicotinic acid anilides reacted similarly with excess chlorosulfonic acid (six equivalents) to give the corresponding 4′-sulfonyl chlorides. In both cases, a larger excess of the reagent was required, probably because of salt formation with the basic nitrogen atom. 2,4-Dichlorophenoxyacetanilide **356** reacted with chlorosulfonic acid (three equivalents) at 50–60 °C (2 hours) to give the corresponding sulfanilyl chloride (**357**, 45%). However, repetition of the reaction using a larger excess of the reagent (seven equivalents) for 3 hours afforded the 6,4′-disulfonyl chloride (**358**, 36%) (Equation 115).[336] The lower reactivity of ring A, as compared with ring B, is probably a consequence of the electron-withdrawing (−I) effect of the two chlorine atoms, whereas ring B is slightly activated by the attached amino group.

However, after sulfonation of ring B in **356**, further attack occurs in ring A to yield the identical 6,4′-disulfonyl chloride **358** (Equation 115). Cinnamic acid anilide, by treatment with a large excess of chlorosulfonic acid, afforded a very high yield of the disulfonyl chloride **359**.[337]

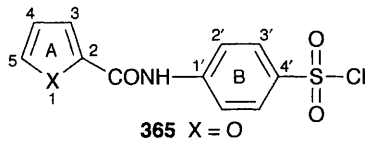


The corresponding *p*-chloroanilide **360**, by warming with a large excess of the reagent at 50 °C, only gave the monosulfonyl chloride **361** in which sulfonation has occurred in ring A, since the chlorine atom reduces the relative reactivity of ring B towards sulfonation. However, *p*-chlorocinnamic acid anilide reacts rapidly (5 minutes) with chlorosulfonic acid at 50 °C to give an excellent yield of the monosulfonyl chloride **362**. It is now ring B which is the more reactive because ring A is deactivated by the electron-withdrawing (−I) effect of the chlorine atom.[336] Several dicarboxylic acid dianilides **363** reacted with a large excess of chlorosulfonic acid to give high yields of the corresponding 4,4′-disulfonyl chlorides **364**.[337,338] For instance, malonic (**363**, $n = 1$), succinic (**363**, $n = 2$) and glutaric (**363**, $n = 3$) acid dianilides reacted with the reagent (12 equivalents) at 50 °C (10 minutes) followed by allowing the mixture to stand at room temperature (3 hours) to yield the corresponding 4,4′-disulfonyl chlorides (80–90% yield).[338] However, the chlorosulfonation of oxalic acid dianilide (**363**, $n = 0$) was more difficult and required heating the substrate with the reagent at 80–85 °C (4 hours) to give a moderate yield (60%) of the 4,4′-disulfonyl chloride (**364**, $n = 0$).[337] The yield was appreciably lower than that obtained from the analogous chlorosulfonation of the higher homologues. Oxalic acid dianilide disulfonyl chloride (**364**, $n = 0$) was difficult to characterize as derivatives because of their very high melting points and low solubility in organic solvents.

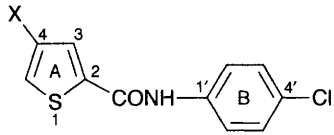


363 X = H
364 X = SO_2Cl

Furan and thiophene-2-carboxanilides reacted with excess chlorosulfonic acid (six equivalents) at room temperature and at 40 °C to give the corresponding *p*-sulfonyl chlorides **365** and **366** in yields of 60 and 80% respectively.[339] In both cases, sulfonation occurred selectively in ring B, since the heterocyclic ring (A) is relatively deactivated by the attached 2-carboxamido moiety and the phenyl group is therefore the preferential site of electrophilic substitution. However, with the thiophene *p*-chloroanilide **367**, chlorosulfonation, under similar conditions, occurred in the thiophene ring (A) giving mainly the 4-sulfonyl chloride **368** since ring B is now deactivated by the stereoelectronic effects of the chlorine atom.[339]



365 X = O
366 X = S



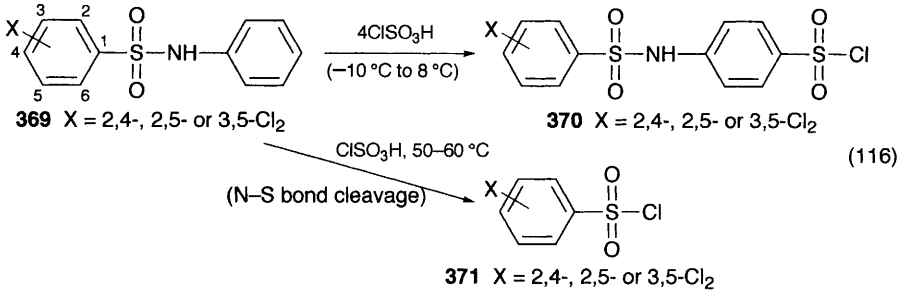
367 X = H
368 X = SO_2Cl

Similar results were observed in the chlorosulfonation of *N*-(*p*-bromo and *p*-nitrophenyl), and *N*-(2′-pyridyl) thiophene-2-carboxamides, since in all these substrates ring B is relatively deactivated in comparison with the heterocyclic ring A. In each compound, chlorosulfonation occurred in the thiophene ring yielding the corresponding 4-sulfonyl chlorides. The yields were lower when strongly electron-withdrawing groups, *e.g.* nitro and 2-pyridyl were present. The latter required the use of a large excess of chlorosulfonic acid (15 equivalents) at 80 °C to give the 4-sulfonyl chloride (42%). A similar result was achieved with a mixture of chlorosulfonic acid (six equivalents) and phosphorus pentachloride (one equivalent), but with chlorosulfonic acid (six equivalents) alone, the product was the 4-sulfonic acid.[339]

In the reaction of *N*-(*p*-carboxyphenyl) thiophene-2-carboxamide with chlorosulfonic acid the only isolated product was thiophene-2-carboxylic acid. These results are perhaps to be anticipated, since electron-withdrawing groups would weaken the amide bond so facilitating carbon–nitrogen bond cleavage.[339]

9.5 Sulfonanilides

It was discovered that 2,4-dichloro-, 2,5-dichloro- and 3,4-dichlorobenzenesulfonanilides **369** react with excess chlorosulfonic acid (four equivalents) at low temperature (−10 to 8 °C) for 2 hours to give good yields (60–85%) of the corresponding N^4-(dichlorobenzenesulfonyl) sulfanilyl chlorides **370** (Equation 116).[340]

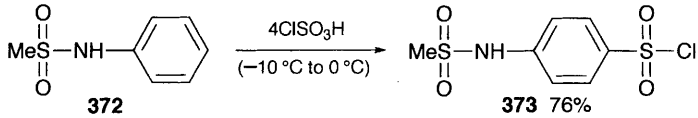


369 X = 2,4-, 2,5- or 3,5-Cl_2 **370** X = 2,4-, 2,5- or 3,5-Cl_2 **371** X = 2,4-, 2,5- or 3,5-Cl_2 (116)

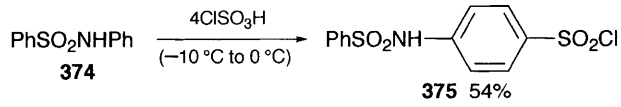
However, when the chlorosulfonation of the dichlorobenzenesulfonanilides **369** was carried out at 50–60 °C, the conditions successfully used in the chlorosulfonation of the analogous dichlorobenzoic acid anilides,[337] nitrogen–sulfur bond cleavage occurred to yield the corresponding dichlorobenzenesulfonyl chlorides **371** (Equation 116).

The difference in behaviour is presumably largely a reflection of the greater strength of the carbon–nitrogen bond (184 kcals mol^{-1}) as compared with that of the nitrogen–sulfur bond (111 kcals mol^{-1}).[340]

Methanesulfonanilide **372** by treatment with excess chlorosulfonic acid (four equivalents) at low temperature (1 hour) yields N^4-(methanesulfonyl) sulfanilyl chloride **373** (76%) (Equation 117). Benzenesulfonanilide **374** similarly reacted with the reagent at low temperature (4 hours) to yield the sulfanilyl chloride **375** (54%) (Equation 118).

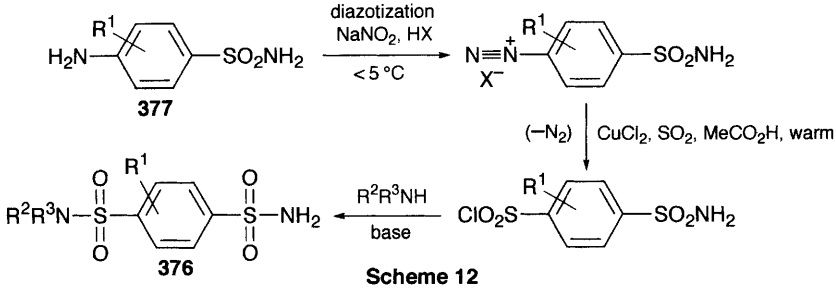


372 **373** 76% (117)



374 **375** 54% (118)

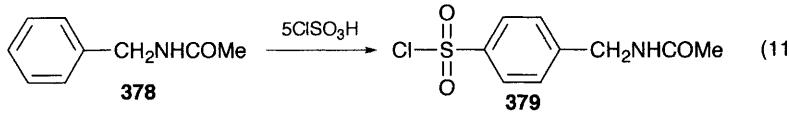
The chlorosulfonation of benzenesulfonamides is employed in the synthesis of substituted benzenedisulfonamides **376** used as vasodilatory drugs.[341] The chlorosulfonation was achieved indirectly by diazotization of the appropriate sulfanilamide **377**, followed by treatment of the diazonium complex with acetic acid, sulfur dioxide and copper(II) chloride as described by Holland *et al.*[342] In the final step, the sulfonyl chloride was condensed with the appropriate amine to give the disulfonamide **376** (Scheme 12).



377 **376**

Scheme 12

N-Acetylbenzylamine **378** reacts with excess chlorosulfonic acid (five equivalents) at 60 °C (2 hours) to give the *p*-sulfonyl chloride **379** (Equation 119).[343]

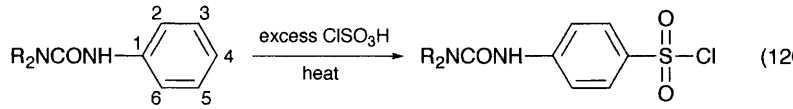


378 **379** (119)

10 Arylureas

10.1 Phenylurea and Related Compounds

Phenylurea[344] and *N,N*-dimethylphenylurea[345] (**380** and **381**) reacted easily with hot chlorosulfonic acid (four equivalents) at 60–80 °C (2 hours) to give the corresponding ureidobenzenesulfonyl chlorides **382** and **383** (Equation 120).

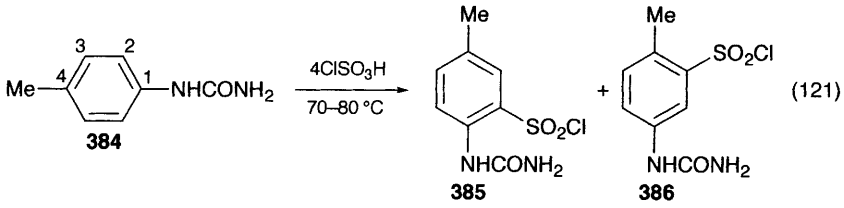


380 R = H, **381** R = Me **382** R = H, **383** R = Me (120)

The conversion of phenylurea **380** into the *p*-ureidobenzenesulfonyl chloride **382** by the action of excess chlorosulfonic acid at 55 °C was first reported by Travagli,[346] although when less reagent (one equivalent) was used at 60 °C a water-soluble product was formed.[344] This was probably the *p*-sulfonic acid resulting from acid-catalysed migration of the initial *N*-sulfonic acid (*cf.* the analogous reaction with amines see Section 9, p 98). The chlorosulfonation of 2-substituted phenylureas occurs under similar conditions: for instance, 2-chloro- and 2-methylphenylurea by heating with chlorosulfonic acid (four equivalents) at 70–80 °C for 4 hours afforded the corresponding 4-sulfonyl chlorides (55% yield).[347] On the other hand, chlorosulfonation of 2-methoxyphenylurea under similar conditions gave a higher yield (80%) of 4-methoxy-3-ureidobenzenesulfonyl chloride, in which the orientation of sulfonation is now controlled by the more powerful electron-donating methoxy group.[348]

When the substituents were in the *m*- or *p*-positions, the chlorosulfonation was more difficult and much lower yields of the sulfonyl chlorides were obtained.[347] For instance, 3-methylphenylurea reacts with chlorosulfonic acid (four equiva-

lents, 70–80 °C, 4 hours) to yield only 15% of the corresponding 4-sulfonyl chloride (sulfonation *p* to the ureido group). With 4-methylphenylurea **384**, chlorosulfonation resulted in an even lower yield (10%) of a mixture of the 2- and 3-sulfonyl chlorides **385** and **386** (Equation 121).



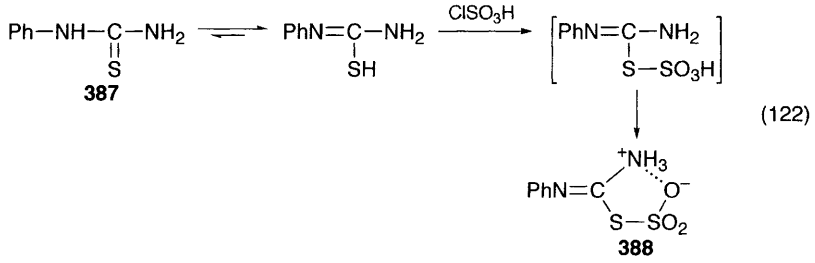
(121)

In the chlorosulfonation of 4-methylphenylurea **384**, electronic factors favour sulfonation *ortho* to the ureido group giving 5-methyl-2-ureidobenzenesulfonyl chloride **385**, while steric considerations favour attack *ortho* to the methyl group leading to 2-methyl-5-ureidobenzenesulfonyl chloride **386**. NMR spectroscopy indicated that the major product of the chlorosulfonation was compound **386**, suggesting that steric factors were paramount.[347]

Attempted chlorosulfonation of 3- and 4-chlorophenylureas failed, presumably as a result of a combination of unfavourable stereoelectronic factors.[345]

Sulfonylureas are an important group of highly potent herbicides which may be used for selective weed control in cereals at very low dose rates.[349] Herbicidal (*p*-sulfamoyl)phenylureas were synthesized from the appropriate phenylureas by mixing them with chlorosulfonic acid at 12–15 °C, followed by heating at 60 °C and the resultant *p*-(chlorosulfonylphenyl)ureas were condensed with the amine.[350]

Phenylthiourea **387**, by warming with chlorosulfonic acid (three equivalents) at 60 °C (3 hours), gave an abnormal product considered to be the iminosulfonic acid **388** which did not react with phosphorus pentachloride[348] (Equation 122).

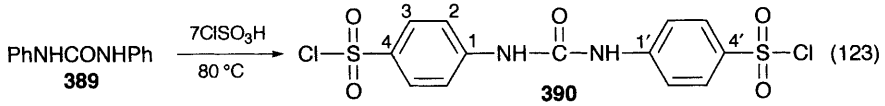


(122)

All attempts to chlorosulfonate phenylthiourea **387** to the *p*-sulfonyl chloride failed and even with a large excess of chlorosulfonic acid (six equivalents) under drastic conditions (120–130 °C, 6 hours), the only product was the iminosulfonic acid **388**. The latter probably arises from sulfonation of the favoured thiol tautomer and the proposed zwitterionic structure of **388** would account for its inertness towards phosphorus pentachloride.[348]

10.2 Diarylureas

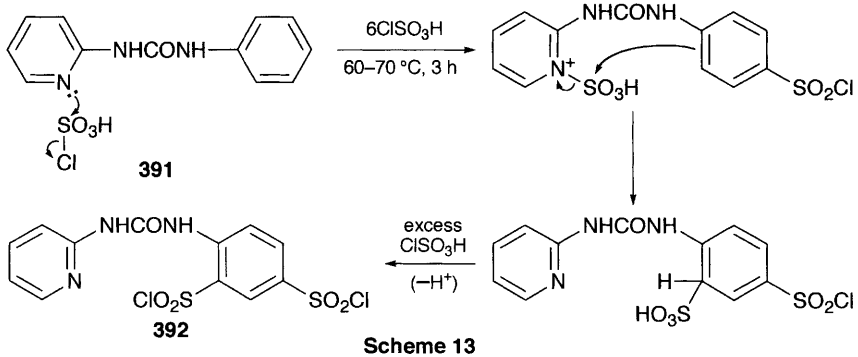
The chlorosulfonation of *N,N'*-diphenylurea **389** with excess chlorosulfonic acid is reported to yield the 4,4'-disulfonyl chloride **390**.[1,344,351,352] Cremlyn *et al.*[344] found that heating diphenylurea with the reagent (seven equivalents) at 80 °C ($1\frac{1}{2}$ hours) gave the disulfonyl chloride **390** in 50% yield (Equation 123). 4-Methyldiphenylurea was similarly chlorosulfonated to give the 4'-sulfonyl chloride.[348]



(123)

N-Phenyl-*N'*-(4-pyridyl)urea reacted normally with excess chlorosulfonic acid (six equivalents) at 70 °C (3 hours) to give the 4'-sulfonyl chloride.[353] In this substrate, sulfonation in the phenyl ring is to be expected since the pyridyl ring is deactivated towards electrophilic substitution by the electron deficient nitrogen atom. However, the 2-pyridyl analogue **391** behaved differently and reacted with an excess of the reagent under similar conditions to give a low yield (20%) of the 2',4'-disulfonyl chloride **392** (Scheme 13).[353]

The formation of the latter compound may involve neighbouring group participation of the lone electron pair on the pyridyl nitrogen atom as shown in Scheme 13. This hypothesis is supported by the observation that the *N'*-(4-pyridyl) analogue reacts normally with chlorosulfonic acid to give the 4'-sulfonyl chloride; in this molecule, neighbouring group participation is unlikely, since the sulfonic acid group is now much further removed from the *ortho*-position of the phenyl ring.[353]

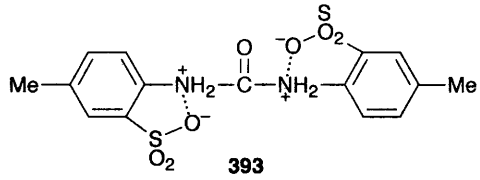


Scheme 13

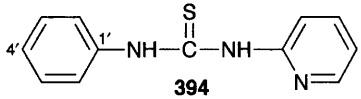
2,2'-Dimethyl- and 3,3'-dimethyldiphenylurea both react with chlorosulfonic acid (six equivalents) at 80–85 °C to give moderate yields of the corresponding 4,4'-disulfonic acids.

It is interesting that although *N,N'*-diphenylurea reacts with excess chlorosulfonic acid to give the 4,4'-disulfonyl chloride, the 2,2'- and 3,3'-dimethyldiphenylureas, on similar treatment, only gave the disulfonic acids. The difference in behaviour is probably due to the steric effects of the methyl groups inhibiting

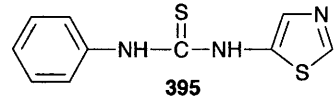
the conversion of the sulfonic acids into the sulfonyl chlorides. The reaction was however successful with phosphorus pentachloride, which is a more powerful chlorinating agent.[344] 4,4′-Dimethyldiphenylurea by reaction with excess chlorosulfonic acid under similar conditions afforded the 2,2′-disulfonic acid **393**. However, the disulfonic acid **393** did not yield the disulfonyl chloride by warming with phosphorus pentachloride, probably because it exists as the zwitterionic structure **393**. In support of this argument, the disodium salt of **393** which cannot form a zwitterion did give the disulfonyl chloride with phosphorus pentachloride.[344]



393



394



395

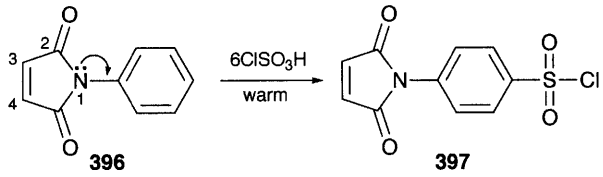
Some diarylthioureas have been treated with chlorosulfonic acid; thus *N*-phenyl-*N*′-(2-pyridyl)- and *N*-phenyl-*N*′-(2-thiazolyl) thioureas **394** and **395** afforded the corresponding 4′-sulfonyl chlorides.[348,353] *N*-Phenyl-*N*′-(2-pyridyl)-thiourea **394**, unlike the analogous urea **391**, did not yield the 2′,4′-disulfonyl chloride and only gave the 4′-sulfonyl chloride. The larger steric size of the sulfur as compared with the oxygen atom presumably caused too much steric hindrance at the *ortho*-position of the phenyl ring to permit disulfonation.[353]

The ionization of ureas, carbazides, carbazones and their thio analogues was studied in chlorosulfonic acid by conductivity, NMR and UV spectral measurements. The results indicated that thiourea is monoprotonated on the sulfur atom.[354] The latter observation may account for the abnormal behaviour of phenylthiourea on treatment with chlorosulfonic acid.

11 Imides

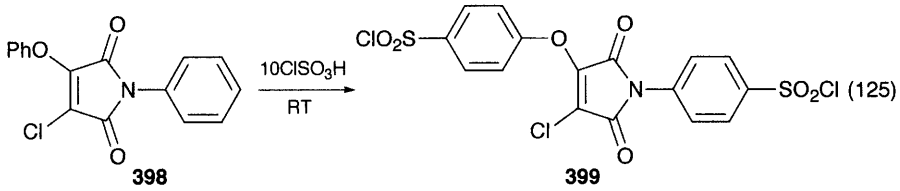
11.1 *N*-Arylmaleimides

N-Arylimides are generally chlorosulfonated by treatment with chlorosulfonic acid. Thus, several *N*-arylmaleimides have been successfully chlorosulfonated by reaction with excess chlorosulfonic acid at 10–30 °C without opening the imido ring.[355] *N*-Phenylmaleimide **396** reacted with excess reagent (six equivalents) at 45–50 °C (1 hour) to give an excellent yield of the *p*-sulfonyl chloride **397**, (83%)[356] (Equation 124). 3,4-Dichloromaleimide also reacted rapidly with the reagent to give the corresponding *p*-sulfonyl chloride (80%).[357]



(124)

3-Chloro-4-phenoxy-*N*-phenylmaleimide **398** reacted with a large excess of chlorosulfonic acid (10 equivalents) to give a high yield (88%) of the disulfonyl chloride **399** (Equation 125).[356]

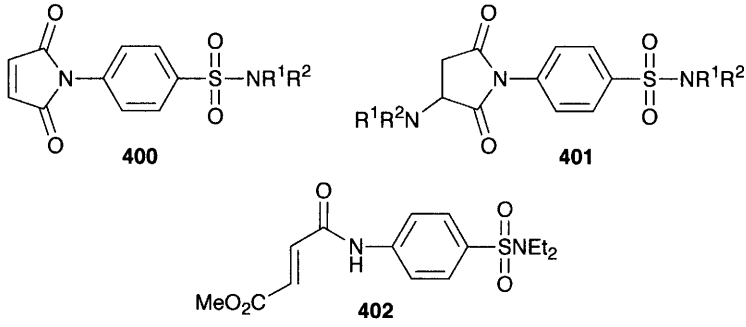


(125)

In this reaction sulfonation occurred, as expected, *para* to both the imino nitrogen atom and the oxygen atom of the phenoxy group.

N-(*p*-Chlorosulfonylphenyl) maleimide **397** can be employed as a dienophile in Diels–Alder reactions without affecting the chlorosulfonyl group, even when the cycloaddition required prolonged refluxing in boiling *o*-xylene (16 hours) as occurred with hexachlorocyclopentadiene.[358]

The reaction of *N*-(*p*-chlorosulfonylphenyl) maleimide **397** with amines R^1R^2NH (two equivalents), gave the corresponding maleimidosulfonamides **400** which resulted from nucleophilic substitution by the amine at the electron deficient sulfur atom.

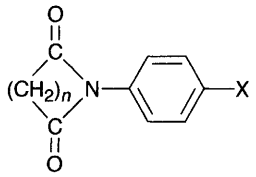


On the other hand, reaction of the sulfonyl chloride **397** with excess morpholine, pyrrolidine and piperidine (three equivalents) afforded a mixture of the sulfonamides **400** and **401**. The succinimidosulfonamide **401** was formed by simultaneous nucleophilic substitution at sulfur and Michael addition of the amine to the activated alkenic double bond. The pure maleimidosulfonamide **400** could be prepared by column chromatography of the mixture. The reaction of *N*-(*p*-chlorosulfonylphenyl) maleimide **397** with excess dimethylamine or diethylamine in methanol as solvent resulted in the formation of ring-opened products. For instance, in the reaction with diethylamine, the methyl ester **402** was formed by base-catalysed nucleophilic ring-opening by the solvent (methanol); this ring

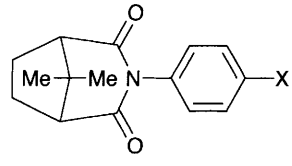
opening was not observed when the reaction was performed in acetonitrile as solvent. Other workers[359] reported that *N*-(*p*-sulfamoylaryl) maleimides reacted with aqueous ammonia to give the corresponding maleamides and that *N*-(*p*-chlorosulfonylphenyl) maleimide **397** with aniline and the *o*-chloro, and *o*- and *p*-methylanilines, afforded the corresponding succinimides **401**.[359]

11.2 *N*-Arylsuccinimides

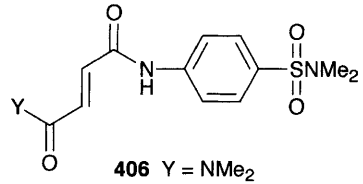
N-Phenylsuccinimide **403**, by warming with excess chlorosulfonic acid (four equivalents), at 70–80 °C (2 hours) gave the *p*-sulfonyl chloride (55%).[285] In later studies *N*-phenylsuccinimide **403**, glutarimide **404**, and camphorimide **405**, by heating with excess reagent, were all converted into the corresponding *p*-sulfonyl chlorides **403–405** (X = SO_2Cl) in yields of 85, 10 and 55% respectively.[360,361]



403 *n* = 2, X = H
404 *n* = 3, X = H



405 X = H

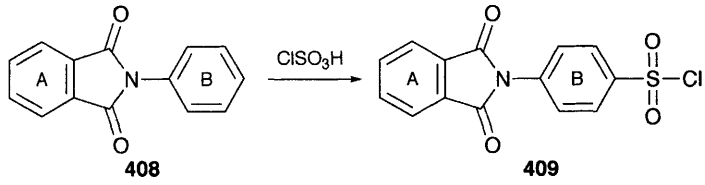


406 Y = NMe_2
407 Y = OMe

The reaction of *N*-(*p*-chlorosulfonylphenyl) succinimide **403** (X = SO_2Cl) with amines may give ring-opened products, depending on the experimental conditions.[361] Thus, the sulfonyl chloride **403** (X = SO_2Cl) reacts with the appropriate amine (two equivalents) in methanol (0 °C to RT) to give the corresponding *p*-(succinimido)benzenesulfonamide. On the other hand, when the sulfonyl chloride was warmed with excess dimethylamine (four equivalents) in acetonitrile at 50 °C, ring-opening occurred to yield the amidosulfonamide **406**. The latter compound, by reaction with boiling methanol, afforded the corresponding methyl ester **407**. When *N*-(*p*-chlorosulfonylphenyl) succinimide **403** (X = SO_2Cl) reacted with dimethylamine in warm methanol a mixture of the sulfonamides **406** and **407** was formed in a ratio of 1:9, showing that when the solvent (methanol) is present in large excess methanolysis is favoured.

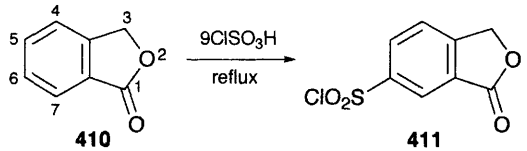
11.3 *N*-Arylphthalimides and Related Compounds

N-Phenylphthalimide **408** reacts with excess chlorosulfonic acid (seven equivalents) at 30–75 °C (2 hours) to give an excellent yield of the *p*-sulfonyl chloride **409** (87%) (Equation 126).[285]



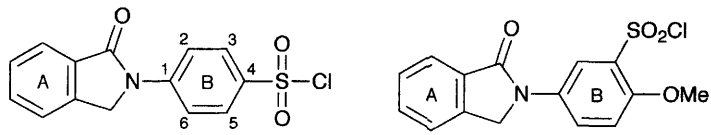
408 **409** (126)

3-Chloro-*N*-phenylphthalimide reacted similarly with excess reagent to give the corresponding *p*-sulfonyl chloride.[362] In these phthalimides sulfonation always occurs in ring B since ring A is strongly deactivated by the two attached electron-withdrawing carbonyl groups. Chlorosulfonation of *N*-(*p*-methoxyphenyl) phthalimide gave 2-methoxy-5-(*N*-phthalimido)benzenesulfonyl chloride; here the orientation of sulfonation is clearly controlled by the powerful electron-donating methoxy group. The related compound phthalide **410**, by refluxing with a large excess of chlorosulfonic acid (nine equivalents) for 3 hours, afforded the 6-sulfonyl chloride **411** (Equation 127).



410 **411** (127)

When the reaction was performed at a lower temperature (100 °C), the product was the 6-sulfonic acid.[363] Sulfonation occurs, as expected, in the 6-position, which is *para* to the electron-donating methylene group. The chlorosulfonation of phthalide is clearly made possible by the activating effect of the methylene group, since neither phthalic acid or phthalic anhydride reacted with chlorosulfonic acid even under forcing conditions.[267] Chlorosulfonic acid (five equivalents) at 60 °C reacts with *N*-phenyl- and *N*-(4-methoxyphenyl) phthalimidine to give the 4- and 3-sulfonyl chlorides **412** and **413** respectively.[364] In these substrates, the phenyl ring B, which is activated by the attached imino nitrogen atom, is preferentially sulfonated since the other phenyl ring A is deactivated by the carbonyl group. In the methoxy derivative, the powerful electron-donating methoxy group dictates the orientation of sulfonation. These compounds (**412** and **413**) are used as fluorescent derivatisation reagents for amines and amino acids in HPLC.[364]

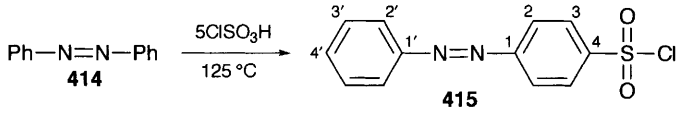


412 **413**

12 Reaction of Chlorosulfonic Acid with Miscellaneous Compounds

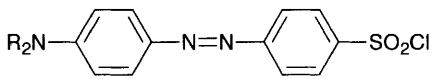
12.1 Azobenzene and Related Compounds

Azobenzene **414** reacts with hot excess chlorosulfonic acid (five equivalents) at 125 °C (1 hour) to give a very high yield (90%) of the *p*-sulfonyl chloride **415** (Equation 128).

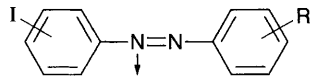


(128)

The procedure for the chlorosulfonation of azobenzene was first reported by Pearl[365] and was successfully repeated by Cremlyn.[366] The comparatively drastic conditions required for the reaction **414**→**415** (Equation 128) are probably due to initial protonation of the azido group in the strongly acidic medium. Attempts were made to extend the procedure to the chlorosulfonation of other azobenzenes. With 4-acetamidoazobenzene, extensive decomposition occurred at 125 °C, which may arise from acid-catalysed migration of the acetyl group into the aromatic nucleus, followed by decomposition of the resultant free amine intermediate.[366] However, when the reaction temperature was reduced to 80 °C, a low yield of the 4′-sulfonyl chloride was isolated. On the other hand, similar efforts to chlorosulfonate *p*-(*N,N*-dimethylamino)azobenzene failed to yield a pure product,[366] but more recently debsyl chloride **416** has been synthesized and is used as a derivatization reagent in HPLC for the separation of amines and amino acids.[367]



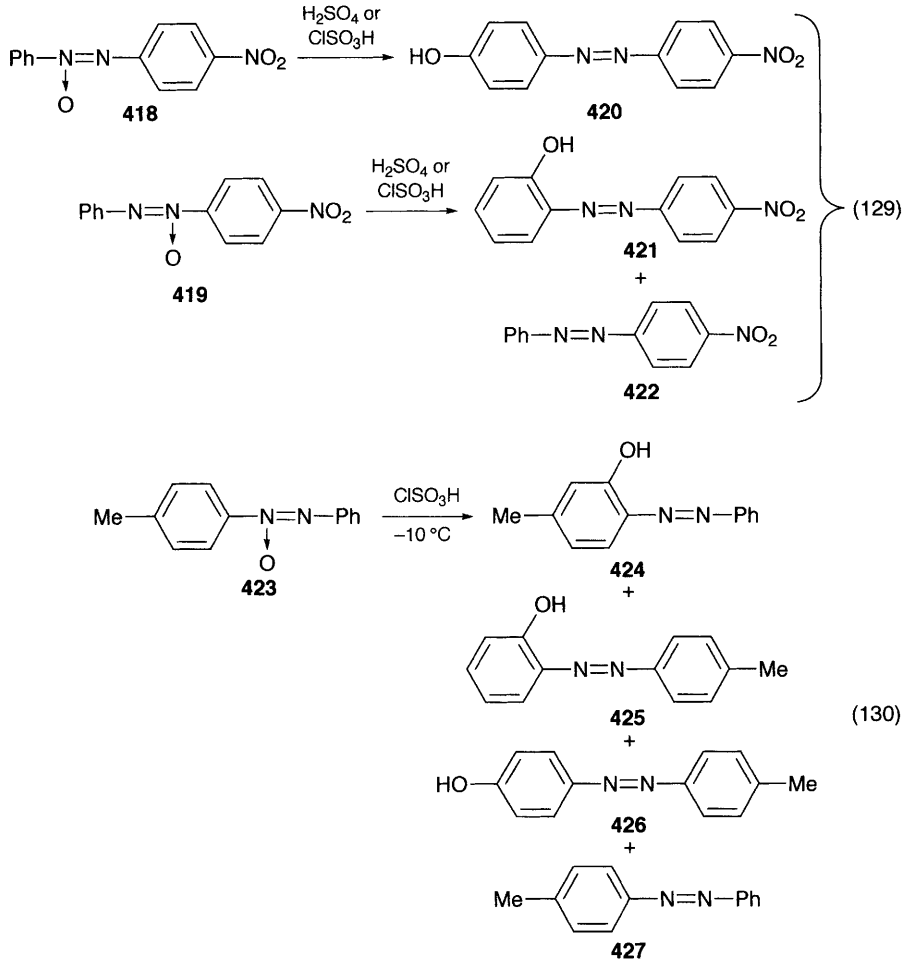
416 R = Me, Et



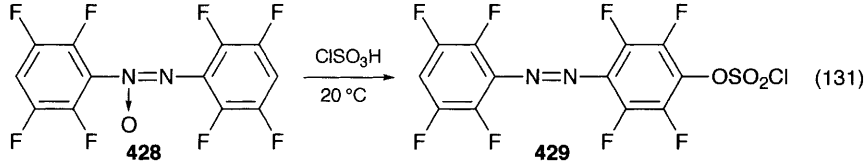
417

Iodoazoxybenzenes **417** react with a mixture of chlorosulfonic acid and 90% sulfuric acid to give mainly the corresponding iodoazobenzenes.[368] When azoxybenzene and the 2,2′-dibromo or dichloro derivatives were treated with 90% sulfuric acid, the 4-hydroxyazobenzenes were obtained in > 40% yield. This is an example of the Wallach rearrangement reaction which has also been studied with the *p*-nitroazoxybenzenes **418** and **419** which afforded the hydroxyazobenzenes **420** and **421**, together with the nitroazobenzene **422** (Equation 129).[369]

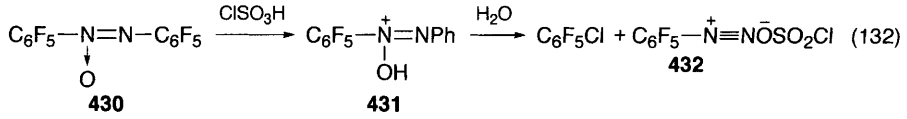
Compound **421** results from interconversion of the monoprotonated azoxybenzenes **418** and **419**. When the reactions were carried out using chlorosulfonic acid, the same mixture of products **420**–**422** was isolated, except that it contained relatively more of the *o*-hydroxyazobenzene **421** as compared with the *p*-isomer **422**.[370] *p*-Methylazoxybenzene **423** rearranges on treatment with chlorosulfonic acid at low temperature (−10 °C) to yield a mixture of the azobenzenes **424**–**427** (Equation 130).



The formation of the two types of *ortho* rearrangement products was not observed in the Wallach rearrangement of azoxybenzene derivatives with sulfuric acid.[370] The Wallach rearrangement of perfluoroazoxybenzenes in chlorosulfonic acid has been studied.[371] 2,2′-, 3,3′-, 5,5′- and 6,6′-Octafluoroazoxybenzene **428** with the reagent at 20 °C afforded the chlorosulfonate ester of 4-hydroxyoctafluoroazobenzene **429** (Equation 131).

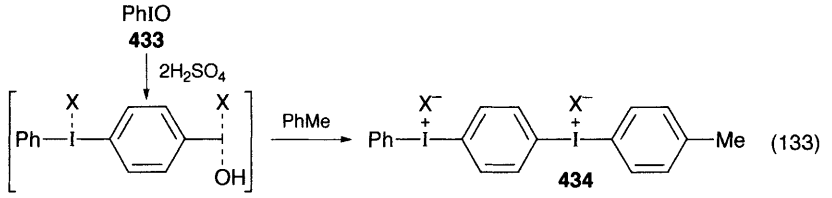


In contrast, the analogous reaction with decafluoroazoxybenzene **430** involves cleavage of the carbon–nitrogen bond and yields pentafluorochlorobenzene **431** and pentafluorodiazonium chlorosulfonate **432** (Equation 132).[371]



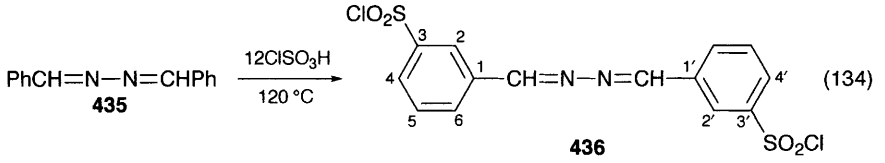
There appear to be no reports of the treatment of azoxybenzenes with warm excess chlorosulfonic acid which might yield the chlorosulfonyl derivatives of the corresponding hydroxyazobenzenes *via* the Wallach rearrangement and subsequent chlorosulfonation.

Iodosylbenzene **433** undergoes self-condensation by treatment with excess sulfuric or chlorosulfonic acid; the initial intermediate reacts with aromatic substrates, *e.g.* benzene, toluene or bromobenzene, to form good yields of the *p*-phenylene bisiodonium salts **434** (Equation 133).[372]



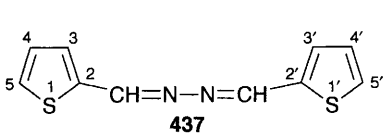
12.2 Azines

Several diaryl azines have been successfully chlorosulfonated by reaction with a large excess of chlorosulfonic acid under forcing conditions. For instance, benzaldehyde azine **435** reacted with the reagent (12 equivalents) at 120 °C (4 hours) to give the 3,3′-disulfonyl chloride **436**, 39% (Equation 134).[373]

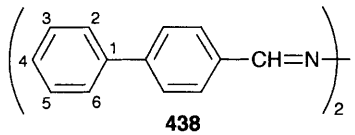


In diaryl azines, the C=N group functions as a deactivating substituent with respect to electrophilic substitution. In agreement, there was no sulfonation at room temperature and by warming at 50–60 °C the reaction remained incomplete. At 120 °C, the yield of the disulfonyl chloride **436** was increased to 70% by addition of excess thionyl chloride after heating with a large excess of chlorosulfonic acid (12 equivalents) for 4 hours. Chlorosulfonation of *o*-, *m*- and *p*-anisaldehyde azines occurred more readily than with benzaldehyde azine and it was achieved by heating the substrate with chlorosulfonic acid (six equivalents) in boiling thionyl chloride (78 °C) as a chlorinating solvent. The more facile reaction of these substrates would be expected in view of the powerful electron-donating properties of the methoxy group. When the chlorosulfonation was repeated under more vigorous conditions (120 °C); the *o*-isomer in particular afforded a much reduced yield (20%) of the disulfonyl chloride, possibly due to partial demethylation in the strongly acidic medium. The orientation of sulfonation in the

anisaldehyde azines was deduced by NMR spectroscopic analysis of the dimethylsulfonamide derivatives and is dictated by the position of the methoxy group. Thus, the *o*-, *m*- and *p*-anisaldehyde azines afforded respectively the 5,5′- (82%), 6,6′- (54%) and the 3,3′- (64%) disulfonyl chlorides.[373] Thiophene-2-carboxaldehyde and biphenyl-4-carboxaldehyde azines **437** and **438** both reacted with excess chlorosulfonic acid (six to eight equivalents) in thionyl chloride at 60 °C (3 hours).



437

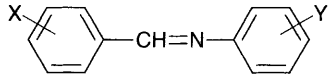


438

The former azine **437** gave a mixture of the 4,4′- and 5,5′-disulfonyl chlorides (87%); while the latter azine **438** afforded the 4,4′-disulfonyl chloride (71%).[373] Both these substrates are electron-rich molecules and hence were chlorosulfonated under much milder reaction conditions than benzaldehyde azine. Attempted chlorosulfonation of furan-2-carboxaldehyde azine with chlorosulfonic acid failed to yield a pure product, presumably because the furan ring has not been sufficiently stabilized by the attached C=N group to prevent decomposition of the substrate in the strongly acidic medium.

12.3 Anils (Schiffs Bases)

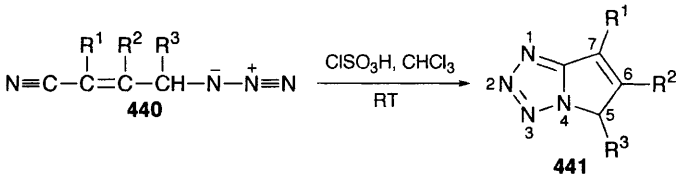
Attempted chlorosulfonation of anils **439** containing different substituents by reaction with chlorosulfonic acid was unsuccessful. The chlorosulfonation was examined under various conditions, including the addition of thionyl chloride, but it always gave complex mixtures of products that could not be characterized as sulfonamides.[374] The failure is probably due to partial hydrolytic decomposition of the crude sulfonyl chloride by attack on the CH=N bond during the aqueous work-up procedure, so that the sulfonyl chloride becomes contaminated with benzaldehydes, amines and other products.[374]



439 X = Y = H or OMe;
X = H, Y = OMe;
X = Cl, Y = OMe

12.4 Nitriles (Cyanides)

(*Z*)-γ-Azido α,β-ethylenenitriles **440** react with chlorosulfonic acid (two equivalents) in chloroform solution at 20 °C (30 minutes) to form the corresponding 5*H*-pyrrolo(1,2-*d*)tetrazoles **441** (Equation 135).[375]

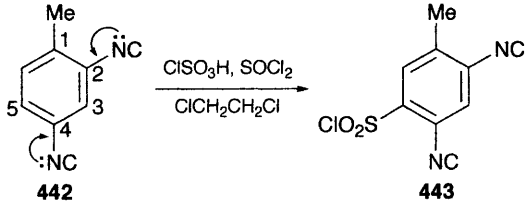


(135)

For instance, azobutenenitrile **440** ($R^1 = Me$, $R^2 = R^3 = H$) reacts with the reagent to give the corresponding 7-methyltetrazole **441**; $R^1 = Me$, 57%. The conversion **440→441** involves a double ring closure and provides a convenient synthetic route to the pyrrolotetrazoles **441**, which represent a new class of fused heterocycles. The stereospecificity of the reaction was demonstrated by the observation that the *E* isomers of the azonitriles **440** were unreactive.

12.5 Isonitriles (Isocyanides)

The isonitrile group, under certain conditions, is unaffected by the action of chlorosulfonic acid. As an example, diisocyanatotoluenesulfonyl chlorides may be prepared by treatment of toluene-2,4-diisocyanide **442**, with chlorosulfonic acid (1.4–14 equivalents) and thionyl chloride (2–14 equivalents) in dichloroethane.[376] The solvent was largely distilled off and the residual paste heated with thionyl chloride–DMF (80 °C), until hydrogen chloride evolution ceased, when the reaction gave 2,4-diisocyanatotoluene-5-sulfonyl chloride **443** (66% yield) (Equation 136).

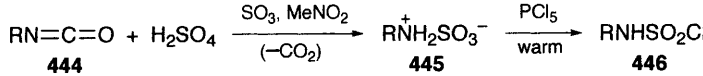


(136)

The orientation of sulfonation clearly indicates that the isocyanide group, unlike the cyanide moiety, functions as an electron-donor substituent *via* the lone electron pair of the nitrogen atom leading to *o*/*p*-attack.

12.6 Isocyanates

Alkyl and arylisocyanates **444** react with oleum to give the corresponding sulfamic acids **445**, which on warming with phosphorus pentachloride yield the sulfamoyl chlorides **446** (Equation 137).[377]



(137)

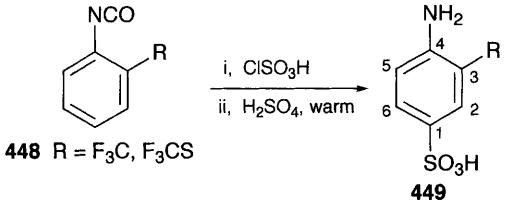
The zwitterionic structure of the sulfamic acid **445** makes it resistant to the chlorinating action of chlorosulfonic acid and its chlorination demands the use of

the more powerful chlorinating agent, phosphorus pentachloride (*cf.* certain arylureas, see Section 10, p 113).

The sulfamic acid **447** as the amine salt may also be obtained by the action of chlorosulfonic acid (three equivalents) on an excess of the corresponding amine in dichloromethane at −10 °C (Equation 138).

$$3RNH_2 + ClSO_3H \xrightarrow[-10\,^\circ C]{CH_2Cl_2} \underset{\mathbf{447}}{RNH_2SO_3^- H_3\overset{+}{N}R} \xrightarrow[warm]{PCl_5} \underset{\mathbf{446}}{RNHSO_2Cl} \qquad (138)$$

The sulfamic acid salt reacts with warm phosphorus pentachloride to yield the sulfamoyl chloride **446**. Several 3-trifluoromethyl-4-aminobenzenesulfonic acids **449** were prepared by the action of chlorosulfonic acid on arylisocyanates **448** followed by heating the reaction mixture with sulfuric acid at 30–60 °C (Equation 139).[378]

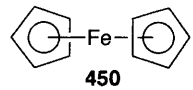


448 R = F_3C, F_3CS **449** (139)

In conclusion, experiments showed that the reaction of alkyl or arylisocyanates with fuming sulfuric acid or chlorosulfonic acid provides a valuable synthetic route to the corresponding sulfamic acids.

12.7 Ferrocene (Dicyclopentadienyliron)

Ferrocene **450** may be sulfonated by treatment with concentrated sulfuric acid in acetic anhydride[379] and it was later found that chlorosulfonic acid in acetic anhydride was a more convenient reagent.[380] The acetic anhydride was used to minimize the concomitant oxidation of the substrate by chlorosulfonic acid. Depending on the ratio of reagent to substrate the product is either ferrocene mono- or disulfonic acid. Sequential treatment of ferrocene with chlorosulfonic acid and phosphorus trichloride in ether affords ferrocene monosulfonyl chloride, and the latter was successfully converted into several ferrocene sulfonamides.[381]

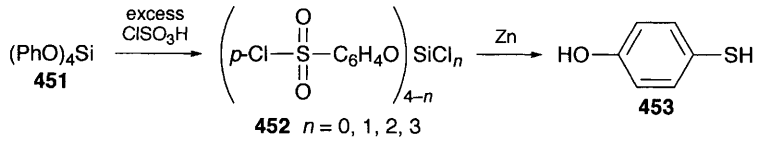


450

Ferrocenecarboxylic acid, the methyl ester and acetylferrocene were all sulfonated by sulfur trioxide–dioxan in the unsubstituted cyclopentadienyl ring;[382] this orientation of sulfonation would be anticipated since all the substituents are electron-withdrawing moieties.

12.8 Silicon Compounds

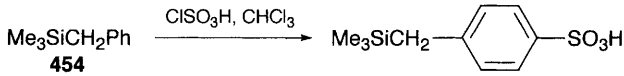
Silicon compounds containing reactive aryl groups may be chlorosulfonated without loss of the silicon atom by the use of chlorosulfonic acid. Thus, tetraphenoxysilane **451** reacted with excess chlorosulfonic acid at 75–85 °C ($2\frac{1}{2}$ hours) to give the sulfonyl chloride **452**.[383] Subsequent reduction of **452** with zinc afforded 4-hydroxyphenylthiol **453** (72% yield, 99.6% purity); this provides an excellent synthetic route to this compound (Equation 140).[383]



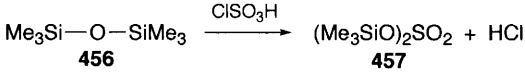
(140)

Another example is provided by the sulfonation of benzyltrimethylsilane **454** with chlorosulfonic acid (one equivalent) in chloroform solution to yield the corresponding *p*-sulfonic acid **455** (Equation 141).[384]

Siloxanes **456** are cleaved by treatment with chlorosulfonic acid to give the corresponding disilyl sulfates **457**[384] (Equation 142).

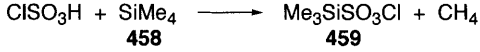


(141)



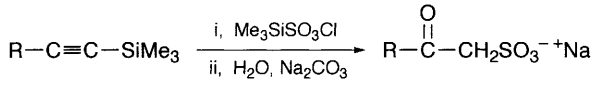
(142)

Chlorosulfonic acid reacts with tetramethylsilane **458** to give trimethylsilyl chlorosulfonate **459** (Equation 143).[384a]

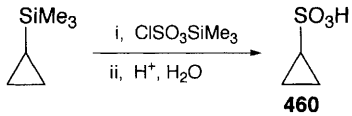


(143)

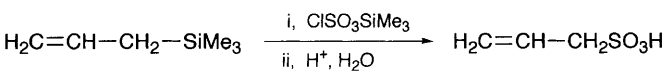
Trimethylsilyl chlorosulfonate **459** is useful as a mild sulfonating agent and it reacts with a range of organic compounds containing the trimethylsilyl group as illustrated by Equations 144–146.[385–389] It was by this synthetic route that cyclopropanesulfonic acid **460** was first prepared (Equation 145).[386] The general mechanism of these reactions is depicted in Scheme 14.



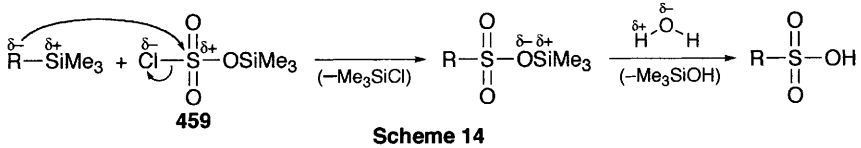
(144)



(145)

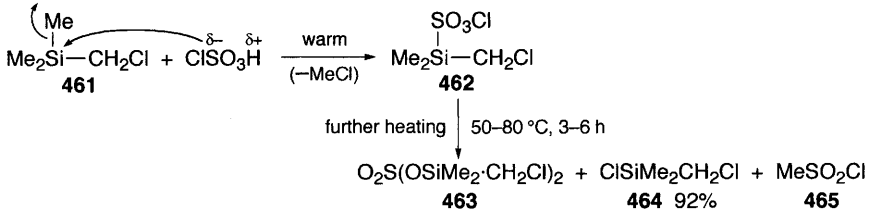


(146)



Scheme 14

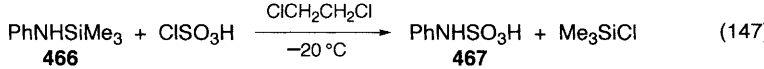
The mechanism involves initial nucleophilic attack by the trimethylsilyl compound on the electrophilic sulfur atom of trimethylsilyl chlorosulfonate **459** with loss of trimethylsilyl chloride. In the second step, the initially formed trimethylsilyl sulfonate is hydrolysed to the corresponding sulfonic acid (Scheme 14). Chlorosulfonic acid reacts as a nucleophile with certain trimethylsilylmethyl compounds with regioselective cleavage of the silicon–carbon (sp^3 hybridized) bond. For instance, trimethylsilylmethyl chloride **461** with chlorosulfonic acid afforded the compound **462**, which on heating gave the compounds **463–465** (Scheme 15).[390]



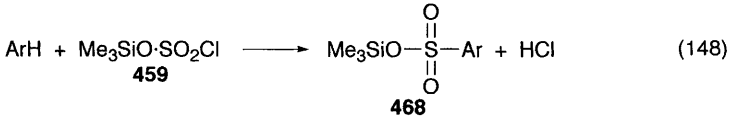
Scheme 15

Anilinotrimethylsilane **466** reacts with chlorosulfonic acid in 1,2-dichloroethane at low temperature to yield phenylsulfamic acid **467** (Equation 147).

The reaction involves initial insertion of sulfur trioxide into the nitrogen–silicon bond of anilinotrimethylsilane **466**; the sulfamic acid **467** was, however, contaminated with small amounts of anilinium salts. It was discovered that the reaction of anilinotrimethylsilane **466** with trimethylsilyl chlorosulfonate **459** gave improved yields of the pure sulfamic acid **467**.[391] Trimethylsilyl chlorosulfonate **459** will effect the sulfosilation of aromatic hydrocarbons to give the trimethylsilyl arenesulfonates **468**[392] (Equation 148).

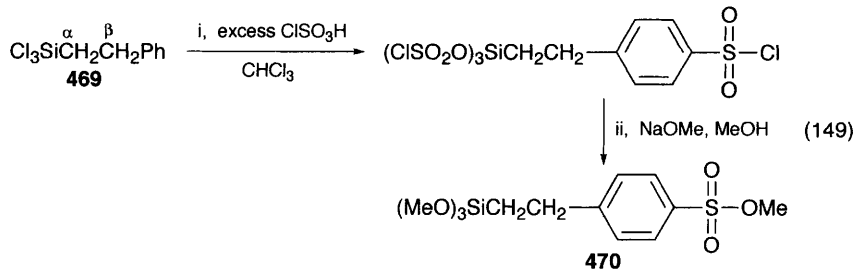


(147)



(148)

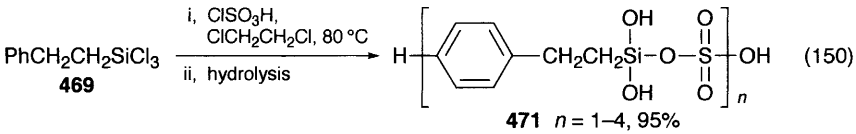
β-Phenylethylsilyl chloride **469**, by treatment with chlorosulfonic acid in dry chloroform at 6–10 °C under argon, afforded the crude sulfonyl chloride which by subsequent neutralization (sodium carbonate) and reaction with sodium methoxide afforded the methylsulfonate **470** (Equation 149); such compounds may be used as modifiers of chromatographic phases.[393]



(149)

In Equation 149, the chlorosulfonation occurs, as expected, in the *para*-position relative to the electron-donating (+I) methylene moiety and simultaneously the three chlorine atoms attached to the silicon atom are sequentially substituted by chlorosulfonate and methoxy groups to give the methylsulfonate **470**. In this context, it is well known[308] that chlorosilanes react with chlorosulfonic acid to yield the corresponding chlorosulfonate esters, as occurs in the first stage of the conversion shown (Equation 149).

The chlorosulfonation of β-phenylethylsilyl chloride **469** may also be applied to the preparation of sulfophenethylsiloxanes, which are used as silicate stabiliziers in antifreeze formulations. In this process, the appropriate trichlorosilane derivative, *e.g.* **469**, is heated with chlorosulfonic acid in 1,2-dichloroethane followed by hydrolysis to give the siloxane **471** (Equation 150).



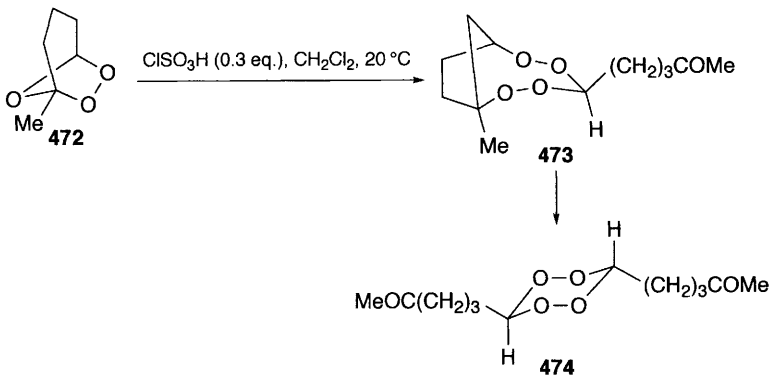
471 n = 1–4, 95%

(150)

Sulfophenethylsiloxanes may also be prepared without the use of a solvent by adding an equimolar mixture of the appropriate trichlorosilane and chlorosulfonic acid as small droplets through a mixing nozzle in a continuous stream of hot air (80–150 °C), followed by hydrolysis of the solid intermediate.[394]

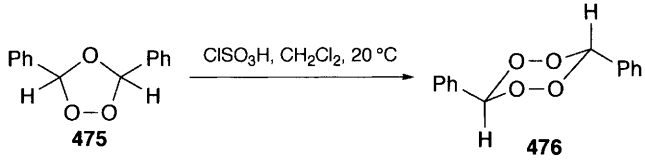
12.9 Ozonides (1,2,4-Trioxolans)

Ozonides react with catalytic quantities of chlorosulfonic acid (0.3 equivalents) in dichloromethane at 20 °C to yield 3,6-dialkyl-1,2,4,5-tetraoxans and/or 1,4-dialkyl-2,3,5,6,11-pentaoxabicyclo[5.3.1]undecanes.[395,396] The reaction of ozonides with chlorosulfonic acid has been extensively investigated by Miura and co-workers.[395–400] The reaction pathways appear to vary with different substituents; the proposed mechanism involves heterolytic fission of the carbon–oxygen bond of the peroxide bridge. For example, methylcyclopentene ozonide **472** reacted stereoselectively with the reagent in dichloromethane to give initially compound **473** which subsequently rearranged to form the *trans* tetraoxan **474** (Equation 151).



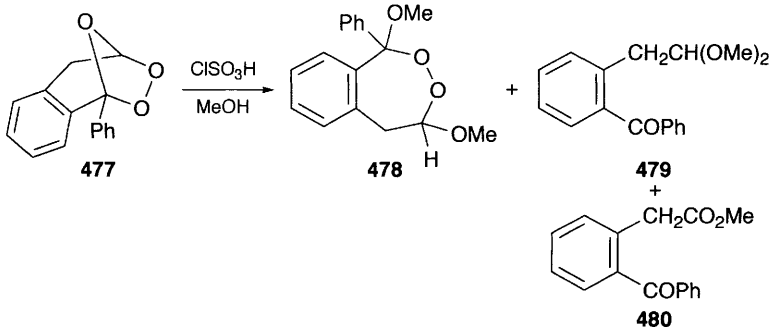
(151)

Phenylcyclopentene ozonide reacted similarly with chlorosulfonic acid, although the same ozonide reacted stereoselectively with antimony pentachloride to yield the *cis* tetraoxan (55%). The conversion of ozonides to tetraoxans by treatment with catalytic amounts of chlorosulfonic acid appears to be a fairly general reaction; thus 1,2-diphenylethylene(stilbene) ozonide **475** yields the corresponding tetraoxan **476**; 41% (Equation 152).



(152)

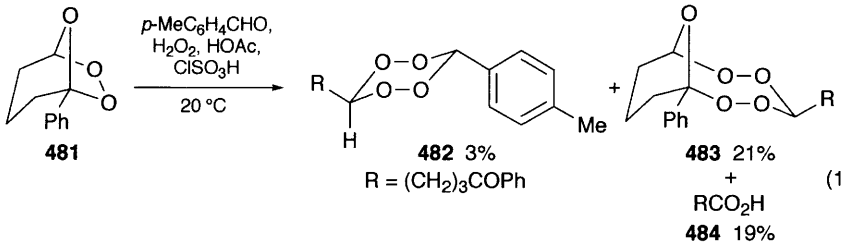
Various ozonides, on treatment with methanol in the presence of trace quantities of chlorosulfonic acid, reacted with selective cleavage of the carbon–oxygen bond of the peroxide bridge to give products formed *via* the corresponding α-methylhydroperoxides. An estimation of the relative order of reactivity of the different ozonides in the reaction was reported.[397] For instance, 1,4-epoxy-4,5-dihydro-*1H*-2,3-benzodioxepin **477** by treatment with methanol containing chlorosulfonic acid (0.03 equivalents) for 1 hour yields a mixture of the compounds **478–480** (Equation 153). However, when the reaction was prolonged (80 hours), the major product was the methyl ester **480** and reaction of the benzodioxepin



(153)

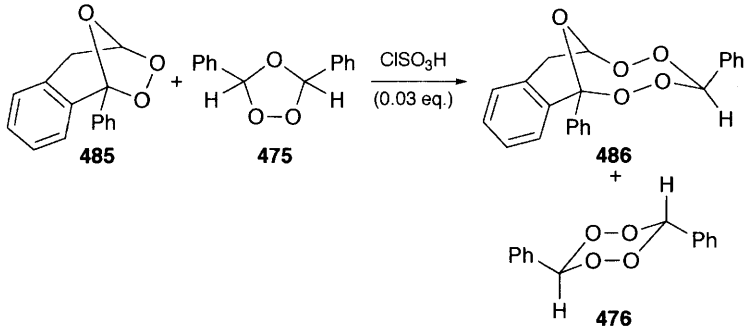
477 with excess chlorosulfonic acid (three equivalents, 3 hours) gave the ester **480** in quantitative yield.[397]

The reaction of ozonides with carbonyl compounds and hydrogen peroxide is catalysed by the presence of chlorosulfonic acid and provides a new synthetic route to the corresponding 2,3,5,6,11-pentaoxabicyclo[5.3.1]undecanes in 3–35% yield.[398] As an illustration, 1-phenyl-6,7,8-trioxabicyclo[3.2.1]octane **481** reacted with *p*-tolualdehyde, hydrogen peroxide and chlorosulfonic acid (0.03 equivalents) in acetic acid at 20 °C (2 hours) to yield a mixture of the products **482–484** (Equation 154).



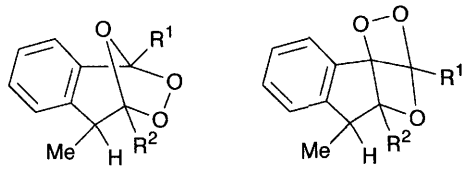
481 → **482** 3% (R = $(CH_2)_3COPh$) + **483** 21% + RCO_2H **484** 19% (154)

The reaction of a mixture of two kinds of ozonides in the presence of an acid catalyst affords the crossed 2,3,5,6,11-pentaoxabicyclo[5.3.1]undecane derivative. For instance, a mixture of 3-phenylindene ozonide **485** and stilbene ozonide **475** reacted with chlorosulfonic acid (0.03 equivalents) to give the crossed 2,3,5,6,11-pentaoxabicyclo[5.3.1]undecane **486**, 25%, together with the tetraoxa compound **476**, 7%, a cyclic peroxide (Equation 155).[399]



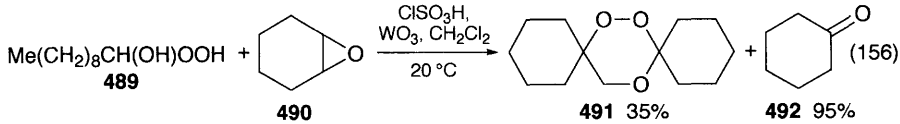
485 + **475** → **486** + **476** (155)

Acidolysis of ozonides provides a novel synthetic route to cyclic peroxides. The reaction of the *exo* and *endo* ozonides of 2,3-disubstituted 1-methylindenes **487** and **488** with chlorosulfonic acid catalysed the interconversion of the *exo*–*endo* ozonide isomers to give an equilibrium mixture containing the two isomers in a ratio of 7:3.[400]



487 **488**

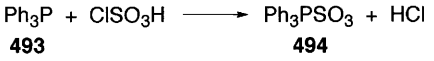
A novel synthesis of ozonides (7–63% yield) involves reaction of a mixture of α-hydroxydecyl hydroperoxide or bis(α-hydroxyalkyl) peroxides and epoxides in the presence of tungstic anhydride (WO_3) and catalytic amounts of chlorosulfonic acid.[401] As an example, the hydroperoxide **489** reacted with cyclohexene oxide **490**, tungstic anhydride and chlorosulfonic acid (0.1 equivalent) in dichloromethane at 20 °C (3 hours) to give the dispiro compound **491** and cyclohexanone **492**, (Equation 156).



489 **490** **491** 35% **492** 95% (156)

12.10 Triphenylphosphine

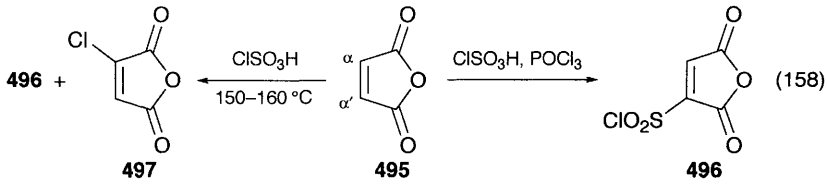
Triphenylphosphine **493** reacts with chlorosulfonic acid to form the triphenylphosphine–sulfur trioxide adduct **494** (Equation 157).[402] In this reaction, the triarylphosphine reacts in an analogous manner to a tertiary amine which with chlorosulfonic acid yields the corresponding amine–sulfur trioxide complex (see Section 9, p 101). The adduct **494** was stable in air and was useful as a coupling reagent in peptide synthesis.[402]



493 **494** (157)

12.11 Maleic Anhydride

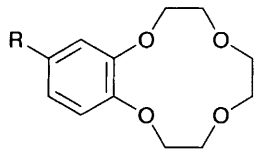
Maleic anhydride **495** reacted with chlorosulfonic acid in phosphorus oxychloride to give the sulfonyl chloride **496**. On the other hand, prolonged treatment of the anhydride **495** with boiling chlorosulfonic acid (150–160 °C) afforded a mixture of the α-chloro derivative **497** and the sulfonyl chloride **496** (Equation 158).[403] This result shows that at 150–160 °C, chlorosulfonic acid is acting both as a sulfonating and a chlorinating agent.



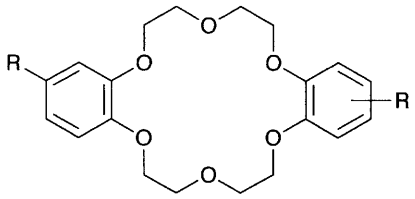
496 + **497** **495** **496** (158)

12.12 Crown Ethers

Monobenzo- and dibenzocrown ethers are chlorosulfonated by reaction with a large excess of chlorosulfonic acid.[404] Monobenzo-12-crown-4, -15-crown-5 and -18-crown-6-ethers, when treated dropwise with chlorosulfonic acid (10 equivalents) in chloroform solution at −10 to −5 °C and the reaction mixture left at RT (five to six hours), gave the corresponding sulfonyl chlorides in 65–75% yield. For instance, monobenzo-12-crown-4-ether **498** afforded the chlorosulfonyl derivative **499**. The orientation of sulfonation is, as expected, *p* to the electron-donating oxygen atom.



498 R = H
499 R = SO_2Cl



500 R = H
501 R = SO_2Cl

Dibenzocrown ethers, namely dibenzo-18-crown-6 and -24-crown-8 by similar treatment with a larger excess of the reagent (20 equivalents) gave the corresponding disulfonyl chlorides. For example, dibenzo-18-crown-6 ether **500** afforded the disulfonyl chloride **501** as a mixture of stereoisomers, showing that chlorosulfonation of the dibenzocrown ethers does not occur regioselectively.[404] The chlorosulfonyl and dichlorosulfonyl derivatives were converted into sulfonamides by reaction with ammonia and amines.

12.13 Organotin Compounds

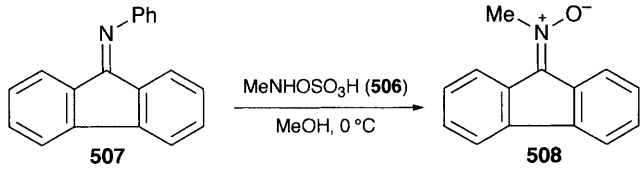
The tetraorganotin compounds **502** and **503** react with chlorosulfonic acid (one equivalent) in carbon tetrachloride at −10 °C with facile specific cleavage of the tin–carbon bonds. In the dialkyl diaryltins, *e.g.* **503**, the tin–aryl carbon bonds are preferentially cleaved.[405] Chlorosulfonic acid at low temperature (−10 °C) cleaves one tin–butyl bond from tetrabutyltin and two tin–aryl bonds from both tetraaryltin and dibutyldiaryltin **503**. The reactions provide a possible one-step synthetic route to the organotin sulfonate esters **504** and **505** respectively.

R_4Sn	Bu_2SnAr_2	$R_nSn(SO_3R)_{4-n}$	$Bu_2Sn(SO_3Ar)_2$
502 R = Bu, Ph, *p*-MeC_6H_4	**503** Ar = Ph, *p*-MeC_6H_4	**504**	**505**

12.14 *N*-Methylhydroxylamine

N-Methylhydroxylamine hydrochloride reacts with chlorosulfonic acid (1.5 equivalents) in ether at room temperature to give the *O*-sulfonic acid **506**.[406] *N*-Methylhydroxylaminesulfonic acid **506** generally reacts with aldimines and ketimines forming the corresponding methylnitrones.[407] For instance, *N*-fluoreny-

lideneaniline **507** reacted with the hydroxylaminesulfonic acid **506** at 0 °C (1 hour) to give fluorenone methylnitrone **508**, 90% yield (Equation 159), which represented an improved synthesis of this compound.



507 **508** (159)

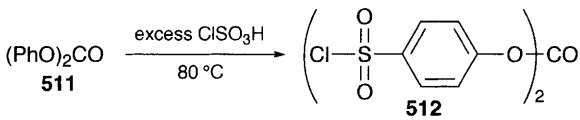
12.15 Alkyl Nitrates

Alkyl nitrates **509** react with chlorosulfonic acid at 15–20 °C to give excellent yields (90–94%) of the corresponding alkyl bisulfates **510** (Equation 160).[408] This reaction provides a useful synthesis of alkyl bisulfates.

$$\underset{\mathbf{509}}{RONO_2} + ClSO_3H \longrightarrow \underset{\mathbf{510}}{ROSO_3H} + NO_2Cl \qquad (160)$$

12.16 Diphenyl Carbonate

Diphenyl carbonate **511**, by heating with excess chlorosulfonic acid at 80 °C (2.5 hours), afforded the disulfonyl chloride **512**, 35% yield (Equation 161).[409] In this reaction, chlorosulfonation occurred, as expected, *para* with respect to the electron donating oxygen atom.



511 **512** (161)

12.17 Fluorocarbon Iodides

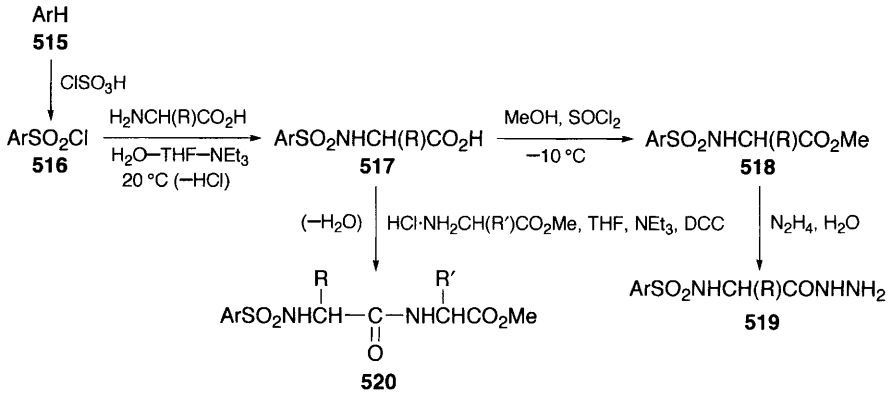
Perfluorocarbon iodides react with chlorosulfonic acid to give perfluorocarbon chlorosulfonates. For example, 1-iodoperfluoropropane **513** reacted with excess of the reagent (10 equivalents) under forcing conditions (in a sealed tube at 130 °C for 65 hours) to yield perfluoropropyl chlorosulfonate **514**) (Equation 162).[410]

$$\underset{\mathbf{513}}{CF_3CF_2CF_2I} \xrightarrow[130\,^\circ C]{10ClSO_3H} \underset{\mathbf{514}\ 89\%}{CF_3CF_2CF_2OSO_2Cl} + [HI] \qquad (162)$$

The fluorocarbon chlorosulfonates, *e.g.* **514**, represent a new class of compounds and their formation by treatment of perfluoroalkyl iodides with chlorosulfonic acid appears to be a useful general preparative procedure.

12.18 Sulfonylamino Acids

El-Sayed and co-workers[412–420] have extensively studied the chemistry and antimicrobial properties of various sulfonylamino acids and their derivatives. The procedure for the synthesis of these compounds is summarized in Scheme 16.



Scheme 16

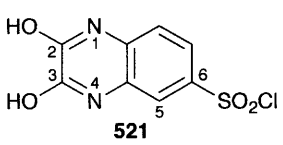
The appropriate aromatic or heteroaromatic substrate **515** was reacted with excess chlorosulfonic acid to yield the sulfonyl chloride **516**, which was condensed with an amino acid in aqueous THF–triethylamine to give the sulfonylamino acid **517**. THF was discovered to be the optimum solvent for the reaction. The amino acids employed included glycine, L-alanine, DL-valine, L-leucine, L-phenylalanine, L-tyrosine and L-proline.

The corresponding sulfonylamino acid methyl esters **518** were prepared by treatment of the sulfonylamino acids **517** with absolute methanol–pure thionyl chloride at low temperature (−5 °C to −10 °C). The esters **518**, by hydrazinolysis with hydrazine hydrate, afforded the hydrazides **519**. The sulfonylamino acids **517** were coupled with the appropriate amino acid methyl ester hydrochloride in THF–water–triethylamine mixture using DCC as the coupling reagent to yield the corresponding sulfonylamino dipeptide methyl esters **520** (Scheme 16). The synthetic sequence depicted in Scheme 16 has been successfully applied to a number of different aromatic sulfonyl chlorides as illustrated by the following examples.

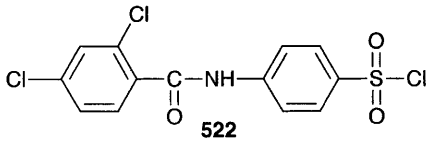
2,3-Dihydroxyquinoxaline, by heating with excess chlorosulfonic acid at 70–80 °C as described by Pirkl[411] gave the 6-sulfonyl chloride **521**. This was then converted into a range of 2,3-dihydroxyquinoxaline-6-sulfonylamino acids, methyl esters and hydrazides. Coupling the sulfonylamino acids with suitable amino acid esters using the DCC method, afforded the corresponding dipeptide methyl esters.[412,413]

N-(2,4-Dichlorobenzoyl)sulfanilyl chloride **522** (prepared as described in ref. 336) was similarly transformed into the corresponding sulfanilyl amino acids, methyl esters, hydrazides and dipeptide methyl esters.[414]

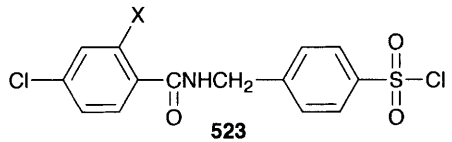
2,4-Dichlorobenzoic acid by treatment with chlorosulfonic acid, as described in ref. 273, afforded the 5-sulfonyl chloride, which was converted into a similar



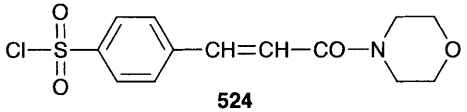
521



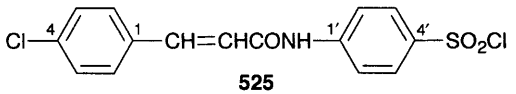
522



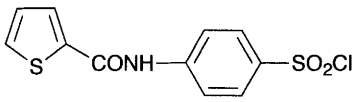
523



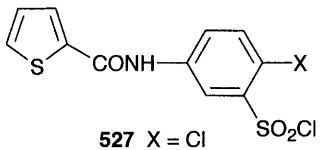
524



525



526



527 X = Cl
528 X = Br

series of novel 2,4-dichlorobenzoic acid-5-sulfonylamino acid derivatives.[415] *N*-Benzyl-*p*-chloro and *N*-benzyl-2,4-dichlorobenzamide were treated with excess chlorosulfonic acid (six equivalents) in boiling chloroform (3 hours) to yield the corresponding *p*-sulfonyl chlorides (**523**, X = H or Cl respectively).[289] The latter were condensed with different amino acids to yield the corresponding sulfonyl-amino acids, methyl esters, hydrazides and the sulfonyl dipeptide methyl esters.[416,417]

Some novel cinnamoylmorpholine-4-sulfonylamino acids were similarly prepared starting from cinnamoylmorpholine-*p*-sulfonyl chloride **524** (prepared by chlorosulfonation of cinnamoylmorpholine as described in ref. 286). The sulfonyl chloride **524** was used to obtain the corresponding cinnamoylmorpholine sulfonylamino acids, methyl esters, hydrazides and the dipeptide methyl esters.[418]

4-Chlorocinnamanilide, by warming with chlorosulfonic acid (12 equivalents) as described in ref. 336, afforded the 4′-sulfonyl chloride **525**. This was converted into the 4-chlorocinnamanilide-4′-sulfonylamino acids, methyl esters, hydrazides and dipeptide methyl esters.[419]

Thiophene-2-carboxanilide and its *p*-chloro and *p*-bromo derivatives reacted smoothly with excess chlorosulfonic acid (six equivalents) at 40 °C to yield the corresponding sulfonyl chlorides **526–528**.[339] The thiophene sulfonyl chlorides were used to prepare the corresponding sulfonylamino acids, methyl esters and hydrazides. The sulfonylamino acids were also coupled with the appropriate amino acid methyl esters to form the sulfonamino dipeptide methyl esters.[420]

Many of the sulfonylamino acids and their derivatives showed moderate antimicrobial activity; the hydrazides were generally less active.

13 References

1 C.M. Suter, *The Organic Chemistry of Sulfur*, Wiley, New York, 1944; Reprinted edition by Intra-Science Research Foundation, Santa Monica, California, 1969, Chapter 3, 195 (this page gives the details of aromatic systems covered and includes the use of chlorosulfonic acid). Chapter 5, p 458 deals with the preparation of aromatic sulfonyl chlorides some of which were made by chlorosulfonic acid, see Tables 2 to 13 (p 463–491).

2 C.M. Suter and A.W. Weston, *Org. React. (NY)*, 1946, **3**, 141.

3 J.P. Bassin, R.J. Cremlyn and F.J. Swinbourne, *Phosphorus, Sulfur and Silicon*, 1991, **56**, 245.

4 H.T. Clarke, G.S. Babcock and T.F. Murray, *Org. Synth. Coll. Vol. 1*, 1941, 78.

5 H. Cerfontain, *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Interscience Publishers, New York, 1968.

6 H.E. Armstrong, *J. Chem. Soc.*, 1871, **24**, 173.

7 K.E. Jackson, *Chem. Rev.*, 1939, **25**, 81.

8 J. Pollak, M. Heimberg-Krauss, E. Katscher and O. Lustig, *Monatsh. Chem.*, 1930, **55**, 358; *Chem. Abs.*, **24**, 4005.

9 H.U. Blank, *Ger.*, DE 2721429, (1978); *Chem. Abs.*, **90**, 87032.

10 W. Schenk, H.U. Blank, F. Hagedorn and W. Evertz, *Ger.*, DE 2743540 (1979); *Chem. Abs.*, **91**, 39128.

11 T. Pfister, W. Schenk and H.U. Blank, *Ger.*, DE 2743541 (1979); *Chem. Abs.*, **47**, 3876.

12 B. Raecke, Henkel and Cie. G.m.b.H., *Ger.*, DE 840278 (1952); *Chem. Abs.*, **91**, 39129.

13 H.U. Blank, *Ger.*, DE 2635281 (1978); *Chem. Abs.*, **88**, 152, 242.

14 H.U. Blank, *Ger.*, DE 2635279 (1978); *Chem. Abs.*, **88**, 152, 243.

15 M. Badzynski, R. Bardyga, M. Domoradzyki, W. Korpal and E. Sobczak, *Pol.*, PL 95629 (1978); *Chem. Abs.*, **90**, 103634.

16 R. Aurnhammer and W. Ludwig, *Ger.*, DE 2135087 (1973); *Chem. Abs.*, **78**, 97324.

17 B.G. Gnedin, N.I. Rudakova and A.A. Spryskov, *Izv. Vyssh. Ucheb. Zaved. Khim. Khim. Tekhnol.*, 1971, **14**(10), 1530; *Chem. Abs.*, **76**, 24842.

18 L.I. Levina, S.N. Patrakova and D.A. Patrushev, *Zh. Obshch. Khim.*, 1958, **28**, 2427; *Chem. Abs.*, **53**, 3120.

19 M.P. van Albada and H. Cerfontain, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1548, 1557.

20 B.G. Gnedin and N.I. Rudakova, *Izv. Vyssh. Ucheb. Zaved. Khim. Khim. Tekhnol.*, 1972, **15**(5), 716; *Chem. Abs.*, **77**, 8740.

21 H. Beckurts and R. Otto, *Chem. Ber.*, 1878, **11**, 2061.

22 L. Harding, *J. Chem. Soc.*, 1921, **119**, 1261.

23 G.H. Birum and R.F. Jensen, US 4713489 (1987); *Chem. Abs.*, **109**, 6216.

24 W.A. Noyes, *Am. Chem. J.*, 1886, **8**, 176.

25 A.A. Spryskov and B.G. Gnedin, *Zh. Obshch. Khim.*, 1963, **33** (4), 1082; *Chem. Abs.*, **59**, 9748.

26 A.B. Kulkarri and R.C. Shah, *J. Indian Chem. Soc., Ind. News Edn.*, 1955, **18**, 22; *Chem. Abs.*, **50**, 7735.

27 J. Ofem and G. Schaffen, US 3686300 (1972); *Chem. Abs.*, **77**, 1396121.

28 I. Ognyanov and A. Zayorora, *Zh. Prik. Khim.*, 1956, **29**, 1299; *Chem. Abs.*, **51**, 1879.

29 Korea Institute of Science and Technology, *Jpn. Kokai*, JP 58162570 (1983); *Chem. Abs.*, **100**, 51268.
30 R. Aurnhammer and R. Koening, *Ger.*, DE 1172258 (1964); *Chem. Abs.*, **61**, 6961; (a) I.A. Popkora and V.A. Kozlov, *USSR*, SU 1622367 (1991); *Chem. Abs.*, **115**, 71116.
31 J.F. Batchelor and J.H. Gorvin, *Ger.*, DE 2344799 (1974); *Chem. Abs.*, **80**, 133258.
32 H.F. Hodson and J.F. Batchelor, US 4103015 (1978); *Chem. Abs.*, **90**, 22816.
33 E.N. Krylov and G.N. Odintsova, *Zh. Org. Khim.*, 1982, **18**(9), 1936; *Chem. Abs.*, **97**, 215203.
34 R.J. Lee, US 3772373 (1973); *Chem. Abs.*, **80**, 26946.
35 Purdue Research Foundation, *Neth.*, NL 7413366 (1976); *Chem. Abs.*, **85**, 186819.
36 M.J. Virnig, US 4100163 (1978); *Chem. Abs.*, **89**, 215, 238.
37 Societe anon. des produits Purs, de Courcelles, *Belg.*, BE 495433 (1950); *Chem. Abs.*, **49**, 4018; (a) R.J. Lee, US 3772373 (1973); *Chem. Abs.*, **80**, 26946.
38 E.H. Huntress and J.S. Autenrieth, *J. Am. Chem. Soc.*, 1941, **63**, 3446.
39 G.P. Chudinova, B.G. Gnedin, A.A. Vinogradov, M.I. Zaitseva and T.V. Nikolaeva, *Izv. Vyssh. Ucheb. Zaved. Khim. Khim. Tekhnol.*, 1977, **20**(1), 54; *Chem. Abs.*, **86**, 189389.
40 J. Pollak and O. Lustig, *Liebigs Ann. Chem.*, 1923, **433**, 191; A.F. Holleman, *Anales soc. españ. fis. quim.*, 1929, **27**, 473; *Chem. Abs.*, **24**, 85.
41 M.S. Malinovskii and G.K. Barabashova, *J. Appl. Chem., USSR*, 1948, **21**, 185; *Chem. Abs.*, **42**, 4967.
42 H.J. Backer, *Recl. Trav. Chim. Pays-Bas*, 1935, **54**, 544.
43 A. Newton, *J. Am. Chem. Soc.*, 1943, **65**, 2439.
44 A.W. Schorger, *J. Am. Chem. Soc.*, 1917, **39**, 2678; (a) A.G. Yukhno, P.N. Belov, M.N. Stopnikova, M.Ya. Tuzyak, V.A. Gerasimenko and T.V. Kireiko, *USSR*, SU 1579918 (1990); *Chem. Abs.*, **113**, 230958.
45 L.I. Smith, *Org. React (NY)*, 1942, **1**, 370.
46 O. Jacobsen, *Chem. Ber.*, 1886, **19**, 1209.
47 L.I. Smith and M.A. Kiess, *J. Am. Chem. Soc.*, 1939, **61**, 989.
48 L.I. Smith and C.O. Guss, *J. Am. Chem. Soc.*, 1940, **62**, 2631.
49 Y. Soma and M. Tanaka, *Jpn. Kokai*, JP 04036265 (1992); *Chem. Abs.*, **117**, 26081.
50 E. Wedekind and D. Schenk, *Chem. Ber.*, 1911, **44**, 201.
51 F.G. Boardwell and G.W. Crosby, *J. Am. Chem. Soc.*, 1956, **78**, 5367.
52 R.J. Cremlyn, F.J. Swinbourne, S. Graham and J. Lynch, *Phosphorus, Sulfur and Silicon*, 1990, **53**, 121.
53 J.P. Bassin, R.J. Cremlyn, J. Lynch and F.J. Swinbourne, *Phosphorus, Sulfur and Silicon*, 1993, **78**, 55; (a) R.J. Cremlyn, F.J. Swinbourne, P. Fitzgerald, N. Godfrey, P. Hedges, J. Lapthorne and C. Mizon, *Indian J. Chem.*, 1984, **23B**, 962.
54 A.E. Knauf and R. Adams, *J. Am. Chem. Soc.*, 1933, **55**, 4704; (a) P. Bergmann, *Z. Chem.*, 1971, **11**, 423; *Chem. Abs.*, **77**, 101021.
55 R.T. Arnold and H.E. Zaugg, *J. Am. Chem. Soc.*, 1941, **63**, 1317.
56 W. Borsche and M. Pommer, *Chem. Ber.*, 1921, **54**, 102.
57 P.C. Datta and D. Mandel, *J. Indian Chem. Soc.*, 1956, **33**, 410; *Chem. Abs.*, **51**, 724.
58 A. Chrzaszczewska and T. Machlanski, *Lodz Towarz. Nauk, Wydzial III, Acta Chem.*, 1966, **11**, 143; *Chem. Abs.*, **66**, 37689.
59 C. Courtot and R. Geoffrey, *Compt. Rend.*, 1924, **198**, 2259.
60 G.B. Bachman and S. Polansky, *J. Org. Chem.*, 1951, **16**, 1690.
61 J.H. Weissberger, E. Weissberger and F.W. Ray, *J. Am. Chem. Soc.*, 1950, **72**, 4253.
62 A.P. Paul and R.F. Beidler, US 3155716, (1964); *Chem. Abs.*, **62**, 502.
63 V.V. Koslov, T.I. Vol'fson, N.A. Kozlova and G.S. Tubyaskaya, *Zh. Obsch. Khim.*, 1962, **32**, 3440; *Chem. Abs.*, **58**, 11289.

64 J. Naloudek, J. Valik and J. Matoulek, *Czech.*, CS 143091 (1971); *Chem. Abs.*, **77**, 75071.
65 B.G. Gnedin, A.A. Spryskov and E.G. Lokshina, *Izv. Vyssh. Ucheb. Khim. Khim. Tekhnol.*, 1967, **10** (7), 774; *Chem. Abs.*, **67**, 116736.
66 A. Corbellini, *Giorn. Chim. ind. appl.*, 1927, **9**, 118; *Chem. Abs.*, **22**, 2938.
67 A. Corbellini and L. Albenga, *Gazz. Chim. Ital.*, 1931, **61**, 111.
68 G. Walter, *Monatsh. Chem.*, 1934, **64**, 287.
69 A.A. Spryskov, *Zh. Obshch. Khim.*, 1951, **21**, 2022; *Chem. Abs.*, **46**, 6008.
70 V. Veselý and F. Stursa, *Collct. Czech. Chem. Commun.*, 1931, **3**, 328; *Chem. Abs.*, **25**, 4877.
71 R.E. Steiger, *Helv. Chim. Acta.*, 1930, **13**, 173.
72 L.F. Fieser and D.M. Bowen, *J. Am. Chem. Soc.*, 1940, **62**, 2105.
73 K. Dziewonski and A. Wulffsohn, *Bull. Pol. Acad. Sci. Chem.*, 1929A, 143; *Chem. Abs.*, **25**, 1514.
74 K. Dziewonski and S. Dziecielewski, *Bull. Pol. Acad. Sci. Chem.*, 1927A, 273; *Chem. Abs.*, **22**, 2164.
75 K. Dziewonski and J. Moszew, *Bull. Pol. Acad. Sci. Chem.*, 1928, 283; *Chem. Abs.*, **23**, 3220.
76 D.C.F. Garbutt, K.G.R. Pachler and J.R. Parrish, *J. Chem. Soc.*, 1965, 2324.
77 M. Menard, L. Mitchell, J. Komlossy, A. Wrigley and F.L. Chubb, *Can. J. Chem.*, 1961, **39**, 729.
78 M. Menard, D. Awang and F.L. Chubb, *Can. J. Chem.*, 1962, **40**, 1738.
79 W.E. Bachmann and J.R. Dice, *J. Org. Chem.*, 1947, **12**, 876.
80 K. Dziewonski and T. Stolyhwo, *Chem. Ber.*, 1924, **57**, 1531.
81 G.T. Morgan and V.E. Yarsley, *J. Soc. Chem. Ind.*, 1925, **44**, 513.
82 K. Dziewonski and A. Kocwa, *Bull. Pol. Acad. Sci. Chem.*, 1928, 405; *Chem. Abs.*, **23**, 2435.
83 H. Cerfontain and Z.R.H. Schaasberg-Nienhuis, *J. Chem. Soc., Perkin Trans. 2*, 1974, 989.
84 K. Dziewonski, B. Grünberg and J. Schoen, *Bull. Pol. Acad. Sci. Chem.*, 1930A, 518; *Chem. Abs.*, **25**, 5419.
85 M.T. Bogert and R.B. Conklin, *Collect. Czech. Chem. Commun.*, 1933, **5**, 187; *Chem. Abs.*, **27**, 4230; (a) L.A. Gifford, F.T.K. Owusu-Daaku and A.J. Stevens, *J. Chromatogr.*, A, 1995, **715**(2), 201.
86 H. Vollmann, H. Becker, M. Correll and H. Streeck, *Liebigs Ann. Chem.*, 1937, **531**, 1.
87 E. Tietze and O. Bayer, *Liebigs Ann. Chem.*, 1939, **540**, 189.
88 A. Schmelzer, US 2032505 (1936); *Chem. Abs.*, **30**, 2771.
89 A. Schemlzer, *Ger.* 654283 (1937); *Chem. Abs.*, **32**, 2372.
90 M. Battegay and P. Brandt, *Bull. Soc. Chim. Fr.*, 1922, **31**, 190; 1923, **33**, 1667.
91 J.O. Morley, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1554, 1560.
92 O. Hinterhofer, *Monatsh. Chem.*, 1975, **106**(1), 67.
93 S.M.G. Solomon and D.J. Hennesey, *J. Org. Chem.*, 1957, **22**, 1649.
94 R. Pschorr, *Chem. Ber.*, 1901, **34**, 3998; R. Pschorr and W. Klein, *Chem. Ber.*, 1901, **34**, 4004.
95 E.H. Huntress and F.H. Carten, *J. Am. Chem. Soc.*, 1940, **62**, 511.
96 R. Nodzu, T. Osaka, H. Kitano and K. Fukui, *Nippon Kagaku Kaishi,* 1951, **76**, 775; *Chem. Abs.*, **51**, 17793.
97 M. Akazawa, S. Tatsumae and S. Yoshino, *Jpn. Kokai*, JP 02049764 (1990); *Chem. Abs.*, **113**, 40146.

98 G.L. Afraimovich, S.M. Danov, V.A. Dozorov, B.V. Danova, S.V. Makarov and G.A. Malova, *Osnovn. Organ. Sintez i Neftekhimiya*, 1978, **9**, 122; *Chem. Abs.*, **90**, 151255.
99 Mitsui Toatsu Chemicals Inc. Japan, *Jpn. Kokai*, JP 58038253 (1983), JP 58049360 (1983); *Chem. Abs.*, **99**, 38224 and **99**, 22122 respectively.
100 M. Meier and W. Tronich, *Eur.*, EP 403947 (1990); *Chem. Abs.*, **115**, 8298.
101 N. Kitagishi, K. Kaneda and S. Kajiwara, *Jpn. Kokai*, JP 03181455 (1991); *Chem. Abs.*, **116**, 41080.
102 Nissan Chemical Industries Ltd, Japan, *Belg.*, BE 890719 (1982); *Chem. Abs.*, **96**, 162332.
103 T. Papenfuhs, *Ger.*, DE 3302647 (1984); *Chem. Abs.*, **102**, 24282.
104 A.E. Erickson, US 2860168 (1958); *Chem. Abs.*, **53**, 9152.
105 Konishi Kagaku Kogyo Co. Ltd, Japan, *Jpn. Kokai*, JP 58206553 (1983); *Chem. Abs.*, **100**, 156364.
106 G. Schaefer and P. Neuman, *Ger.*, DE 3704932 (1988); *Chem. Abs.*, **109**, 210705.
107 R.J. Cremlyn and T. Cronje, *Phosphorus Sulfur*, 1979, **6**, 495.
108 V.J. Leslie and J.B. Rose, US 3830781 (1974); *Chem. Abs.*, **82**, 171675.
109 V.J. Leslie and J.B. Rose, US 3917715 (1975); *Chem. Abs.*, **84**, 31898.
110 J. Stewart, *J. Chem. Soc.*, 1922, **121**, 2555.
111 E. Gebauer-Fülnegg and H. Figdor, *Monatsh. Chem.*, 1927, **48**, 627.
112 W. Davies and H.G. Poole, *J. Chem. Soc.*, 1927, 1122.
113 S. Hussain, P.A. Swaroop, M. Kifayatulla, R. Narsimha and R. Vaidyeswaran, *Indian Pat.*, IN 150341 (1982); *Chem. Abs.*, **99**, 139483.
114 W.V. Farrar, *J. Chem. Soc.*, 1960, 3063.
115 I.R.A. Bernard, G.E. Chivers, R.J. Cremlyn and K.G. Mootoosamy, *Aust. J. Chem.*, 1974, **27**, 171.
116 G.E. Chivers, R.J. Cremlyn and R.A. Martin, *Chem. Ind.* (London), 1975, 130.
117 G.E. Chivers, R.J. Cremlyn, T.N. Cronje and R.A. Martin, *Aust. J. Chem.*, 1976, **29**, 1573.
118 E.B. McCall and W. Cummings, *Brit.*, GB 964543 (1964); *Chem. Abs.*, **61**, 9433; E.B. McCall and S.A. Hughes, *Brit.*, GB 976201 (1964); *Chem. Abs.*, **62**, 7681.
119 E. Ager, B. Iddon and H. Suschitzky, *J. Chem. Soc. (C)*, 1970, 1530.
120 M. Ballister and S. Olivella, 'Aromatic and Alkaromatic Chlorocarbons' in *Polychloroaromatic Compounds*, H. Suschitzky (ed), Plenum Press, London, 1974, 6.
121 M. Kulka, *J. Org. Chem.*, 1959, **24**, 235.
122 G.W. Seymoor, V.S. Salvin and W.D. Jones, US 2511547 (1950); *Chem. Abs.*, **45**, 653.
123 W. Brodt and T. Papenfuhs, *Ger.*, DE 3618219 (1987); *Chem. Abs.*, **108**, 133408.
124 E.V. Zakharov, V.I. Zetkin, M.Ya. Fishkis and V.S. Nakhshynov, *Zh. Org. Khim.*, 1965, **1**(10), 1866; *Chem. Abs.*, **65**, 3394.
125 Y. Fukunaga, M. Umemoto, M. Ura and T. Asano, *Jpn. Kokai*, JP 02157257 (1990); *Chem. Abs.*, **113**, 171671.
126 K.M. Roizen and I.M. Bilik, *Metody Poluch. Khim. Reaktiv. Prop.*, 1969, **20**, 118; *Zh. Khim.*, 1971, Abs. No 2 Zh, 248; *Chem. Abs.*, **76**, 59123.
127 R.D. Rossi and D.K. Ray-Chaudhuri, US, 4510324 (1985); *Chem. Abs.*, **103**, 37200.
128 A. Tzikas, *Eur.*, EP 36840 (1981); *Chem. Abs.*, **96**, 36888.
129 V.D. Simonov, L.V. Voronkova and N.F. Popova, *Khim. Prom-St.*, 1985, **9**, 526; *Chem. Abs.*, **105**, 114655.
130 S. Jiang, Z. Xiang, L. Wang and T. Yao, *Huaxue Shijie*, 1983, **24**(1), 8; *Chem. Abs.*, **99**, 104891.
131 E. Koch, *Chem. Ber.*, 1890, **23**, 2319.
132 O. Jacobsen, *Chem. Ber.*, 1888, **21**, 2821.

133 E. Paternò and F. Canzoneri, *Gazz. Chim. Ital.*, 1881, **11**, 124.
134 G. Carrara, *Gazz. Chim. Ital.*, 1889, **19**, 173, 502.
135 E. Jünger and A. Klages, *Chem. Ber.*, 1896, **29**, 314.
136 W. Kelbe and K. Pathe, *Chem. Ber.*, 1886, **19**, 1546.
137 A. Töhl and A. Müller, *Chem. Ber.*, 1893, **26**, 1008.
138 A. Töhl and R. Eckel, *Chem. Ber.*, 1893, **26**, 1099.
139 O. Jacobsen, *Chem. Ber.*, 1886, **19**, 1218: 1889, **22**, 1580.
140 A. Töhl and A. Geyger, *Chem. Ber.*, 1892, **25**, 1533.
141 C. Courtot and C.C. Lin, *Bull. Soc. Chim. Fr.*, 1931, **49**(4), 1047.
142 T. Sonoi, H. Tatsu, S. Saito, S. Sterlin, C. Rafailovic, F. Victor and N.I. Dalyagina, *Ger.*, DE 19625376 (1996); *Chem. Abs.*, **126**, 172028.
143 H.E. Armstrong and S. Williamson, *Proc. Chem. Soc.*, 1886, 233; 1887, 145.
144 H.E. Armstrong and R.P. Wynne, *Chem. News*, 1890, **61**, 285.
145 H.E. Armstrong and S. Williamson, *Chem. News.*, 1886, **54**, 256.
146 H.E. Armstrong, *Chem. News*, 1887, **56**, 241.
147 H.E. Armstrong and R.P. Wynne, *Chem. News*, 1887, **55**, 91; 1887, **57**, 8.
148 W. Houlding, *Chem. News*, 1889, **59**, 226.
149 H.E. Armstrong and R.P. Wynne, *Chem. News*, 1890, **61**, 273.
150 H.E. Armstrong and R.P. Wynne, *Chem. News*, 1889, **59**, 189.
151 W.M. Heller, *Chem. News*, 1889, **60**, 58.
152 K. Dziewónski, J. Schoen and M.A. Glazner, *Bull. Pol. Acad. Sci. Chem.*, **1929A**, 636; *Chem. Abs.*, **25**, 1518.
153 Badische Anilin-und Sodafabrik, *Ger.*, DE 260562; *Chem. Zentr,* II, 1913, 104.
154 G. Schroeter and S. Götzky, *Chem. Ber.*, 1927, **60**, 2035.
155 W.R. Hodgkinson and F.E. Matthews, *J. Chem. Soc.*, 1883, **43**, 166.
156 H.H. Hodgson and J.S. Whitehurst, *J. Chem. Soc.*, 1944, 482.
157 M. Meier and R. Wagner, *Ger.*, DE 4006666 (1991); *Chem. Abs.*, **115**, 255806.
158 M. Umemoto, M. Ura, S. Kosho and H. Hashimoto, *Jpn. Kokai*, JP 62252745 (1987); *Chem. Abs.*, **109**, 109991.
159 L.V. Pokopeva, *Khim. Promst. (Moscow)*, 1980, **2**, 28; *Chem. Abs.*, **93**, 238958.
160 V.I. Zetkin and V.V. Lebedev, *Zh. Prikl. Khim. (Leningrad)*, 1976, **49**(11), 2520; *Chem. Abs.*, **86**, 106085.
161 H. Limpricht, *Chem. Ber.*, 1885, **18**, 2191.
162 J. Saito, T. Tamura, Y. Kurashi, S. Uzawa, N. Matsumoto and N. Yamaguchi, *Eur.*, EP 173918 (1986); *Chem. Abs.*, **105**, 56341.
163 W.J. Karslake and R.C. Huston, *J. Am. Chem. Soc.*, 1914, **36**, 1245.
164 W. Horstmann, *Eur.*, EP 289847 (1988); *Chem. Abs.*, **100**, 75049.
165 W. Brodt and T. Papenfuhs, *Ger.*, DE 3618219 (1987); *Chem. Abs.*, **108**, 133408.
166 R.J. Cremlyn, *J. Chem. Soc. (C)*, 1966, 1229.
167 O. Jerabek, *Chem. Prum.*, 1976, **26**(7), 352; *Chem. Abs.*, **85**, 159, 574.
168 S. Kojima, M. Hatano and S. Yanaka, *Jpn. Kokai*, JP 01168662 (1989); *Chem. Abs.*, **112**, 157842.
169 K. Dziewoński and T. Orzelski, *Bull. Pol. Acad. Sci. Chem.*, **1926A**, 347; *Chem. Abs.*, **22**, 1160.
170 E.E. Gilbert, US 767994 (1985); *Chem. Abs.*, **106**, 158919.
171 V.V. Lebedev, V.I. Zetkin and V.I. Kosorotov, *Kinet. Katal.*, 1978, **19**(5), 1323; *Chem. Abs.*, **90**, 54591.
172 R. Taylor, *Electrophilic Aromatic Substitution*, Wiley, Chichester, 1990, Chapter 8.
173 G.N. Burkhardt, *J. Chem. Soc.*, 1933, 337.
174 R.D. Haworth and A. Lapworth, *J. Chem. Soc.*, 1924, **125**, 1300.

175 A.A. Spryskov and B.G. Gnedin, *Zh. Org. Khim.*, 1965, **1**(11), 1946; *Chem. Abs.*, **64**, 9534; *J. Org. Chem. USSR*, 1965, **1**, 1983.
176 M. Orlowski, *Chem. Ber.*, 1875, **8**, 332.
177 A.A. Spryskov and B.G. Gnedin, *Izv. Vyssh. Ucheb. Zaved, Khim. Khim. Tekhnol.*, 1964, **7** (6), 935; *Chem. Abs.*, **62**, 14440.
178 J. Feigenbaum and C.A. Neuberg, *J. Am. Chem. Soc.*, 1941, **63**, 3529.
179 K. Mazec and J. Gniot-Szulzycka, *Bull. Pol. Acad. Sci. Chem.*, 1989, **37**(9–12), 371; *Chem. Abs.*, **114**, 142787.
180 J. Pollak and E. Gebauer-Fülnegg, *Monatsh. Chem.*, 1925, **46**, 383.
181 S.B. Cilianu, O.D. Eugen, V. Cornelia, I. Cristian and M. Teodorescu, *Rom.*, RO 63236 (1978); *Chem. Abs.*, **92**, 41572.
182 R.J. Cremlyn and T. Cronje, *Phosphorus Sulfur*, 1979, **6**, 413; (a) T.A. Sullivan and V.G. Witterholt, US 4556733 (1985); *Chem. Abs.*, **104**, 148503.
183 American Cynamid Co., USA, *Belg.*, BE 845158 (1979); *Chem. Abs.*, **83**, 46391.
184 E. Katscher, H. Lehr, A. Harnisch and L. Steinhardt, *Monatsh. Chem.*, 1930, **56**, 381.
185 I.G. Turynachik, E.K. Blinova, E.V. Lebedev and B.S. Shopoval, *Sb. Tr. Vses. Ob'edin. Neftekhim*, 1976, **11**, 88; *Zh. Khim. Abs.*, No 9, 161 (1977); *Chem. Abs.*, **87**, 134268.
186 E.J. Cragoe, R.L. Smith and G.E. Stokker, *Ger.*, DE 2723635 (1977); *Chem. Abs.*, **88**, 89358.
187 A. Braendstroem, G. Strandlund and P. Langerstroem, *Acad. Chem. Scand.*, Ser B, 1980, **34**, 467; *Chem. Abs.*, **94**, 120495.
188 J. Pollak and E. Gebauer-Fülnegg, *Monatsh. Chem.*, 1926, **47**, 109.
189 O. Litvay, E. Riesz and L. Landau, *Chem. Ber.*, 1929, **62**, 1863.
190 J.S. Esteve, *Span.* ES 512680 (1983); *Chem. Abs.*, **99**, 10.
191 J. Pollak and E. Gebauer-Fülnegg, *Monatsh. Chem.*, 1925, **46**, 499.
192 W.D. Peterson, US 2487586 (1949); *Chem. Abs.*, **44**, 3022; (a) Y. Ban, T, Shimizu, K. Tabuchi and T. Shimozaki, *Jpn. Kokai,* JP 09227499 (1997); *Chem. Abs.*, **127**, 234175.
193 J. Pollak and E. Gebauer-Fülnegg, *Montash. Chem.*, 1926, **47**, 537.
194 J. Pollak, E. Gebauer-Fülnegg and E. Blumenstock-Halward, *Monatsh. Chem.*, 1928, **49**, 187.
195 J. Baddiley, J.B. Payman and E.G. Bainbridge, *Brit.*, GB 186515 (1921); *Chem. Abs.*, **17**, 289.
196 E. Gebauer-Fülnegg and A. Glückmann, *Monatsh. Chem.*, 1929, **53–54**, 100.
197 J. Hojer, E. Stasek and V. Vesely, *Czech.*, CS 187275 (1981); *Chem. Abs.*, **96**, 52038.
198 J.F. Russ and G.L. Wiesner, *Ger.*, DE 2831992 (1979); *Chem. Abs.*, **90**, 186667.
199 E. Gebauer-Fülnegg and E. Haemmerle, *J. Am. Chem. Soc.*, 1931, **53**, 2648.
200 E. Gebauer-Fülnegg and A. Schlesinger, *Chem. Ber.*, 1928, **61**, 781.
201 H. Beckurts and R. Otto, *Chem. Ber.*, 1878, **11**, 2061; (a) E.H. Huntress and F.H. Carten, *J. Am. Chem. Soc.*, 1940, **62**, 603.
202 L.A. Carpino and B. Cohen, US 4575541 (1986); *Chem. Abs.*, **105**, 7069.
203 M.S. Morgan and L.H. Cretcher, *J. Am. Chem. Soc.*, 1948, **70**, 375.
204 M.L. Hultquist *et al.*, *J. Am. Chem. Soc.*, 1951, **73**, 2558.
205 R.J. Cremlyn and R. Hornby, *J. Chem. Soc.* (C), 1969, 1341.
206 M. Fujino, M. Wakimasu and C. Kitada, *J. Chem. Soc. Chem. Commun.*, 1982, **8**, 445.
207 M. Fujino, M Wakimasu and C. Kitada, *Chem. Pharm. Bull.*, 1981, **29**, 2825; *Chem. Abs.*, **96**, 85948.
208 T. Minami, R. Ohashi, H. Umeda, R. Kinishi and A. Shimida, *Eur.*, EP 466096 (1992); *Chem. Abs.*, **116**, 235240.
209 H. Zammarlik, *C.R. Acad. Sci., Ser. C*, 1971, **273**(25), 1756; *Chem. Abs.*, **76**, 112855.

210 M. Daeuble, N. Greif and R. Fikentscher, *Ger.*, DE 2116560 (1972); *Chem. Abs.*, **78**, 17526.
211 S. Kida, S. Yoshimoto, K. Masuda, Y. Kaneko and K. Kadokura, *Jpn. Kokai*, JP 61258247 (1986); *Chem. Abs.*, **107**, 87042.
212 W.R. Deem, *Brit.*, GB 1404351 (1975); *Chem. Abs.*, **83**, 192878.
213 J. Percival, *Chem. News*, 1889, **59**, 226.
214 A. Lapworth, *Chem. News*, 1895, **71**, 205.
215 E.G. Amphlett and H.E. Armstrong, *Proc. Chem. Soc.*, 1887, 144.
216 C.M. Suter, *J. Am. Chem. Soc.*, 1931, **53**, 1112.
217 R.J. Thomas, US 3845015 (1974); *Chem. Abs.*, **82**, 112647.
218 H. Motokawa, K. Okuse, K. Tsuji and E. Mitsui, *Jpn. Kokai*, JP 51091230 (1976); *Chem. Abs.*, **85**, 159, 675.
219 T. Ehama, Y. Hirose, T. Tsukuru, T. Tomimoto and M. Taniguchi, *Jpn. Kokai*, JP 7445034 (1974); *Chem. Abs.*, **81**, 105009.
220 T. Ehama, Y. Hirose, T. Tsukuru, T. Tomimoto and M. Taniguchi, *Jpn. Kokai*, JP 7445035 (1974); *Chem. Abs.*, **81**, 105010.
221 T. Ehama, Y. Hirose, T. Tsukuru, T. Tomimoto and M. Taniguchi, *Jpn. Kokai*, JP 7436652 (1974); *Chem. Abs.*, **81**, 105012; (a) Z. Brzozowski and T. Mizerski, *Pol.*, PL 145599 (1989); *Chem. Abs.*, **112**, 118450.
222 H. Ono and T. Mitsudori, *Jpn. Kokai*, JP 47013895 (1972); *Chem. Abs.*, **77**, 48071.
223 R.J. Cremlyn, T. Cronje and K.H. Goulding, *Aust. J. Chem.*, 1979, **32**, 445.
224 R.J. Cremlyn, S. Montgomery, Y. Ng and D. Simpson, *Phosphorus Sulfur*, 1982, **12**, 341.
225 K.H. Goulding, T. Cronje and R.J. Cremlyn, *Pestic. Sci.*, 1982, **13**, 23.
226 C.M. Suter, J.P. McKenzie and C.E. Maxwell, *J. Am. Chem. Soc.*, 1936, **58**, 717.
227 J. Moir, *Proc. Chem. Soc.*, 1906, **22**, 259.
228 R. Otto and J. Tröger, *Chem. Ber.*, 1893, **26**, 993.
229 J. Chatt and A.A. Williams, *J. Chem. Soc.*, 1956, 3246.
230 H. Hata, M. Kawamura, K. Kato and Y. Iida, *Jpn. Kokai*, JP 0206945 (1990); *Chem. Abs.*, **113**, 131740.
231 C. Mizon, GRSC Project Thesis, Hatfield Polytechnic, 1983.
232 E. Riesz and W. Frankfurter, *Montash. Chem.*, 1928, **50**, 68.
233 A.W. Weston and C.W. Suter, *J. Am. Chem. Soc.*, 1939, **61**, 389.
234 E.H. Woodruff, *J. Am. Chem. Soc.*, 1944, **66**, 1799.
235 G. Nakai, M. Abe and H. Takagaka, *Jpn. Kokai*, JP 63234059 (1987); *Chem Abs.*, **109**, 54493.
236 R.E. Philion, *Ger. Offen.*, DE 2728641 (1978); *Chem. Abs.*, **90**, 137468.
237 Yamanouchi Pharmaceutical Co. Ltd, *Jpn. Kokai*, JP 57136561 (1982); *Chem. Abs.*, **98**, 16433; (a) D.D. Chapman, *Heterocycles*, 1984, **21**, 597.
238 A. Lapworth, *J. Chem. Soc.*, 1898, **73**, 402.
239 J.L. Work and J.E. Herweh, *J. Polym. Sci.*, Part A-I, 1968, **6**, 2028.
240 R.J. Cremlyn and S.W. Ahmad, *Egypt. J. Chem.*, 1985, **28**(6), 529.
241 D.A. Stauffer, US 3636077 (1972); *Chem. Abs.*, **76**, 112896.
242 P. Neumann, H. Eilingsfeld, A. Heinz and A. Aumeller, *Eur.*, EP 351615 (1990); *Chem. Abs.*, **113**, 23371; (a) E. Fumagalli and R. Bond, *Fr. Demande*, FR 2791057 (2000); *Chem. Abs.*, **134**, 4756.
243 R. Otto and A. Rossing, *Chem. Ber.*, 1886, **19**, 2417.
244 M.V. Kolotilo, G.V. Esipov, N.A. Onishchenko and N.Y. Pilipenko, *USSR*, SU 1685930 (1991); *Chem. Abs.*, **116**, 193907.
245 R.F. Meyer, *J. Heterocycl. Chem.*, 1966, **3**(2), 174.

246 I.S. Ioffe and Z.I. Pavlova, *J. Gen. Chem. (USSR)*, 1944, **14**, 144; *Chem. Abs.*, **39**, 2287.
247 R.J. Cremlyn, F.J. Swinbourne and O.O. Shode, *J. Chin. Chem. Soc.*, 1984, **31**, 383.
248 R.J. Cremlyn, F.J. Swinbourne and E. Mookerjee, *J. Indian Chem. Soc.*, 1986, **25B**, 562.
249 R.J. Cremlyn, F.J. Swinbourne, P. Bassin, D. Dane, K. Higgins, P. Mitchell, J.A.S. Cavaleiro, F.J. Domingues and M. Dias, *Phosphorus Sulfur, Silicon*, 1991, **63**, 385.
250 R.J. Cremlyn, F.J. Swinbourne and L. Goodman, *Phosphorus, Sulfur, Silicon*, 1986, **28**, 395.
251 R.J. Cremlyn, F.J. Swinbourne, P.A. Carter and L. Ellis, *Phosphorus, Sulfur, Silicon*, 1990, **47**, 267.
252 R.J. Cremlyn and H.T. Prates, *Phosphorus, Sulfur, Silicon*, 1993, **79**, 257.
253 R.J. Cremlyn, S. Graham and H.T. Prates, *Phosphorus, Sulfur, Silicon*, 1994, **97**, 199.
254 R.J. Cremlyn, J.P. Bassin, S. Graham and D. Saunders, *Phosphorus, Sulfur, Silicon*, 1993, **84**, 135.
255 R.J. Cremlyn, M.J. Frearson and S. Graham, *Phosphorus, Sulfur, Silicon*, 1995, **107**, 205.
256 A. Zakrzewski, M. Kartawik, T. Plachocka and E. Golata, *Pol.*, PL 140625 (1987); *Chem. Abs.*, **111**, 87424.
257 G. Walter, W. Baumbach, K. Hintzmann, D. Junghans, L. Zoelich and W. Siebert, *Ger.*, DD 269846 (1989); *Chem. Abs.*, **112**, 178384.
258 E. Sauer, K. Polz, G. Schopf and J. Bendig, *J. Prakt. Chem.*, 1991, **333**, 467; (a) H. Ida, S. Tobishima, N. Sato, N. Yoneyama, Y. Hotta, I. Itahana and Y. Hagiwara, *Eur.*, EP 1044964 (2000); *Chem. Abs.*, **133**, 296283.
259 R.J. Cremlyn, O.O. Shode and F.J. Swinbourne, *J. Chem. Soc. Perkin Trans. 1*, 1983, 2181.
260 R.J. Cremlyn, F.J. Swinbourne, O.O. Shode and J. Lynch, *J. Heterocycl. Chem.*, 1987, **24**, 117.
261 R.J. Cremlyn, J.M. Lynch and F.J. Swinbourne, *Phosphorus, Sulfur, Silicon*, 1991, **57**, 173.
262 Sumitomo Chemicals Co. Ltd, *Jpn. Kokai*, JP 8254162 (1982); *Chem. Abs.*, **97**, 127301.
263 T. Davies, M.A. Weaver and R.R. Giles, US 4403092 (1983); *Chem. Abs.*, **99**, 195567.
264 G.A. Tolstikov, B.M. Lerman and F.Z. Galin, *Zh. Org. Khim.*, 1977, **13**(8), 1634; *Chem. Abs.*, **87**, 200896.
265 W. Loewe and T. Braden, *Arch. Pharm.* (Weinheim, Ger.), 1991, **324**(6), 385; (a) J.P. Bassin, *Phosphorus, Sulfur, Silicon*, 1996, **112**, 285.
266 S. Smiles and J. Stewart, *J. Chem. Soc.*, 1921, **119**, 1792.
267 R.J. Cremlyn, *J. Chem. Soc. (C)*, 1968, 11.
268 M.S. Hadley and E.A. Watts, *Eur.*, EP 42705 (1981); *Chem. Abs.*, **96**, 163011.
269 A.M. Islam, I.B. Hannout and M.M. Atwa, *Egypt. J. Chem.*, 1974, **17**(5), 689; *Chem. Abs.*, **86**, 171047.
270 R.J. Cremlyn, F.J. Swinbourne, J. Atherall, L. Courtney, T. Cronje, P. Davis, S. Langston and M. Rogers, *Phosphorus Sulfur*, 1980, **9**, 155.
271 R.J. Cremlyn, F.J. Swinbourne, S. Plant, D. Saunders and C. Sinderson, *Phosphorus Sulfur*, 1981, **10**, 323.
272 A.M. El-Naggar and M.M. Gaffar, *Pak. J. Sci.*, 1982, **25**(5), 157; *Chem. Abs.*, **98**, 198706.
273 G.B. Jackman, V. Petrow, O. Stephenson and A.M. Wild, *J. Pharm. Pharmacol.*, 1962, **14**, 679; *Chem. Abs.*, **59**, 6298.

274 R.A. Coburn, R.T. Evans, R.J. Genco and M.T. Clark, *Eur.*, EP 198366 (1986); *Chem. Abs.*, **106**, 84180.
275 A.M. El-Naggar, I.M. Ismail, M.R. Zaher and M.H. El-Hakim, *Glas. Hem. Drus. Beograd.*, 1984, **49**(9), 527; *Chem. Abs.*, **103**, 716737.
276 G.R. Brown, J.K. Landquist and D.R. Summers, *J. Chem. Soc., Perkin Trans. 1*, 1978, 633.
277 F.J. Moore and G.R. Tucker, *J. Am. Chem. Soc.*, 1927, **49**, 258.
278 Gh. Botez and C. Onisciu, *Bul. Inst. Politeh. Iasi*, 1965, **10**(3–4), 139; *Chem. Abs.*, **64**, 634.
279 C. Onisciu, M. Grigoras and Gh. Botez, *Rom.*, RO 69149 (1979); *Chem. Abs.*, **95**, 6912.
280 R. Hasegawa, *Jpn. Kokai*, JP 63045272 (1988); *Chem. Abs.*, **109**, 73329.
281 D.I. Schuetze, R. Schmitz and K. Wunderlich, *Ger.*, DE 3117055 (1982); *Chem. Abs.*, **98**, 55573.
282 R.J. Cremlyn, K. Burrell, K. Fish, I. Hough and D. Mason, *Phosphorus Sulfur*, 1982, **12**, 197.
283 D. Becker and H.J.E. Loewenthal, *Tetrahedron*, 1992, **48**(12), 2515.
284 R.J. Cremlyn, F.J. Swinbourne and R. Mguni, *Phosphorus Sulfur*, 1980, **8**, 321.
285 R.J. Cremlyn, K. Thandi and R. Wilson, *Indian J. Chem.*, 1984, **23B**, 94.
286 R.J. Cremlyn, O. Obiorah and G. Singh, *Indian J. Chem.*, 1986, **25B**, 559.
287 R.J. Cremlyn and R.W. Pannell, *Aust. J. Chem.*, 1978, **31**, 2669.
288 H. Ahrens and C. Rufer, *Ger. Offen.*, DE 2153528 (1973); *Chem. Abs.*, **79**, 18755.
289 R.J. Cremlyn, L. Ellis and A. Pinney, *Phosphorus, Sulfur, Silicon*, 1989, **44**, 167.
290 O. Lustig and E. Katscher, *Monatsh. Chem.*, 1927, **48**, 87.
291 W. Logemann, P. Giraldi and S. Galimberti, *Liebigs Ann. Chem.*, 1959, **623**, 157.
292 J.H. Short and U. Biermacher, *J. Am. Chem. Soc.*, 1960, **82**, 1135.
293 H.L. Yale, K. Losee and J. Bernstein, *J. Am. Chem. Soc.*, 1960, **82**, 2042.
294 H.L. Yale and F. Sowniski, *J. Org. Chem.*, 1960, **25**, 1824.
295 K. Inukai and K. Hosokawa, *Kogyo Kagaku Zasshi*, 1963, **66**, 1402.
296 S.R. Tamat and D.E. Moore, *J. Pharm. Soc.*, 1983, **72**(2), 180.
297 K. Dziewónski and M. Russocki, *Bull. Acad. Pol. Sci., Ser., Sci. Chem.*, 1929A, 506; *Chem. Abs.*, **25**, 1503.
298 H.E. Fierz, E. Schittler and H. Waldmann, *Helv. Chim. Acta*, 1929, **12**, 663.
299 C.D. Hurd and N. Kharasch, *J. Am. Chem. Soc.*, 1947, **69**, 2113.
300 L.J. Audrieth, M. Sveda, H.H. Sisler and M.J. Butler, *Chem. Rev.*, 1940, **26**, 49.
301 B.I. Kissin, G.A. Timokhin and N.N. Faeshkina, *USSR*, SU 633858 (1978); *Chem. Abs.*, **90**, 87035.
302 G. Booth, *Synth. Commun.*, 1983, **13**(8), 659; *Chem. Abs.*, **99**, 194541.
303 Y. Chen, *Huaxue Shijie*, 1988, **29**(10), 444; *Chem. Abs.*, **110**, 136957.
304 H.L. Yale, US 3886275 (1975); *Chem. Abs.*, **83**, 179138.
305 H.H. Mrozik, US 4001406 (1977); *Chem. Abs.*, **86**, 96016.
306 Y. Morisawa, M. Katoka, K. Kitano and K. Kusano, *Jpn. Kokai*, JP 53021171 (1978); *Chem. Abs.*, **89**, 6238.
307 Agency of Industrial Sciences and Technology, Japan, *Jpn. Kokai*, JP 55141448, JP 55141460 (1980); *Chem. Abs.*, **94**, 121075, 121167.
308 E.E. Gilbert, *Sulfonation and Related Reactions*, Interscience Publishers, New York, 1965.
309 Ajinomoto Co. Inc., *Jpn. Kokai*, JP 59134751 (1984); *Chem. Abs.*, **101**, 210548.
310 N. Sakota, S. Nomura and S. Ito, *Jpn. Kokai*, JP 03024039 (1991); *Chem. Abs.*, **114**, 22873.

311 I.S. Yoffe and S.S. Bravina, *Zh. Obshch. Khim,* 1944, **14**, 968; *Chem. Abs.* **39**, 4597.
312 K. Carpenter, B.J. Heywood, E.W. Parnell, J. Metivier and R. Boesch, US 3823008 (1974); *Chem. Abs.*, **83**, 92404.
313 L. Blangey, H.E. Fierz-David and G. Stamm, *Helv. Chim. Acta*, 1942, **25**, 1162.
314 S. Smiles and J. Stewart, *Org. Synth. Coll. Vol.* 1, Wiley, New York, 1941, 8.
315 R.J. Cremlyn, *An Introduction to Organosulfur Chemistry*, Wiley, Chichester, 1996.
316 B.G. Yasnitskii, *Zh. Obshch. Khim.*, 1956, **26**, 2346; *Chem. Abs.*, **51**, 4985.
317 K. Matsuura, *Jpn. Kokai*, JP 7712697 (1977); *Chem. Abs.*, **86**, 157722.
318 K. Matsuura and H. Ikeda, *Jpn. Kokai*, JP 7712146 (1977); *Chem. Abs.*, **87**, 39114.
319 V.N. Shumov, Z.I. Shramova, B.V. Shemeryankin, V.G. Veronin, N.G. Kuzina, Z.A. Panfilova and A.K. Yudin, *Khim.-Farm. Zh.*, 1977, **11**(6), 95; *Chem. Abs.*, **87**, 134269.
320 M. Badzynski, R. Bardyga, M. Domoradzki, W. Korpal and E. Sobczak, *Pol.*, PL 98199 (1978); *Chem. Abs.*, **91**, 140557.
321 F. Cavagna, T. Grewer, O. Jaenicke and H. Zeininger, *Chem.-Ing.-Tech.*, 1978, **50**(1), 51; *Chem. Abs.*, **88**, 111158.
322 A. Swinarski, A. Grodzicki and J. Glowinska, *Przem. Chem*, 1973, **52** (8), 553; *Chem. Abs.* **80**, 59618; (a) X. Kong, Y. Teng, Z. Zhang and T. Zhang, *Shenyang Huagong Xueyuan Xuebao*, 1998, **12**(2), 117; *Chem. Abs.*, **132**, 139057; (b) L. Gu, *Shanghai Huagong*, 1999, **24(6)**, 26, 30; *Chem. Abs.*, **131**, 117698; (c) W. Wambach, *Ger. Offen.*, DE 19732814 (1999), *Chem. Abs.*, **130**, 126586.
323 R.J. Cremlyn, *J. Chem. Soc. (C)*, 1967, 77.
324 J.P. English, J.H. Clark, J.W. Clapp, D. Seeger and R. Ebel, *J. Am. Chem. Soc.*, 1946, **68**, 453.
325 R.J. Cremlyn and O.O. Shode, *J. Chem. Soc. Pak.*, 1986, **8**, 409.
326 Wakunaga Pharmaceutical Co. Ltd, *Jpn. Kokai*, JP 58162847 (1983); *Chem. Abs.*, **100**, 85428.
327 R.J. Cremlyn and R. Hornby, *J. Chem. Soc. (C)*, 1969, 1341.
328 A. Badawa, A. El-Bayouki and V.R. Zakaria, *Orient. J. Chem.*, 1985, **1**(2), 78; *Chem.Abs.*, **104**, 3315.
329 W. Rauner, R. Fischer, H.P. Korthals, H. Laqua, E. Schlenz, D. Merkel, and L. Zoelch, *Ger. (East)*, DE 222304 (1985); *Chem. Abs.*, **104**, 109213.
330 W.L.F. Armarego, *Aust. J. Chem.*, 1972, **25**(1), 221.
331 D.R. Brittain *et al.*, *Eur.*, EP 469888 (1992); *Chem. Abs.*, **116**, 193931.
332 G.M. Strongin, M.W. Kulikova, N.M. Milova and O.G. Zaitseva, *Khim.-Farm. – Zh.*, 1987, **21**(11), 1374; *Chem. Abs.*, **109**, 37589.
333 O.B. Lavrova and A.K. Shiryaev, *USSR*, SU 1684278 (1991); *Chem. Abs.*, **116**, 214163.
334 R.J. Cremlyn, *J. Chem. Soc.*, 1963, 1329.
335 L.N. Goldyrev and I.Ya. Postovskii, *J. Appl. Chem. (USSR)*, 1938, **11**, 316.
336 R.J. Cremlyn, F.J. Swinbourne, A. Batchelor, R. Honeyman, D. Nash, O. Shode and A. Patel, *Indian J. Chem.*, 1983, **22B**, 1029.
337 R.J. Cremlyn, F.J. Swinbourne, J.G. Bloy, K. Pathak and O.O. Shode, *J. Chem. Soc. Pak.*, 1985, **7**, 111.
338 R.J. Cremlyn, S.D. Lewis and R.J. Nunes, *J. Chem. Soc. Pak.*, 1986, **8**(4), 491.
339 R.J. Cremlyn, F.J. Swinbourne and O.O. Shode, *J. Chem. Soc. Pak.*, 1986, **8**(3), 323.
340 R.J. Cremlyn, F.J. Swinbourne, P. Devlukia and O.O. Shode, *Indian J. Chem.*, 1984, **23B**, 249; *Chem. Abs.*, **101**, 230063.
341 P.E. Cross, B. Gadsby, G.F. Holland and W.M. McLamore, *J. Med. Chem.*, 1978, **21**(9), 845; *Chem. Abs.*, **89**, 122905.
342 G.F. Holland, W.H. Funderburk and K.F. Finger, *J. Med. Chem.*, 1963, **6**, 307.

343 G.W. Evans and B. Milligan, *Aust. J. Chem.*, 1967, **20**, 186.
344 R.J. Cremlyn, D. Leonard and R. Motwani, *J. Chem. Soc. Perkin Trans 1*, 1973, 500.
345 G.E. Chivers, R.J. Cremlyn, R. Guy, R. Honeyman and P. Reynolds, *Aust. J. Chem.*, 1975, **28**, 413.
346 G. Travagli, *Ann. Chim. Farm.*, 1940, 148: *Chem. Abs.*, **37**, 1998.
347 R.J. Cremlyn and R.A. Martin, *Aust. J. Chem.*, 1974, **27**, 435.
348 N. Akhtar, N.V. Badami, R.J. Cremlyn and K.J. Goulding, *Phosphorus Sulfur*, 1977, **3**, 293.
349 R.J. Cremlyn, *Agrochemicals: Preparation and Mode of Action*, Wiley, Chichester, 1991.
350 O. Scherer and G. Horlein, *US*, DE 3660436 (1972); *Chem. Abs.*, **77**, 61640.
351 H. Schweitzer and K. Burr, *Ger.*, DE 532399 (1929); *Chem. Abs.*, **26**, 3262.
352 G.J. Braz, M.V. Lizgunova and A.A. Chemeriskaya, *J. Appl. Chem. (USSR)*, 1946, **19**, 379; *Chem. Abs.*, **41**, 1215.
353 N.V. Badami, R.J. Cremlyn and F.J. Swinbourne, *Aust. J. Chem.*, 1977, **30**, 1793.
354 S.A. Zaidi and Z.A. Siddiqi, *J. Inorg. Nucl. Chem.*, 1975, **37**, 1806; *Chem. Abs.*, **83**, 169151.
355 A.D. Biba, A.A. Rositskii and A.S. Bespalyi, *USSR*, SU 418472 (1974); *Chem. Abs.*, **80**, 133070.
356 R.J. Cremlyn and R. Nunes, *Phosphorus Sulfur*, 1987, **31**, 245.
357 R.J. Cremlyn, F.J. Swinbourne and R. Nunes, *Quim. Nova*, 1984, **7(2)**, 118; *Chem. Abs.*, **105**, 190827.
358 R.J. Cremlyn, F.J. Swinbourne and R. Nunes, *Phosphorus Sulfur*, 1987, **33**.
359 M.M. Kremlev, N.E. Kul'chitskaya, A.D. Biba and V.D. Romanenko, *Ukr. Khim. Zh.*, 1971, **37**(9), 924; *Chem. Abs.*, **77**, 19296.
360 R.J. Cremlyn and R. Nunes, *J. Chem. Soc. Pak.*, 1987, **9**(4), 611; *Chem. Abs.*, **109**, 190165.
361 R.J. Cremlyn and R. Nunes, *Gazz. Chim. Ital.*, 1987, **117**, 183.
362 R.J. Cremlyn, F.J. Swinbourne and R. Nunes, *Quim. Nova*, 1985, **8**(1), 61; *Chem. Abs.*, **108**, 5636.
363 R. D'Costa and V.V. Nadkarny, *J. Indian Chem. Soc.*, 1975, **52**, 333.
364 Y. Tsuruta, Y. Date and K. Kohashi, *J. Chromatogr.*, 1990, **502**(1), 178; *Chem. Abs.*, **112**, 175025.
365 I.A. Pearl, *J. Org. Chem.*, 1945, **10**, 205.
366 R.J. Cremlyn, *J. Chem. Soc., Supplement* 2, 1964, 6235.
367 J.K. Lin and S.S. Wu, *J. Chin. Biochim. Soc.*, 1985, **14**(1), 10; *Chem. Abs.*, **106**, 175877.
368 J. Yamamoto, H. Kunikata and M. Umezu, *Nippon Kagaku Kaishi*, 1983, 78; *Chem. Abs.*, **98**, 178840.
369 J. Yamamoto, K. Kagehi, H. Aimi, N. Hamada and M. Umezu, *Tottori Daigaku Kogakuku Kenkyn Hokoku*, 1976, **6**(1), 64; *Chem. Abs.*, **86**, 29218.
370 J. Yamamoto, *Yuki Gosei Kagaku Kyokai Shi*, 1973; **31**(7), 605; *Chem. Abs.*, **79**, 145722.
371 G.G. Furin, O.I. Andreevskaya, A.I. Rezvukhin and G.G. Yakabson, *J. Fluorine Chem.*, 1985, **28**(1), 1; *Chem. Abs.*, **103**, 159925.
372 T. Kitamura, K. Nagata, T. Nakamura, R. Furuki and H. Taniguchi, *Tetrahedron*, 1995, **51**(22), 6229.
373 R.J. Cremlyn, F.J. Swinbourne, S. Graham, J.A.S. Cavaleiro, F.J. Domingues and M. Dias, *Phosphorus Sulfur Silicon*, 1991, **60**, 57.
374 R.J. Cremlyn, unpublished observations, University of Hertfordshire, 1991.

375 J.-P. Dulcare, M. Tawil and M. Santelli, *J. Org. Chem.*, 1990, **55**(2), 571.
376 D. Dieterich, *Ger.*, DE 2855938 (1980); *Chem. Abs.*, **93**, 151099.
377 T. Bieber, *J. Am. Chem. Soc.*, 1953, **75**, 1405.
378 G. Buettner and E. Klauke, *Ger. Offen.*, DE 2238340 (1972); *Chem. Abs.*, **80**, 120541.
379 V. Weinmayr, *J. Am. Chem. Soc.*, 1955, **77**, 3009.
380 G.R. Knox and P.L. Pauson, *J. Chem. Soc.*, 1958, 692.
381 D.W. Slocum and W. Achermann, *Synth. React. Inorg-Met.-Org. Chem.*, 1982, **12**(4), 397; *Chem. Abs.*, **97**, 72525.
382 N. Nesmeyanov and O.A. Reutov, *Inv. Acad. Nauk. SSSR, Ser. Khim*, 1959, 926; *Chem. Abs.*, **54**, 469.
383 S. Higeta and K. Maruyama, *Jpn. Kokai*, JP 60174762 (1985); *Chem. Abs.*, **104**, 33856.
384 V. Bažant, V. Chvalovský and J. Rathouský, *Organosilicon Compounds*, Academic Press, New York, 1965, 291; (a) M. Birot, J. Dunogues, N. Duffaut, R. Calas and M. Lefore, *Bull. Soc. Chim. Fr.*, 1978, 11–12, Pt. 1,442.
385 R. Calas and P. Bourgeois, *C.R. Acad. Sci. Ser. C*, 1969, **268**, 1525; *Chem. Abs.*, **71**, 49176.
386 M. Grignon-Dubois, J. Dunogues and R. Calas, *Tetrahedron Lett.*, 1976, 1197.
387 P. Bourgeois, G. Merault, N. Duffaut and R. Calas, *J. Organomet. Chem.*, 1973, **59**, 145.
388 M. Grignon-Dubois, J.P. Pillot, J. Dunogues, N. Duffaut, R. Calas and B. Henner, *J. Organomet. Chem.*, 1977, **124**, 135.
389 P. Bourgeois, R. Calas and G. Merault, *J. Organomet. Chem.*, 1977, **141**, 23.
390 M. Bordeau, S.M. Djamei and J. Dunogues, *Bull. Soc. Chim. Fr.*, 1986, **3**, 413; *Chem. Abs.*, **106**, 156551.
391 F. Kanetani, E. Okada and K. Negoro, *Bull. Chem. Soc. Jpn.*, 1986, **59**(8), 2517; *Chem. Abs.*, **107**, 59083.
392 K. Hofmann and G. Simchen, *Liebigs Ann. Chem.*, 1982, **2**, 282; *Chem. Abs.*, **96**, 142, 944.
393 V. Vaisarova and J. Hetflejs, *Czech.*, CS 225073 (1983); *Chem. Abs.*, **105**, 205780.
394 E.J. Panek, T.M. Schmitt, P. Davis and J.S. Ku, US 4575559 (1986); *Chem. Abs.*, **105**, 205780.
395 M. Miura and M. Nojima, *J. Chem. Soc. Chem. Commun.*, 1979, 467.
396 M. Miura and M. Nojima, *J. Am. Chem. Soc.*, 1980, **102**(1), 288.
397 M. Miura, M. Nojima and S. Kusabayashi, *J. Chem. Soc. Perkins Trans. 1*, 1980, 2909.
398 M. Miura, A. Ikegami, M. Nojima and S. Kusabayashi, *J. Chem. Soc. Chem. Commun.*, 1980, **24**, 1279.
399 M. Miura, M. Nojima, S. Kusabayashi and S. Nagase, *J. Am. Chem. Soc.*, 1981, **103**(7), 1789.
400 M. Miura, A. Ikegami, M. Nojima, S. Kusabayashi, K. McCullough and S. Nagase, *J. Am. Chem. Soc.*, 1983, **105**(8), 2414.
401 M. Muira, M. Nojima and S. Kusabayashi, *J. Chem. Soc. Chem. Commun.*, 1981, **12**, 581.
402 I. Galpin, G.W. Kenner and A. Marston, *Bioorg. Chem.*, 1979, **8**(3), 323; *Chem. Abs.*, **92**, 129297.
403 V.G. Gruzdev and G.V. Gruzdev, *Zh. Obshch. Khim.*, 1986, **56**(8), 1872; *Chem. Abs.*, **107**, 175796.
404 L.N. Markovskii, D.M. Rudkevich and V.I. Kal'chenko, *J. Org. Chem. (USSR)* (Engl. Transl.), 1989, **25**(3), 1803; *Chem. Abs.*, **112**, 216892.
405 S.N. Bhattacharya, P. Raj and I. Hussain, *Indian J. Chem., Sect. A*, 1978, **16A**(12), 1108; *Chem. Abs.*, **91**, 57130.

406 E. Schmitz, R. Ohme and D. Murawski, *Chem. Ber.*, 1965, **98**, 2516.
407 M.A. Abou-Gharbia and M.M. Joullie, *Org. Prep. Proced. Int.*, 1979, **11**(2), 95.
408 L.T. Eremenko and G.V. Oreshko, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 1982, **1**, 222; *Chem. Abs.*, **96**, 142209.
409 R.G. Feasey and J.B. Rose, *Ger. Offen.*, DE 2135532 (1972); *Chem. Abs.*, **76**, 72260.
410 M. Haupschein and M. Braid, *J. Am. Chem. Soc.*, 1961, **83**, 2500.
411 J. Pirkl, *Czech.*, CS 117041 (1965); *Chem. Abs.*, **65**, 13737.
412 A.M. El-Naggar, F.A. Kora and R.A. El-Sayed, *J. Serb. Chem. Soc.*, 1986, **51(9–10)**, 441.
413 F.A. Kora, M.E. Hussain and R.A. El-Sayed, *Polish J. Chem.*, 1988, **62**, 749; *Chem. Abs.*, **112**, 179846.
414 R.A. El-Sayed, *J. Serb. Chem. Soc.*, 1991, **56**(6), 311; *Chem. Abs.*, **115**, 208506.
415 R.A. El-Sayed, N.S. Khalaf, F.A. Kora and M.F. Badie, *J. Chem. Soc. Pak.*, 1992, **14**(1), 49.
416 R.A. El-Sayed, *Phosphorus, Sulfur, Silicon*, 1997, **131**, 207.
417 R.A. El-Sayed, *J. Serb. Chem. Soc.*, 1998, **63**(8), 601.
418 R.A. El-Sayed, N.S. Khalaf, M. Gazzar and F.A. Kora, *J. Indian Chem. Soc.*, 1992, **69**, 558.
419 R.A. El-Sayed, *J. Serb. Chem. Soc.*, 1998, **63**(8), 607.
420 R.A. El-Sayed, *Chem. Heterocycl. Comp.*, (Eng. Transl.), 1998, **34**(7), 796.

CHAPTER 5

The Reaction of Chlorosulfonic Acid with Aliphatic Compounds

The early work on the sulfonation of aliphatic compounds is described in Suter's book;[1] there are also several general references[2-6] which include the use of chlorosulfonic acid in the sulfonation of aliphatic compounds. Aliphatic compounds are generally less reactive towards sulfonating reagents than aromatic species, because they are less nucleophilic in character and so are less susceptible to attack by an electrophilic reagent like chlorosulfonic acid.

1 Hydrocarbons

Saturated aliphatic hydrocarbons (alkanes) generally do not react with chlorosulfonic acid, although the more nucleophilic unsaturated hydrocarbons (alkenes and alkynes) are often reactive and may sometimes be directly sulfonated by the reagent.

1.1 Alkanes

The direct sulfonation of alkanes is not generally of much practical significance as a synthetic route to alkanesulfonic acids as these are usually more conveniently obtained indirectly by reaction of the appropriate alkyl halide with sodium sulfite or hydrosulfite.[7]

Alkanes are easily oxidised by sulfur trioxide, oleum and chlorosulfonic acid; consequently, attempted sulfonation of an n-alkane by such reagents generally leads to a complex mixture of products and the yields of the alkanesulfonic acids are very low.[1,2,5] Chlorosulfonic acid has, however, proved useful for sulfonating low pressure polyethylene film.[2] The ease of replacement of the hydrogen atoms of an alkane by the sulfonic acid group follows the order;

$$\text{tertiary H} > \text{secondary H} > \text{primary H}$$

consequently, tertiary alkanes may be directly sulfonated under the appropriate

conditions. For instance, 2-methylpropane or tertiary butane **1** is readily converted into the sulfonic acid **2** by treatment with sulfur trioxide or chlorosulfonic acid in cold chloroform (Equation 1).

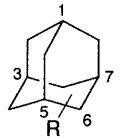
$$\underset{\mathbf{1}}{Me_3C{-}H} \xrightarrow[CHCl_3]{ClSO_3H \text{ or } SO_3} \underset{\mathbf{2}}{Me_3C{-}SO_3H} \qquad (1)$$

Chlorosulfonic acid generally reacts relatively fast in the cold with branched chain alkanes, such as 2-methyl- and 2,4-dimethylbutane, but reaction is only very slow with straight chain n-alkanes. The difference in reactivity has been utilized in the production of pure straight chain hydrocarbons from petroleum.[8,9]

The branched chain alkanes yield water-soluble sulfonic acids which can be extracted from the mixture by water treatment leaving the insoluble n-alkanes behind. The reported explosion which occurred on mixing chlorosulfonic acid with n-hexane[10] is probably associated with trace impurities of water and alkenes, both of which react vigorously with the reagent.[11] Synthetic detergents have been manufactured by direct sulfonation of a dearomatised, desulfurised kerosene from petroleum distillates with chlorosulfonic acid using ethyl and butyl acetate as two separate solvent systems.[12]

Alkanes (C_1–C_5) can be polymerized by treatment with a combination of a strong Lewis acid and a strong Brønsted acid. For example, n-pentane, by reaction with a mixture of chlorosulfonic acid and antimony pentafluoride at 30 °C (18 hours), gave oligomeric branched poly-n-pentane.[13] Some of the polymers derived from the lower alkanes were useful as petrol additives.[13]

Treatment of the hydrocarbon adamantane (**3**; R = H) with chlorosulfonic acid provides a new method for the preparation of polychloroadamantanes.[14,15] The reaction of adamantane with excess chlorosulfonic acid (8–10 equivalents) may yield either mono-, di- or trichloroadamantanes depending on both the reaction time and the relative amount of reagent used. It was also found that the maximum yield of the 1-chloride **3**, 61% was obtained by using four equivalents of chlorosulfonic acid at 20 °C for 1 hour.[15]



3 R = 1-Cl
4 R = 1,3-Cl_2
5 R = 1,3,5-Cl_3
6 R = 1,3,6-Cl_3
7 R = 1,3,5,7-Cl_4

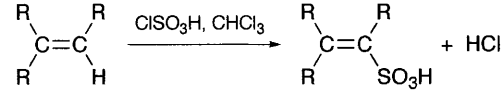
When the reaction was allowed to continue for 100 hours, it gave the 1,3-dichloride **4**, 90%. When the ratio of chlorosulfonic acid to adamantane was further increased, the reaction yields a mixture of the 1,3,5- and 1,3,6-trichloroadamantanes **5** and **6**; the use of eight equivalents of the reagent afforded the maximum yield of 1,3,6-trichloroadamantane. 1,3,5,7-Tetrachloroadamantane

7 was prepared by heating the 1,3,5-trichloro derivative **5** with chlorosulfonic acid at 50 °C.

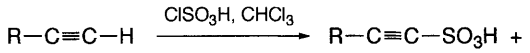
Alkanedisulfonic acids are prepared by heating an alkanesulfonic acid with chlorosulfonic acid at 70–160 °C in the presence of air (oxygen), optionally over an activated charcoal catalyst. Methanesulfonic acid reacted with chlorosulfonic acid at 100 °C (1 hour) to give a mixture containing methanedisulfonic acid (34%).[16] (For further details see Chapter 9 p 267.)

1.2 Alkenes and Alkynes

The enhanced electron density of unsaturated aliphatic hydrocarbons (alkenes and alkynes) allows them to be directly sulfonated on the terminal carbon atom by the action of chlorosulfonic acid[6] (Equations 2 and 3).



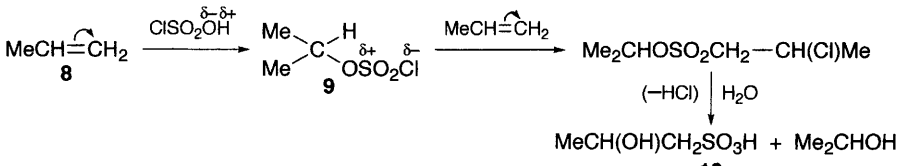
(2)



(3)

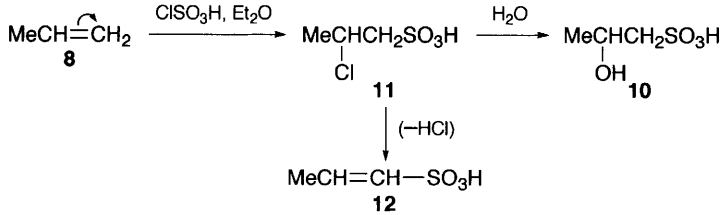
In alkenes, it is the vinylic hydrogen atom that is replaced by the sulfonic acid group. Bakker and Cerfontain[16a] recently studied the sulfonation of alkenes by chlorosulfonic acid, acetyl sulfate and trifluoroacetyl sulfate. Linear alkenes reacted with chlorosulfonic acid in deuterochloroform as solvent at −40 °C to give the corresponding sec-alkyl chlorosulfonates, after initial protonation of the alkene by the strongly acidic reagent. On the other hand, chlorosulfonic acid in the presence of 1,4-dioxan as solvent reacted differently with alkenes, since the reagent is now in the form of the oxonium complex. Under these conditions, the reaction gives corresponding *β*-sultones, *via* a *syn* cycloaddition of sulfur trioxide across the alkenic double bond. Thus, cyclopentene with chlorosulfonic acid (1.1 equivalents) in dioxan (2.2 equivalents) and deuterochloroform at 0 °C afforded a quantitative yield of 1,2-cyclopentane sultone.[16a]

2-Pentene reacts with chlorosulfonic acid (one equivalent) in chloroform solution at 0–5 °C to give a mixture of the 2- and 3-sulfonic acids (80 and 20% respectively),[17] indicating that preferential attack occurs at the most nucleophilic carbon atom. Chlorosulfonic acid in a non-polar solvent may also react with alkenes, *e.g.* propene **8**, by addition to give the chlorosulfonate ester **9**; such esters, however, react further with alkenes so the overall reaction is as shown (Scheme 1).



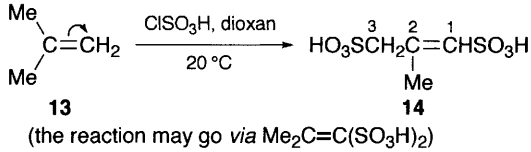
Scheme 1

The final isolated product, after the aqueous work-up procedure, was 2-hydroxypropanesulfonic acid **10**.[2] Many industrial studies used chlorosulfonic acid in diethyl ether; the complex is prepared by dropwise addition of chlorosulfonic acid to diethyl ether at 0 °C. Under these conditions, the initial product of the reaction of propene **8** with chlorosulfonic acid in diethyl ether is probably the chlorinated sulfonic acid **11**. The chlorine atom in this compound is very reactive and consequently the isolated products are generally the alkenesulfonic acid **12** or the hydroxysulfonic acid **10** (Scheme 2).[2]



Scheme 2

2-Methylpropene (isobutene, **13**) by treatment with chlorosulfonic acid in dioxan at 20 °C afforded 2-methylpropene-1,3-disulfonic acid **14** (Equation 4).[18] The disulfonic acid **14** precipitated out from the reaction mixture as the dioxan salt; this compound may arise from rearrangement of the sterically unfavourable 2-methylpropene-1,1-disulfonic acid (Equation 4).



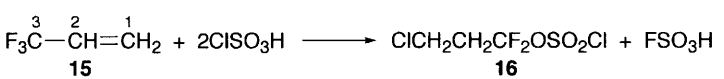
(4)

(the reaction may go *via* $Me_2C{=}C(SO_3H)_2$)

Treatment of long chain alkenes containing at least eight carbon atoms and one double bond, *e.g.* 1-hexadecene, with chlorosulfonic acid and then with 20% sodium hydroxide, yielded useful wetting/cleansing agents.[19]

The reaction of chlorosulfonic acid with alkenes may be affected by attached groups, *e.g.* electron-withdrawing halogen and carboxylic acid moieties.

The electrophilic addition of chlorosulfonic acid to 3,3,3-trifluoropropene **15** was found to yield mainly 3-chloro-1,1-difluorochlorosulfonate **16** (Equation 5).[20]

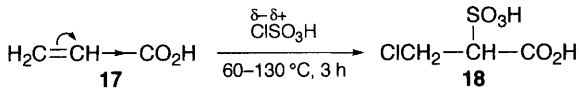


(5)

The addition is facilitated by polarization of the alkenic double bond by the powerful electron-withdrawing (–I) effect of the attached trifluoromethyl group and the reaction probably occurs *via* the 1,1-difluoroallylic cation with solvent-assisted ionization of the initial step.[20]

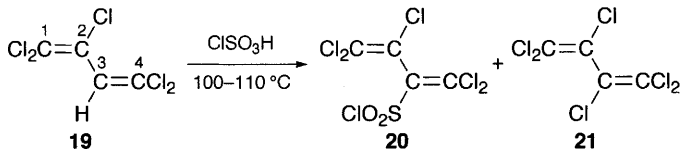
The attachment of a carboxylic acid group to an alkenic double bond also increases the degree of polarization of the double bond and consequently

chlorosulfonic acid adds to acrylic acid **17** to give 3-chloro-2-sulfopropionic acid **18** (Equation 6).[21]



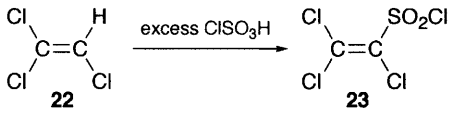
(6)

1,1,2,4,4-Pentachloro-1,3-butadiene **19** by heating with excess chlorosulfonic acid at 100–110 °C gave a mixture of the 3-sulfonyl chloride **20**, 30% and hexachlorobutadiene **21**, 16% (Equation 7).[22] The products presumably result from chlorosulfonation and chlorination respectively of the reactive 3-alkenic hydrogen atom by the reagent.

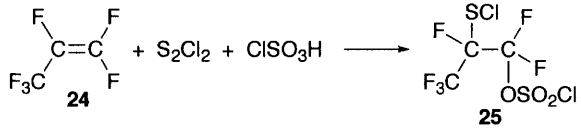


(7)

In a similar type of reaction, 1,1,2-trichloroethene or dichlorovinyl chloride **22** reacts with chlorosulfonic acid to give the trichlorovinylsulfonyl chloride **23** (Equation 8).[23] In this reaction, the reactive alkenic hydrogen atom is again chlorosulfonated by the reagent.



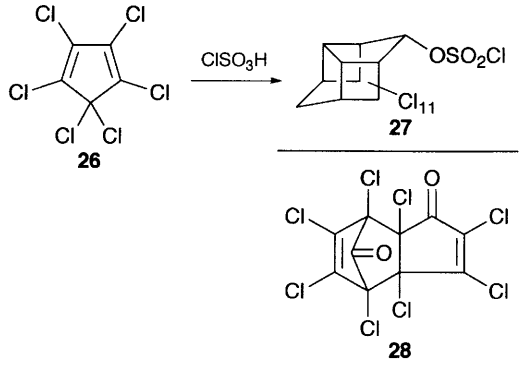
(8)



(9)

Hexafluoropropene **24** reacts with sulfur chlorides, *e.g.* sulfur monochloride, in the presence of chlorosulfonic acid to form the adduct **25** (Equation 9).[24] The reaction involves the co-addition of both reagents across the polarized alkenic double bond.

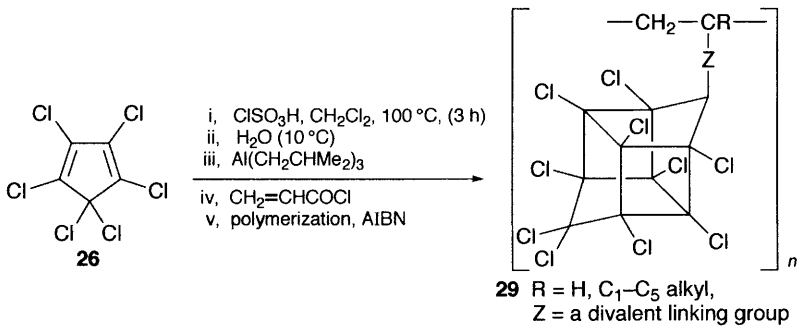
Hexachlorocyclopentadiene **26** reacts with chlorosulfonic acid to give undeca-chloropentacyclodecyl chlorosulfonate ester **27** (Equation 10).[25]



(10)

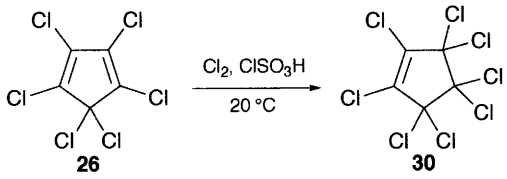
The structure of the product **27** was confirmed by X-ray crystallographic analysis and a mechanism for its formation proposed.[24] The product was definitely not the indene-1,8-dione **28** previously claimed by McBee and Newcomer[26,27] although the reaction was performed following their experimental conditions.

More recently,[28] polymers containing decachlorocyclodecyl groups **29** have been synthesised by sequential treatment of hexachlorocyclopentadiene **26** with chlorosulfonic acid, isobutyl aluminium hydride and acryloyl chloride followed by polymerization of the resultant acrylate ester in the presence of AIBN as catalyst (Equation 11). The polymers possess high refractive indexes and are used in the manufacture of plastic optical materials.[28] The first step of the sequence probably involves formation of the chlorosulfonate ester as shown in Equation 10 (see Section 2, p 153).



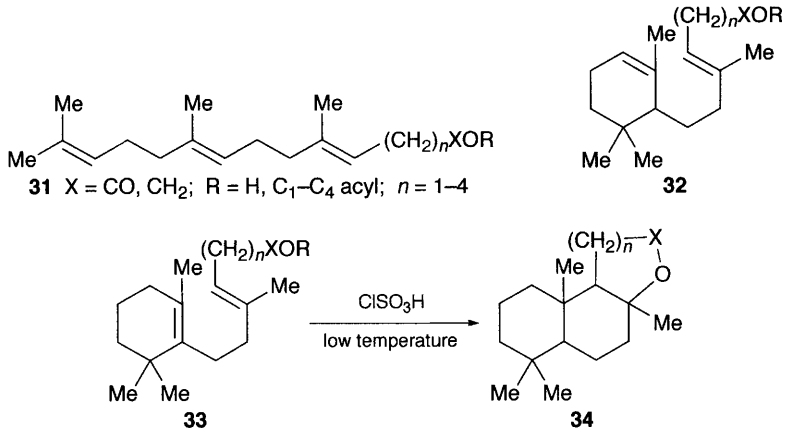
(11)

Hexachlorocyclopentadiene **26** can be chlorinated to octachlorocyclopentadiene **30** (Equation 12). The transformation is achieved by passing chlorine gas into a solution of the diene **26** in chlorosulfonic acid at *ca.* 20 °C for 5 hours.[29] When the reaction mixture was cooled (10 °C), octachlorocyclopentadiene **30** precipitated out; this procedure provides a useful synthetic route to perchlorinated cyclopentenes.



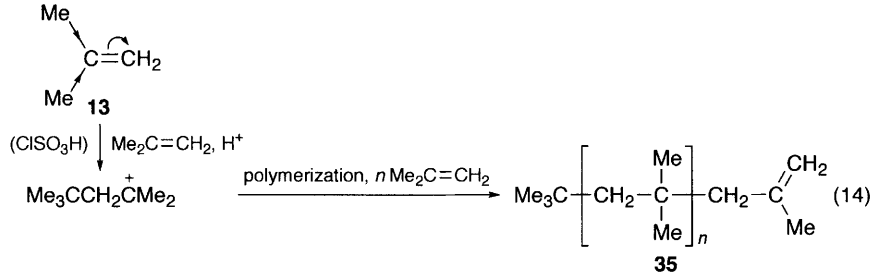
26 **30** (12)

Alkatriene derivatives **31** and the cyclohexenes **32** and **33** reacted with chlorosulfonic acid at controlled temperatures to give the cyclic terpenes **34** which are useful as perfumes (Equation 13).[30]



(13)

Alkenes may be polymerized in the presence of strongly acidic reagents as catalysts, *e.g.* sulfuric or chlorosulfonic acid. Ethene is not polymerized by this procedure, but it works well with alkenes containing electron donor groups, such as isobutene **13** which, under the appropriate conditions, yields polyisobutene **35** (Equation 14).



(14)

Chlorosulfonic acid may also be used to chlorosulfonate certain polymers which may increase branching and cross linking of the polymer chains and possibly enhance some useful physical properties of the polymer.[2] The chlorosulfonation of polymers is, therefore, of considerable industrial significance (see Chapter 8, p 247).

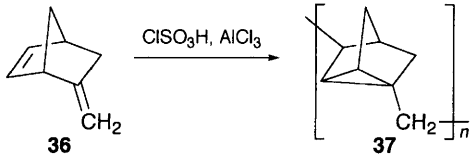
Polymerization catalysts containing titanium chloride and chlorosulfonic acid in hexane have shown high activity for the polymerization of propene to isotactic

polypropene.[31] The method can also be successfully applied to the copolymerization of propene and α-alkenes.

Polyethene has been reacted with chlorosulfonic acid to form products containing SO_3, OSO_3, Cl, OH, CO and CO_2 groups and double bonds which form cross-linking bridges and promote the entrance of further groups. The sulfur content of the products is dependent on the reaction temperature, the gel formation and the quantity of chlorosulfonic acid. The products were useful as cation-exchange polymers.[32,33]

Polyvinyl fluoride (PVF) has been sulfonated by treatment of PVF films with chlorosulfonic acid. These materials provide new types of polymer-based proton conductors and the state of water in sulfonated PVF membranes has been studied by FTIR spectroscopy.[34]

5-Methylenebicyclo[2.2.1]hept-2-ene **36**, by treatment with a mixture of chlorosulfonic acid and aluminium chloride as catalyst, suffered cationic polymerization to yield the polymer **37** (Equation 15).[35] In this reaction, chlorosulfonic acid or aluminium chloride alone is not an effective catalyst.

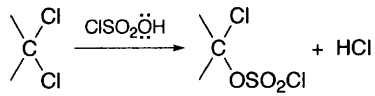


36 **37** (15)

2 Alkyl Halides

In reactions, chlorosulfonic acid is often employed as a solution in halogenated solvents. It dissolves readily in such solvents, provided that they contain hydrogen, *e.g.* chloroform, dichloromethane, 1,2-dichloro- or tetrachloroethane. On the other hand, the reagent is only sparingly soluble in halogenated solvents without hydrogen, *e.g.* carbon tetrachloride or tetrachloroethene.

Halogenated solvents may be successfully used for reactions with chlorosulfonic acid, provided that the substrate is more reactive than the solvent under the experimental conditions (see Chapter 4, p 47). However, under forcing conditions, alkyl halides can react with the reagent; the reaction involving replacement of one or more halogen atoms by the chlorosulfonate group.[2] The process occurs especially in compounds containing the dichloromethylene ($Cl_2C=$) group and is depicted in Equation 16.



(16)

With hexachlorocyclopentadiene, the initially formed chlorosulfonate ester may react further to give undecacyclopentacyclodecyl chlorosulfonate, as described in Section 1, p 150.

In another example, perfluorocarbon iodides react with a large excess of chlorosulfonic acid (10 equivalents) under forcing conditions, namely prolonged heating under pressure, to give the corresponding perfluorocarbon chlorosulfonates as the major product together with some of the perfluorocarbon chloride.[2,36] Thus, 1-iodoperfluoropropane **38**, by heating with the reagent at 130 °C for 65 hours, afforded a good yield of the chlorosulfonate **39**, 89% and the chloride **40**, 11% (Equation 17). The minor product **40** is probably formed by chlorination of the chlorosulfonate **39** since the relative yield of the chloride **40** increases with the reaction temperature.

$$\underset{\mathbf{38}}{F_3C{-}CF_2{-}CF_2{-}I} \xrightarrow[130\ ^\circ C]{10ClSO_3H} \underset{\mathbf{39}}{F_3C(CF_2)_2OSO_2Cl} + \underset{\mathbf{40}}{F_3C(CF_2)_2Cl} + [HI] \qquad (17)$$

In the reaction shown in Equation 17, other products include sulfur dioxide, crystalline iodine and iodine chlorides resulting from the side reactions shown in Scheme 3.

$$ClSO_3H \rightleftharpoons SO_3 + HCl$$
$$2HI + SO_3 \longrightarrow I_2 + H_2O + SO_2$$
$$I_2 \xrightarrow{ClSO_3H} ICl + ICl_3 + \text{other products}$$

Scheme 3

The reaction with chlorosulfonic acid has been successfully extended to the telomer iodides **41**, which, by heating with excess chlorosulfonic acid yield the corresponding chlorosulfonates **42** (Equation 18).[36]

It has been discovered that chlorosulfonic acid is much more reactive towards substrates containing a CH_2CF_2I group, as compared with the analogous perfluorinated compounds, and these reactions often proceed at low temperatures as illustrated by the conversion of compound **43**→**44** (Equation 19).

$$\underset{\mathbf{41}}{F_3C(CF_2)_2{-}[CF_2{\cdot}\underset{CF_3}{CF}{-}]_n{-}[CF_2CF_2]_mI} \xrightarrow[150\ ^\circ C,\ 17\ h]{ClSO_3H} \underset{\mathbf{42}}{C_3F_7[CF_2\underset{CF_3}{CF}{-}]_n{-}[CF_2CF_2]_mOSO_2Cl} \qquad (18)$$

$$\underset{\mathbf{43}}{C_2F_5\underset{CF_3}{CF}(CH_2CF_2)_3I} + ClSO_3H \xrightarrow{0\ ^\circ C} \underset{\mathbf{44}}{C_2F_5\underset{CF_3}{CF}(CH_2CF_2)_3OSO_2Cl} + [HI] \qquad (19)$$

The fluorocarbon chlorosulfonates represent a new class of compound and are useful intermediates in the synthesis of fluorocarbon carboxylic acids and derivatives.[36]

3 Aliphatic Alcohols

Alcohols, like phenols, suffer *O*-sulfonation, but phenols also undergo *C*-sulfonation on the aromatic nucleus (see Chapter 4, p 61). Chlorosulfonic acid is

a valuable reagent for the sulfation (*O*-sulfonation) of alcohols;[1–3,5] the reaction yields the corresponding alkyl hydrogen sulfate **45** (Equation 20). The reagent was first introduced by Claesson[1,37] in 1879 for the preparation of methyl and ethyl hydrogen sulfates. In the reaction, the hydrogen sulfates are formed at low temperatures, −5 to −80 °C; at higher temperatures other products, *e.g.* alkenes, dialkyl sulfates and ethers, may become significant.[3]

$$ROH + ClSO_3H \longrightarrow \underset{\mathbf{45}}{ROSO_3H} + HCl \qquad (20)$$

Chlorosulfonic acid is generally the favoured reagent for the sulfation of alcohols; the reaction is rapid, complete, goes at low temperatures and yields a good quality product. With liquid alcohols, no solvent is necessary, but when using solid alcohols, the sulfation may be performed in suitable solvents, for instance, chloroform, carbon tetrachloride or tetrachloroethane, at temperatures usually in the range of −10 to 30 °C.[2] The use of the appropriate solvent may reduce the formation of byproducts.

The procedure can be used for the sulfation of long chain alcohols, including those containing functional groups, *e.g.* amide, ester, ether and nitro groups. Alkyl sulfates were made by treatment of higher primary aliphatic alcohols with a slight excess of the reagent (1.01–1.02 equivalents) in a suitable solvent.[38] The sulfation may also be carried out in the presence of an added organosilicon compound, *e.g.* polymethylsiloxane (0.05–0.25%).[39] Chlorosulfonic acid is also effective in the sulfation of long chain secondary alcohols, whereas the use of sulfur trioxide causes extensive dehydration.[2]

The chlorosulfonic acid–ether complex[4] is a milder reagent than free chlorosulfonic acid for the sulfation of alcohols and is outstanding in respect of yield and purity of the alkyl hydrogen sulfates **45** produced. The use of chlorosulfonic acid in diethyl ether at low temperature (−50 °C) is a standard method for sulfation of higher (C_8–C_{28}) primary and secondary alcohols.[40] The latter have also been successfully sulfated using a mixture of chlorosulfonic acid in acetic acid; the active entity here is probably acetyl sulfate.[2] This method has been adapted for the synthesis of very pure sodium alkyl sulfates for use as detergents; thus chlorosulfonic acid and 1-dodecanol were successively added to acetic acid at low temperature (−10 to −15 °C), the solid product was neutralized with sodium carbonate and unreacted alcohols extracted with solvents to give 98.6% pure dodecanyl sodium sulfate.[41]

The sulfation of higher alcohols, ethoxyalcohols and acid amides by chlorosulfonic acid and sulfur trioxide has been examined under various reaction conditions in an effort to optimize the manufacture of foam detergents.[42]

The batchwise sulfation of alcohols by chlorosulfonic acid may be effected by gradual addition of the reagent to the alcohol at *ca.* 30 °C, often in the presence of chloroform (25–35% by weight) as solvent. The process is performed in special steel or glass-lined reactors to avoid corrosion by the evolved hydrogen chloride gas. The continuous sulfation of higher alcohols, *e.g.* dobanol 23, has also been effected by reaction with chlorosulfonic acid in the presence of nitrogen

gas using a high speed gas flow.[43] Other procedures employ liquid sulfur dioxide as the solvent which adiabatically reduces the heat of reaction by vaporization; the process may also be carried out *in vacuo* which removes the hydrogen chloride, reduces corrosion and yields a purer product.[1]

In the laboratory, linear primary (C_{12}–C_{16}) alcohols are conveniently sulfated with chlorosulfonic acid. The effect of various experimental conditions, namely reagent, alcohol ratio, reaction rate and temperature, were assessed.[44] The sulfation of higher alkanols, *e.g.* dodecyl alcohol or secondary alcohols may be achieved on an industrial scale by stirring the alcohol with chlorosulfonic acid (one equivalent) using a special reactor.[45] However, in the large scale manufacture of detergents by the sulfation of higher alcohols, sulfur trioxide is now generally the preferred sulfating reagent (see Chapter 8, p 242).

Cyclic alcohols are sulfated by reaction with chlorosulfonic acid or pyridine–sulfur trioxide complex. The former reagent, in the presence of *N,N*-dimethylaniline in chloroform at −12 to 20 °C, converted cyclohexanol into sodium cyclohexyl sulfate after neutralization with aqueous sodium hydroxide.[46] The latter reagent was successfully applied to the sulfation of sterols, namely cholesterol, ergosterol and lanosterol;[47] however, later studies (see p 158) showed that chlorosulfonic acid could also be used.

3.1 Glycols

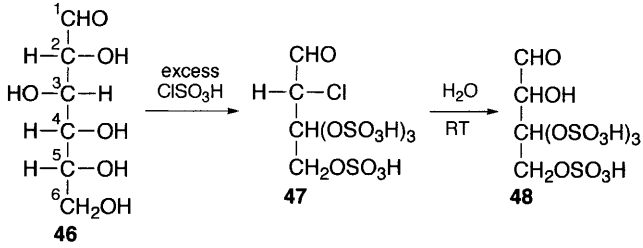
Ethylene glycol reacts with chlorosulfonic acid (one equivalent) to give the monohydrogen sulfate, while the use of an excess of the reagent affords the dihydrogen sulfate.[1] Propylene glycol reacts similarly with excess chlorosulfonic acid in dichloromethane at 10 °C to yield the dihydrogen sulfate.[48] The action of excess reagent on glycerol (propane-1,2,3-triol) at 0 °C esterifies all three hydroxyl groups to give glyceryl trihydrogen sulfate. The action of water on the product readily removed two of the sulfate groups yielding the 2-monohydrogen sulfate which was relatively stable towards hydrolysis.[1] In contrast, when glycerol was heated with chlorosulfonic acid at 100–170 °C, the product was a glyptal resin.[3] Treatment of erythritol (butane-1,2,3,4-tetrol) with chlorosulfonic acid afforded a mixture of the mono- and tetrahydrogen sulfates.[1]

3.2 Carbohydrates

Carbohydrates can be sulfated by treatment with chlorosulfonic acid, but with such polyhydroxy compounds, the reaction often yields a complex mixture of sulfates. However, in some cases, the use of an equimolar quantity of the reagent in chloroform or pyridine solution at low temperature may result in monosulfation, since the primary hydroxyl groups are more readily sulfated.[2] This is generally more effectively achieved by the use of a suitably blocked carbohydrate, *e.g.* isopropylidene derivatives, in the sulfation reaction.[2,49]

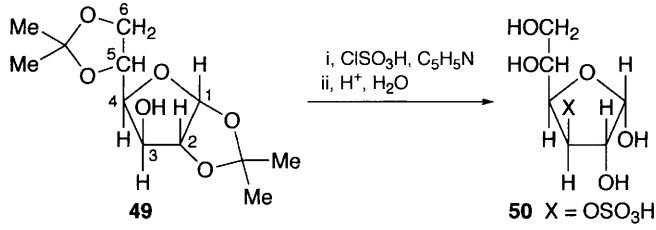
D-Glucose **46** reacted with excess chlorosulfonic acid to give the α-chloroglucose derivative **47**, which with water afforded glucose tetrahydrogen sulfate **48** by hydrolysis of the chloro group (Equation 21).[1] The chloroglucose derivative **47**

has also been obtained by reaction of excess chlorosulfonic acid on dextrin, starch and cellulose.[1]



(21)

Monosaccharide sulfates are conveniently prepared by treatment of a solution of the selectively blocked sugar derivative in pyridine with chlorosulfonic acid.[2,49] For example, 1,2:5,6-di *O*-isopropylidene D-glucofuranose **49**, by reaction with the reagent in pyridine, afforded the corresponding sulfate. The latter, by mild acid hydrolysis (selective removal of the isopropylidene groups) gave a good yield of glucose-3-sulfate **50** (Equation 22).

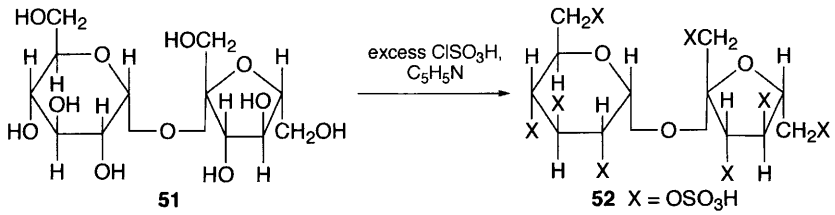


(22)

Sodium alkyl glucoside sulfates containing 10–14 carbon atoms are useful surfactants in shampoos. They were prepared by stirring the appropriate α,β-glucoside with chlorosulfonic acid in chloroform at 15 °C for 1 hour, followed by neutralization with aqueous sodium hydrogen carbonate.[50]

The monosaccharides glucose and galactose both reacted with excess chlorosulfonic acid in pyridine to give a mixture of the mono-, di-, tri- and tetrahydrogen sulfates.[1]

Later work[51] showed that the disaccharide sucrose **51** by treatment with chlorosulfonic acid in pyridine or 2-picoline afforded the octasulfate **52** in which all eight hydroxyl groups have been esterified (Equation 23). The product **52** was subsequently converted into glucose octasulfate basic aluminium complex which is used in the treatment of ulcers and wounds.[51]



(23)

Carbohydrate sulfates are important in polysaccharide chemistry as several sulfated polysaccharides occur naturally in seaweeds, and human tissue contains heparin, the blood anticoagulating agent, a sulfated polysaccharide which also contains *N*-sulfate groups.[49,52] Sulfation of polysaccharides by chlorosulfonic acid–pyridine leads to the incorporation of pyridinium substituents on a proportion of the reducing end groups.[53]

Sulfation of jute cellulose with chlorosulfonic acid in pyridine at 30 °C gave partially water-soluble cellulose sulfate with a degree of substitution of 1.56.[54] Water-soluble sodium cellulose sulfates containing 1–3 sulfate groups were prepared by treatment of cellulose with the reagent in pyridine followed by reaction with sodium carbonate.[55]

Hydroxyethyl starch sulfates are obtained by reaction with chlorosulfonic acid in pyridine which can be converted into metal salts, *e.g.* the sodium salt, by reaction with sodium carbonate; these salts are useful as pharmaceutical diluents.[56]

Sulfonated organic polyhydroxysilanes, useful in cosmetic preparations, are made by sulfation of the hydroxyalkyl groups with chlorosulfonic acid.[57]

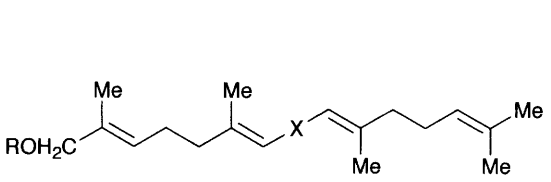
Chlorosulfonic acid has been extensively used in the sulfation of many natural products. Vitamin C (L-ascorbic acid)-2-sulfate is prepared by treatment of 5,6-*O*-isopropylidene-L-ascorbic acid with chlorosulfonic acid; the product was converted into the sodium salt which is added to poultry feeds to increase the thickness of the egg shells.[58] Vitamin C may also be directly sulfated by treatment with excess chlorosulfonic acid (eight equivalents) in pyridine at room temperature (48 hours), followed by neutralization (sodium hydroxide) to give the sodium salt of ascorbic acid-2,5,6-trisulfate.[59]

The sulfate esters of 6-hydroxymelatonin and *N*-acetylseratonin have been prepared by reaction of the parent compounds with chlorosulfonic acid in DMF; sulfation by this procedure is simple and rapid.[60,61] The natural metabolite of melatonin, melatonin-6-sulfate, has been demonstrated to be identical to the synthetic product.[61]

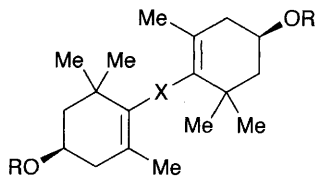
Peptides and amino acids may be sulfated: the hydroxyl groups of serine and threonine reacted with chlorosulfonic acid in trifluoroacetic acid to give the *O*-sulfate esters.[62] The free amino groups did not react since they were completely protonated in the strongly acidic media and the rates of sulfonation were determined. Peptides containing the above amino acids were also sulfated. The aromatic amino acids tyrosine and tryptophan, by treatment with chlorosulfonic acid–trifluoroacetic acid, afforded the arylsulfonic acid derivatives.[62] In the solid phase synthesis of cholecystokinin-33, tyrosine has been sulfated to the *O*-sulfate with chlorosulfonic acid and this was incorporated into the peptide sequence.[63]

In studies on carotenoid sulfates, the sodium salts of lycoxanthin sulfate **53** and zeaxanthin sulfate **54** were synthesised by treatment of lycoxanthin **55** or zeaxanthin **56** with chlorosulfonic acid in pyridine, followed by reaction with aqueous sodium hydroxide.[64]

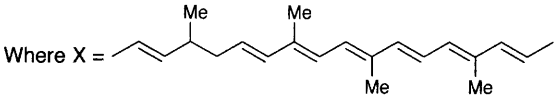
Sterols may also be conveniently sulfated by reaction with chlorosulfonic acid in organic solvents, followed by neutralization with bases, *e.g.* sodium methoxide,



53 R = SO_3Na
55 R = H



54 R = SO_3Na
56 R = H



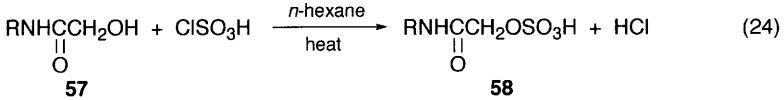
to give the corresponding sodium steryl sulfates, useful as emulsifiers in cosmetic preparations. By this procedure, cholesterol was sulfated in dichloromethane to give cholesteryl sulfate.[65]

Novel heparin-like materials can be made by sulfation of hydroxypropyl chitosan gel by reaction with chlorosulfonic acid and formamide. The product is a polyanion adsorbent which can be used in the purification of low density lipoproteins from plasma.[66] Chitosan sulfate was prepared by reaction of chitosan with chlorosulfonic acid–amide complex in the presence of nitrite salts.[67]

In the sulfonation of unsaturated alcohols, powerful sulfonating reagents tend to attack the double or triple bond as well as the hydroxyl group; consequently, milder reagents are preferred for selective *O*-sulfation. Studies of the sulfation of oleyl and elaidyl alcohols showed that the purest product (97% purity) was obtained using chlorosulfonic acid–urea, followed by sulfur trioxide–pyridine (96%), sulfamic acid (93%), sulfur trioxide–dioxan (90%) and chlorosulfonic acid–sodium chloride (60%).[2] With sperm oil, the use of chlorosulfonic acid–urea afforded 99% sulfation with 90% retention of the double bond.[2]

The use of chlorosulfonic acid (1.5–1.6 equivalents) converted petroleum-derived unsaturated alcohols (one equivalent) into alkyl sulfates (92% conversion) with good surfactant properties.[68]

N-Alkylamidoalkanols **57** reacted with an equimolar quantity of chlorosulfonic acid in an inert solvent, *e.g.* n-hexane, to yield the corresponding sulfates **58** (Equation 24). The sulfates from higher *N*-alkylamidoalcohols, *e.g.* *N*-lauryl-2-hydroxyacetamide and *N*-decyl-4-hydroxybutyramide, after neutralization with sodium hydroxide, were useful surfactants.[69,70]



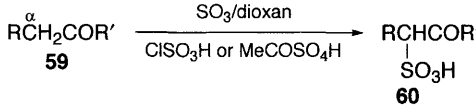
57 **58** (24)

With aromatic alcohols, like benzyl alcohol, chlorosulfonic acid may react by either *C*- or *O*-sulfonation or both depending on the experimental conditions.

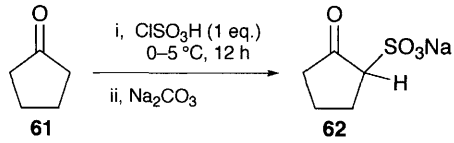
4 Aliphatic Carbonyl Compounds

4.1 Aldehydes and Ketones with and without α-Hydrogen Atoms

Aliphatic aldehydes (**59**; R′ = H) and ketones (**59**; R′ = alkyl) containing α-hydrogen atoms may be converted into the corresponding α-sulfonic acids **60** by treatment with sulfur trioxide–dioxan, chlorosulfonic acid or acetyl sulfate (Equation 25).[1,2,4,5] The favoured reagent for the sulfonation was generally sulfur trioxide–dioxan at −5 to 5 °C in dichloroethane as solvent.[4] Acetyl sulfate was also a useful sulfonating reagent, especially with diketones, and it was milder and more selective than chlorosulfonic acid.[71] However, the reactivity of chlorosulfonic acid may be moderated by complexation with dioxan, ether or urea.[5,72] Even ketones with tertiary hydrogens, *e.g.* di(isopropyl) ketone (2,4-dimethylpentan-3-one), react with sulfur trioxide–dioxan to give good yields of the α-sulfonic acids.[2] Long chain (C_{13}–C_{17}) aliphatic ketones are sulfonated with chlorosulfonic acid and cyclopentanone **61** is converted into the sodium sulfonate **62** by treatment with the reagent (one equivalent) at 0–5 °C (12 hours), followed by neutralization (sodium carbonate) (Equation 26).[73]

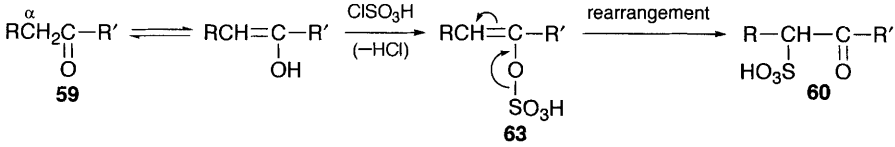


(25)



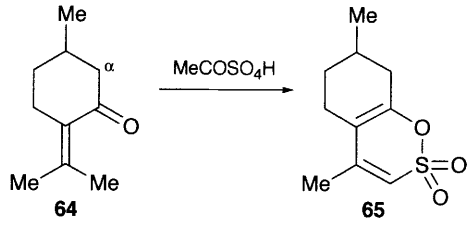
(26)

The sulfonation of aldehydes (**59**; R′ = H) and ketones (**59**; R′ = alkyl) occurs *via* the enolic form which then reacts with the sulfonating reagent to yield the *O*-sulfonate **63** which subsequently rearranges to the α-sulfonic acid **60** (Scheme 4). Aldehydes and ketones without α-hydrogen atoms do not react with sulfonating agents in the same way, but they may react with the carbonyl group (see p 164).



Scheme 4

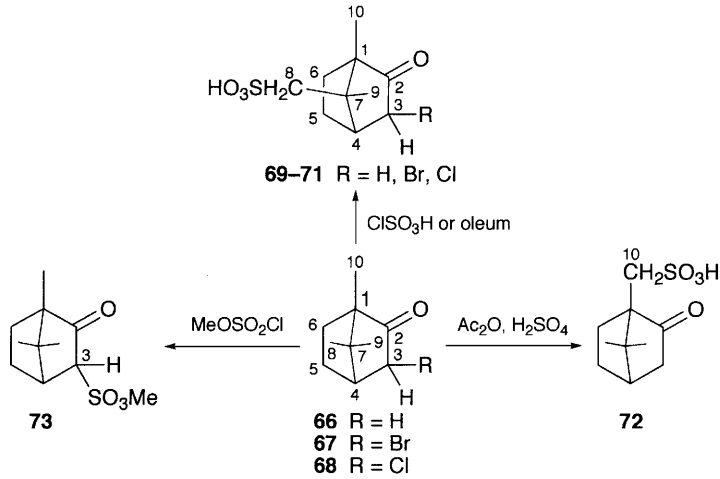
Unsaturated aldehydes and ketones also do not always undergo α-sulfonation. For example, pulegone **64** reacts with acetyl sulfate to give the cyclic sulfonate **65** (Equation 27).[1]



(27)

4.2 Camphor

Camphor **66** also does not generally sulfonate in the α-position and the orientation of sulfonation depends on the reagents used.[1] With chlorosulfonic acid or oleum, camphor **66** and the 3-bromo- or 3-chloro derivatives **67** and **68** yield the corresponding 8-sulfonic acids **69–71** (Scheme 5).[1,74]



Scheme 5

The orientation of sulfonation in compound **69** was shown by X-ray crystallography[75] and two-dimensional NMR studies[76] to be on the geminal methyl group remote from the carbonyl moiety. In other studies,[77] camphor-8-sulfonic acid was also prepared by reaction of camphor with chlorosulfonic acid (two equivalents) in boiling chloroform (12 hours); 3-bromocamphor was similarly converted into the corresponding 8-sulfonic acid.[77] The action of chlorosulfonic acid on camphor is unusual, because even when a large excess of the reagent is employed only the sulfonic acid was isolated; normally under these conditions, the sulfonyl chloride would be formed. The resistance of camphorsulfonic acid towards chlorination may be associated with hydrogen bonding between the carbonyl and sulfonic acid groups. Some support for this hypothesis derives from previous studies (see Chapter 4, p 113) which demonstrated that those diarylureasulfonic acids capable of existing as a zwitterionic structure could not be converted into their sulfonyl chlorides by treatment with chlorosulfonic acid.

In contrast, camphor **66**, by reaction with concentrated sulfuric acid–acetic anhydride (acetyl sulfate), gave the 10-sulfonic acid **72** (Scheme 5). The orientation of sulfonation in compound **72** was confirmed by X-ray crystallographic analysis of the sulfonanilide derivative.[78]

Methyl chlorosulfonate has been recommended as a methylsulfonating reagent.[1] It reacts with camphor **66**, under essentially neutral conditions, to give camphor-3-methyl sulfonate **73** (Scheme 5) which can be hydrolysed to the 3-sulfonic acid.

Methyl chlorosulfonate **74** may be prepared by reaction of chlorosulfonic acid with either methyl sulfate or methyl chloroformate (Equations 28 and 29).[1]

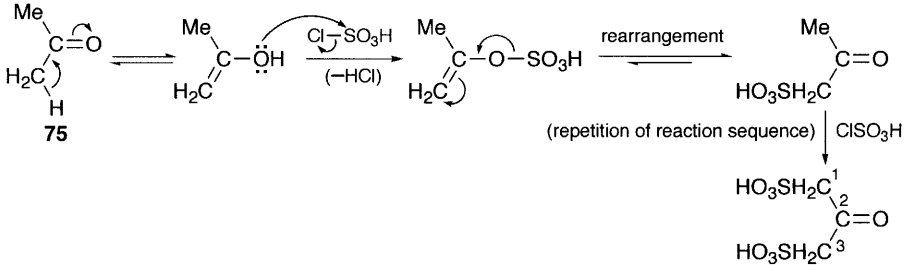
$$ClSO_3H + Me_2SO_4 \longrightarrow \underset{\mathbf{74}}{MeOSO_2Cl} + MeHSO_4 \qquad (28)$$

$$ClSO_3H + ClCO_2Me \longrightarrow \underset{\mathbf{74}}{MeOSO_2Cl} + HCl + CO_2 \qquad (29)$$

Camphor-3-sulfonic acid may also be obtained (73% yield) by treatment of camphor with sulfur trioxide–dioxan at −35 °C, followed by standing the reaction mixture at room temperature (4 hours) and neutralization with sodium hydroxide.[79] This reaction and that with methyl chlorosulfonate probably proceed *via* the enolic form of the ketone. The formation of 8- and 10-camphorsulfonic acids is considered to involve Wagner and Nemetkin rearrangements of the carbocations formed in the acidic media.[79]

As mentioned in Chapter 4, p 83, 3-benzylidenecamphor reacts with excess chlorosulfonic acid (six equivalents) to give a good yield of the *p*-sulfonyl chloride; surprisingly there was no attack on the camphor ring. Other arylidenecamphor derivatives reacted similarly with chlorosulfonic acid, giving exclusive sulfonation of the aryl ring (see Chapter 4, p 83).

Acetone (propan-2-one) **75** reacted with chlorosulfonic acid in dichloromethane at low temperature (< 20 °C) followed by refluxing the mixture (3–3½ hours) to give the 1,3-disulfonic acid **76**, 75–100% yield.[80] The disulfonation occurs *via* enolization of the ketone as depicted in Scheme 6.



Scheme 6

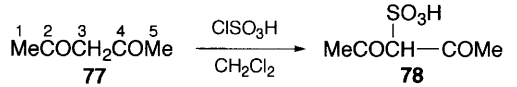
4.3 Di- and Polyketones

The sulfonation procedure was extended to acetylacetone (2,4-pentanedione, **77**) which, on treatment with chlorosulfonic acid in dichloromethane, afforded the

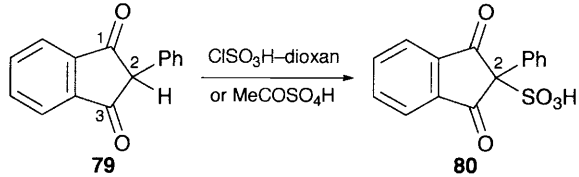
monosulfonic acid **78**, which was characterized by the ^{13}C and ^{1}H NMR spectra (Equation 30).[81]

The product **78** resulted from preferential enolization of the carbonyl group involving the most reactive (acidic) 3-hydrogen atom; consequently with this substrate, there was selective 3-sulfonation.

Several β-diketones are sulfonated by treatment with sulfur trioxide–dioxan, *e.g.* 1,3-indandione yields the 2-sulfonic acid.[82] 2-Phenyl-1,3-indandione **79** reacts with acetyl sulfate or chlorosulfonic acid in dioxan or ether to give the 2-sulfonic acid **80**;[2,83] the reaction occurring *via* the enolic form of the diketone (Equation 31). On the other hand, when the diketone **79** was treated with chlorosulfonic acid in a non-polar solvent only the phenyl ring was sulfonated;[2,83] presumably because under these conditions enolization was not favoured.



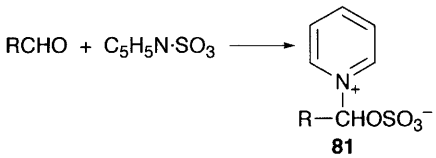
(30)



(31)

Polyketones can be sulfonated by reaction with chlorosulfonic acid; the products are chemically reactive and are useful as strongly acidic esterification catalysts and ion-exchange resins. The sulfonation of ethylene–carbonyl copolymer was achieved by treatment of the substrate with chlorosulfonic acid in dichloroethane at 0 °C.[84]

Substituted and unsubstituted aliphatic aldehydes react with the sulfur trioxide–pyridine complex (obtained by reaction of chlorosulfonic acid with pyridine) in boiling 1,2-dichloroethane to give good yields of the betaine salts **81** (Equation 32).[85]



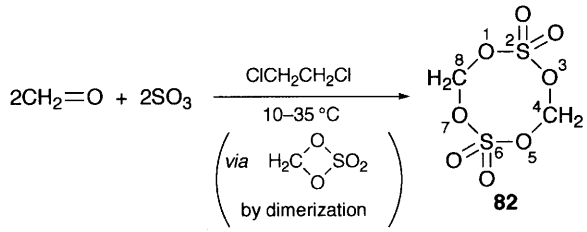
(32)

In this reaction, the sulfur trioxide–pyridine complex adds to the carbonyl group of the aliphatic aldehyde to yield the 1-alkyl-1-(1-proto-1-pyridyl)-1-methanesulfate derivative **81**.

4.4 Paraformaldehyde

As previously mentioned (p 160), aliphatic aldehydes containing α-hydrogen atoms react with sulfonating reagents to yield the corresponding α-sulfonic acids.

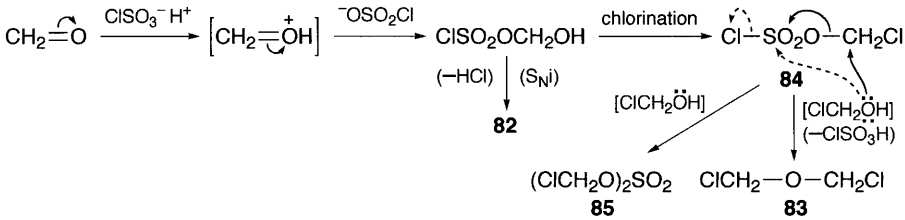
Aliphatic aldehydes without α-hydrogens can also react with sulfonating reagents *via* the carbonyl group. Thus paraformaldehyde reacts with 50% oleum or a 10% solution of sulfur trioxide in 1,2-dichloromethane as solvent at 10–35 °C to give methylene sulfate which exists as the dimer **82** (Equation 33).[86]



(33)

Paraformaldehyde also reacts with a mixture of chlorosulfonic acid and sulfuric acid at 0 °C (2 hours) to yield dichlorodimethyl ether (**83**).[87]

Extensive studies of the reaction of chlorosulfonic acid and other formaldehyde-generating chemicals, have been carried out by Fuchs and Katscher.[88] The results have been reviewed in detail by Jackson,[3] and they demonstrate that formaldehyde can react with chlorosulfonic acid to give a variety of different products **82–85** depending on the reaction conditions. When the reaction is carried out below 70 °C, followed by distillation of the mixture under reduced pressure (14 mmHg), the products were chloromethyl chlorosulfonate **84** and methylene sulfate **82**. The initial step of the reaction probably involves protonation of the carbonyl group of the aldehyde by chlorosulfonic acid and addition of the chlorosulfonate anion giving hydroxymethyl chlorosulfonate which, by chlorination, yields chloromethyl chlorosulfonate **84** (Scheme 7).

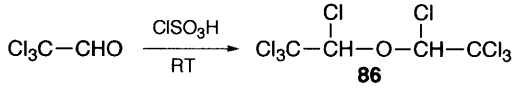


Scheme 7

The formation of the other products may be explained as follows: dichlorodimethyl ether **83** may arise as a result of attack by the hypothetical intermediate chloromethanol on the methylene carbon atom of chloromethyl chlorosulfonate **84**. On the other hand, if the attack by chloromethanol occurs on the sulfur atom of **84**, as shown by the dotted lines, the product would be dichlorodimethyl sulfate **85** (Scheme 7).

Acetaldehyde and paraldehyde both react vigorously with chlorosulfonic acid forming dark, water-soluble products, which are not analogous to those obtained from formaldehyde.[3] It is possible that the products derived from acetaldehyde may result from competing reactions of the reagent with the α-hydrogen atoms of the methyl group. This hypothesis gains some support from the observation that

chloral (trichloroacetaldehyde) reacts with chlorosulfonic acid at room temperature to give octachlorodiethyl ether **86** (Equation 34).



(34)

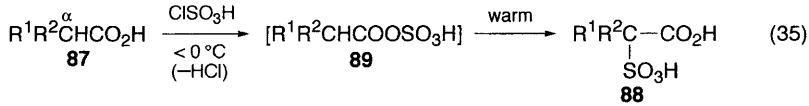
Metachloral and chloral hydrate similarly afforded the octachloroether **86** on treatment with chlorosulfonic acid.[88]

It was discovered[89] that the organic phase of a mixture of paraformaldehyde, chlorosulfonic acid and hydrochloric acid reacted with acetic anhydride, sulfuric acid and chlorosulfonic acid at 60–120 °C to yield chloromethyl acetate (78%). The product was obtained after neutralization with sodium hydrogen carbonate, and could be stored for several months without decomposition.

5 Aliphatic Carboxylic Acids and Derivatives

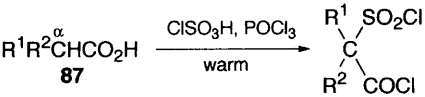
5.1 Aliphatic Carboxylic Acids

The sulfonation of aliphatic carboxylic acids has been extensively studied: the action of chlorosulfonic acid or sulfuric acid on acetic acid yields sulfoacetic acid, and by treatment with sulfur trioxide at low temperature it was possible to isolate the intermediate mixed anhydride.[1] Such intermediates are also postulated to form in the reaction of aromatic acids with chlorosulfonic acid (see Chapter 4, p 89). Several aliphatic carboxylic acids **87**, containing at least one α-hydrogen atom, *e.g.* n-butanoic, isobutanoic, pentanoic and 3-methylbutanoic acids, have been converted into the corresponding α-sulfonic acids **88** by treatment with chlorosulfonic acid at < 0 °C (Equation 35).[1,2,5] The sulfonation probably proceeds *via* the mixed anhydride **89**, which on warming rearranges to give the sulfonic acid **88**.



(35)

The aliphatic acids **87**; $R^1 = H$, C_1–C_4 alkyl; $R^2 = H$, Me, Et, reacted with a warm mixture of chlorosulfonic acid and phosphorus oxychloride to yield the mixed chloride **90** (Equation 36)[89a] and when monosubstituted carboxylic acids **87**; R = H, Cl were heated at 105–110 °C with the same mixture of reagents (2.2 equivalents), the corresponding disulfonyl chlorides **91** were formed with simultaneous loss of carbon dioxide (Equation 37).[6,90]



(36)

$$\underset{\textbf{87}\ R = H \text{ or } Cl}{\overset{\alpha}{RCH_2CO_2H}} \xrightarrow[105\text{–}110\,^{\circ}C]{ClSO_3H,\ POCl_3\ (2.2\ eqs.)} \underset{\textbf{91}\ R = H,\ 75\%\ \text{or}\ R = Cl,\ 65\%}{RCH(SO_2Cl)_2} + CO_2 \qquad (37)$$

A comparative study[91] of the sulfonation of saturated aliphatic carboxylic acids showed that the long chain members with alkyl radicals containing more than eight carbon atoms were more easily α-sulfonated than the lower analogues and were useful detergents.[2,92] The optimum sulfonation reagent was found to be liquid sulfur trioxide in a halogenated solvent; chlorosulfonic acid was almost as good, but the reaction needed a higher temperature and resulted in a darker-coloured product. Sulfur trioxide–dioxan was also an effective reagent, but chlorosulfonic acid–urea did not react.

Aliphatic carboxylic acids **92**, containing at least six carbon atoms, and their anhydrides, amides, chlorides, esters or nitriles, are sulfonated by heating with chlorosulfonic acid in an inert solvent and distilling off the solvent after the evolution of gas has ceased. The products are water-soluble sulfonic acids **93**, useful as wetting or emulsifying agents, detergents or specialist solvents (Equation 4).[93] Higher alkyl formates **94**; R = pentyl, dodecyl, *etc.*, by treatment with chlorosulfonic acid (one equivalent) in boiling carbon tetrachloride, afforded the corresponding alkyl hydrogen sulfates **95** (Equation 39).[94]

$$\underset{\textbf{92}\ n = 5, 7, 9, 11, 13 \text{ or } 17}{C_nH_{2n+1}CO_2H} \xrightarrow[\text{reflux}]{ClSO_3H,\ CCl_4} \underset{\textbf{93}}{\overset{\alpha}{C_{n-1}H_{2n}CHCO_2H}\ (SO_3H)} \qquad (38)$$

$$\underset{\textbf{94}}{HCO_2R} + ClSO_3H \xrightarrow[\text{reflux}]{CCl_4} \underset{\textbf{95}}{RSO_4H} + CO + HCl \qquad (39)$$

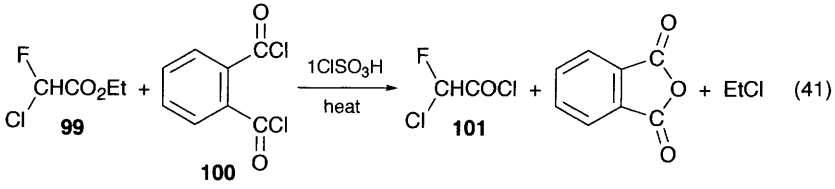
Chloroacetic acid **96**, by heating with chlorosulfonic acid at 140–150 °C, gave the α-sulfonic acid **97** accompanied by chloromethanedisulfonic acid **98** as a byproduct (Equation 40).[95]

$$\underset{\textbf{96}}{\overset{\alpha}{ClCH_2CO_2H}} \xrightarrow[140\text{–}150\,^{\circ}C]{ClSO_3H} \underset{\textbf{97}}{ClCHCO_2H\ (SO_3H)} + \underset{\textbf{98}}{ClCH(SO_3H)_2} \qquad (40)$$

Long chain linear, branched or unsaturated ethoxycarboxylic acids containing 10–25 carbon atoms are sulfonated by treatment with chlorosulfonic acid (one equivalent) in an appropriate solvent, *e.g.* carbon tetrachloride or trichloroethene. The sulfonation may also be performed by the reagent in the presence of an *N,N*-dimethylamide catalyst without a solvent.[96] By this procedure, ethoxyoleic acid was sulfonated at 10 °C and the product neutralized with sodium hydroxide to give the corresponding sodium sulfate.[96]

5.2 Carboxylic Esters

The reaction of carboxylic acid esters with a mixture of chlorosulfonic acid and phthaloyl chloride affords a useful one-step procedure for the conversion of esters directly into the acyl chlorides.[97] For instance, heating an equimolar mixture of chlorofluoroacetate **99**, phthaloyl chloride **100** and chlorosulfonic acid afforded chlorofluoroacetyl chloride **101** (88% yield) (Equation 41).[97]

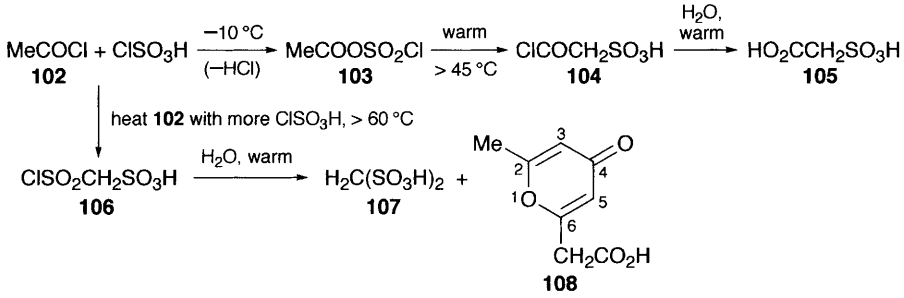


(41)

5.3 Alkanoyl Chlorides

The reaction of chlorosulfonic acid with the first three alkanoyl chlorides was extensively investigated by Krajčinovič[1] and afforded some interesting results which were reviewed by Jackson.[3]

Acetyl chloride (ethanoyl chloride, **102**) reacts with the reagent (one equivalent), even at low temperature (−10 °C), with evolution of hydrogen chloride to yield acetyl chlorosulfonate **103** which, by warming above 45 °C, rearranges to sulfoacetyl chloride **104**, and the latter by hydrolysis gave sulfoacetic acid **105** (Scheme 8).



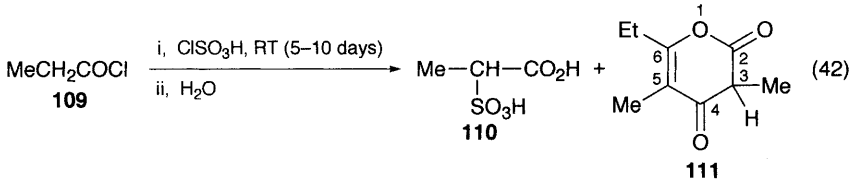
Scheme 8

When acetyl chloride **102** was heated with more chlorosulfonic acid above 60 °C, the intermediate acetyl chlorosulfonate **103** was converted into chlorosulfonylmethanesulfonic acid **106**, which by hydrolysis afforded methanedisulfonic acid **107**. Ether extraction of the reaction mixture also gave a small amount (*ca.* 3%) of a condensation product suggested to be 2-methylpyran-4-one-6-acetic acid **108** (Scheme 8).[3]

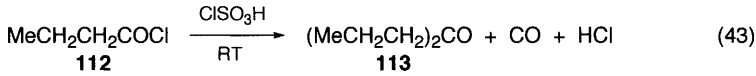
Propanoyl chloride **109** was reacted with an equal weight of chlorosulfonic acid at room temperature (5–10 days), poured onto cold water and extracted with ether to give a mixture of sulfopropionic acid **110** (from the aqueous layer) and a

substantial amount of a condensation product, probably 6-ethyl-3,5-dimethylpyran-2,5-dione **111**, from the ether extract (Equation 42).[3]

Chlorosulfonic acid only reacted slowly with butanoyl chloride **112** at room temperature with continuous evolution of hydrogen chloride and carbon monoxide. The reaction did not yield any butanesulfonic acid, and ether extractions gave 4-heptanone **113** (Equation 43).[1,3] The results showed that with these alkanoyl chlorides, the greater the number of carbon atoms in the substrate, the fewer the number of moles of the chloride that condense. Thus, 4 moles of acetyl chloride **102** condense to form 2-methylpyran-4-one-6-acetic acid **108** (Scheme 8); while 3 moles of propanoyl chloride **109** condense to yield the pyranedione **111** (Equation 42), and 2 moles of butanoyl chloride **112** form 4-heptanone **113** (Equation 43). The condensation products from acetyl chloride are only isolated at higher temperatures, whereas those derived from the other alkanoyl chlorides decompose at higher temperatures and consequently they are only isolated at room temperature.



(42)

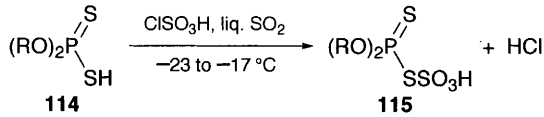


(43)

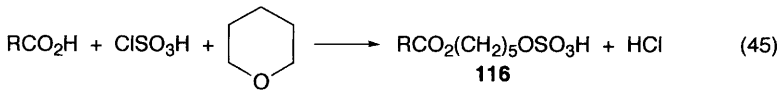
O,O-Dialkylthiophosphoric acids, *e.g.* the 2-ethylhexyl derivative **114**; R = $CH_2CH(Et)(CH_2)_3Me$, react with chlorosulfonic acid (one equivalent) in liquid sulfur dioxide at −23 to −17 °C to give the corresponding thiosulfonic acid **115** (Equation 44).[98]

Chlorosulfonic acid reacts with unsaturated carboxylic acids: with oleic acid (*cis*-9-octadecenoic acid) the reagent gives sulfooleic acid with loss of hydrogen chloride.[3] On the other hand, with 10-undecenoic acid the product was hydroxysulfoundecenoic acid in which hydroxyl and sulfonic acid groups have added across the double bond.[99]

Chlorosulfonic acid reacts with a mixture of a long chain aliphatic carboxylic acid and pentamethylene oxide with cleavage of the cyclic ether, yielding a long chain alkyl sulfate **116** (Equation 45).[2]



(44)

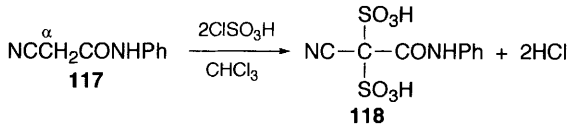


(45)

Alkyl derivatives of cyclic ethers behave in a similar manner yielding surface active sulfates valuable as detergents.

5.4 Dicarboxylic Acids and Derivatives

Sulfomalonic acid is too unstable for isolation, but some related compounds are known.[1,3] Cyanoacetamide did not react with chlorosulfonic acid, although the anilide **117** is claimed[3,100] to react with the reagent in chloroform solution to form the disulfonic acid **118** in which sulfonation has occurred exclusively at the methylene hydrogens (Equation 46).



(46)

or NC—CH(SO_3H)CONH—C$_6$H$_4$—SO_3H

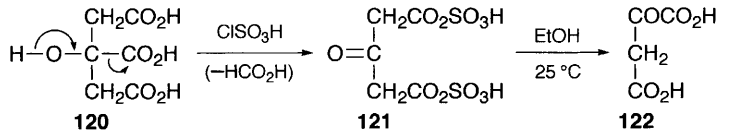
119

The reactivity of the methylene hydrogen atoms towards the reagent apparently increased when the phenyl moiety of **117** was substituted by tolyl and naphthyl radicals which was suggested to be associated with their electronegativity.[3,100] The proposed structure of the disulfonic acid **118** seems unlikely, since cyanoacetamide is inert towards chlorosulfonic acid while anilides are readily sulfonated by the reagent in the aryl ring (see Chapter 4, p 103).

In view of these results, it is probable that at least one of the sulfonic acid groups enters the aromatic nucleus giving the isomeric disulfonic acid **119** as the more likely structure for the product (Equation 46).

The sulfonation of malondianilide by chlorosulfonic acid (two equivalents) was also claimed[101] to occur exclusively at the methylene hydrogens, but this is probably incorrect, since the compound is known[102] to react with excess reagent by sulfonation of the phenyl rings giving the 4,4′-disulfonyl chloride. The structure proposed[101] for the product from the action of chlorosulfonic acid on methyl malondiarylamides is also unlikely since at least one of the sulfonic acid groups probably enters the aryl ring.

A solution of chlorosulfonic acid in 1,2-dichloroethane reacts with citric (2-ketopropan-1,2,3-tricarboxylic) acid **120** to give the disulfate ester **121**, which on treatment with absolute alcohol at 25 °C affords 2-ketobutanedioic acid **122** (94–96% yield) (Equation 47).[103]



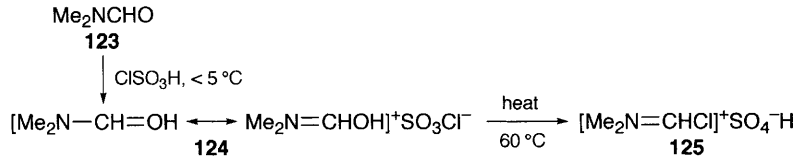
(47)

The action of chlorosulfonic acid on citric acid differs from that of fuming sulfuric acid which yields acetonedicarboxylic acid. The procedure outlined by Equation 47 may be extended to the synthesis of other ketoacids.

5.5 Amides

Fatty alkanolamides are sulfated by treatment with chlorosulfonic acid in the presence of a low molecular weight alcohol, *e.g.* methanol or isopropanol (15–20%), to give a co-sulfate of the alcohol and the alkanolamide. For instance, this was achieved by heating tallow isopropanolamide with methanol and chlorosulfonic acid at 45 °C.[104]

Chlorosulfonic acid reacts with DMF **123** at low temperature (< 5 °C) yielding a mesomeric salt **124** which, by heating at 60 °C, was converted into a new Vilsmeier adduct **125** (Scheme 9).[105]



Scheme 9

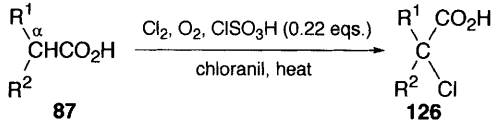
Generally, chlorosulfonic acid forms complexes with amides, *e.g.* DMF, formamide and urea. Complexation moderates the sulfonating power of the acid and such mild sulfonating reagents are valuable in the sulfonation of sensitive substrates where more powerful sulfonating reagents would cause unwanted side reactions. For instance, the chlorosulfonic acid–urea complex formed in liquid sulfur dioxide has been successfully used in the sulfation of oleyl alcohol (see Section 3, p 159), while the DMF–chlorosulfonic acid complex is useful in the sulfation of complex phenolic compounds.[2,4]

5.6 α-Halogenation of Carboxylic Acids

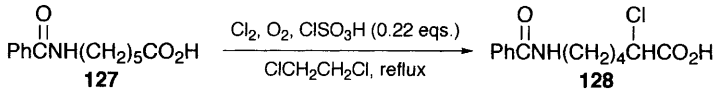
Chlorosulfonic acid, under the appropriate conditions, is a valuable catalyst for the selective α-halogenation of aliphatic carboxylic acids and the reaction has been extensively investigated. Chlorosulfonic acid functions as an acidic enolization catalyst and is used in conjunction with the appropriate halogen and a suitable radical trapper, *e.g.* oxygen or chloranil. The latter removes free radicals and thus inhibits radical halogenation of the acid at other positions of the alkyl chain. The chlorination of the aliphatic acid **87** by this procedure affords the corresponding α-chloroacid **126** in excellent yield (73–82%) (Equation 48).[106]

Chlorosulfonic acid was a more effective catalyst for halogenation than sulfuric acid, possibly because it forms a more homogeneous mixture and is a stronger acid. The α-chlorination process probably occurs *via* enol or ketene intermediates[106] and chlorosulfonic acid was more potent than other acidic catalysts. The α-chlorination of 3-methylbutanoic (isovaleric) acid by heating with a mixture of oxygen, chlorine, chlorosulfonic acid and chloranil at 140 °C (3 hours) afforded the α-chloro derivative (78% yield).[107] 6-Benzoylaminohexanoic acid **127** was similarly α-chlorinated by bubbling a 2:1 (vol/vol) mixture of chlorine and oxygen for 3 hours through a refluxing solution of the acid **127**

and chlorosulfonic acid (1.1 equivalents) in 1,2-dichloroethane to give the α-chloroacid **128** (72–80% yield) (Equation 49).[108]



(48)



(49)

The selective α-chlorination of propionic acid was achieved by heating the acid with a mixture of chlorine, chlorosulfonic acid and oxygen in a semibatch reactor at 70–110 °C. The kinetics of the chlorination were autocatalytic, when the concentration of the chlorosulfonic acid catalyst was kept constant. The primary product was sulfopropionic acid and the autocatalytic kinetics were explained by a mechanism involving acid-catalysed enolization of the key intermediate, propanoyl chloride, as the rate-determining step.[109]

The kinetics for the semibatch α-chlorination of saturated long chain aliphatic carboxylic acids by chlorine, oxygen and chlorosulfonic acid at 90–130 °C were described by a kinetic model comprising three rate-determining stages: an acid-catalysed enolization step followed by two further steps involving chlorination of the enol.[110] By this procedure, straight chain saturated aliphatic acids containing 4, 6, 8, 10 and 12 carbon atoms were selectively α-chlorinated in high yields when the catalyst (chlorosulfonic acid) was gradually added to the reaction mixture.[111]

An improved procedure for the α-chlorination of long chain alkyl carboxylic acids with alkyl radicals $> C_8$ involves the use of a cyanoquinone (TCNQ, 0.005 equivalents) instead of oxygen as the free radical inhibitor.[112] This modification results in an enhanced α-chlorination reaction that is unaffected by chain length and which requires a shorter reaction time with a reduced amount of chlorosulfonic acid catalyst (0.003 equivalents). It gives a better yield with negligible polychlorination and the product was more easily purified.[112] As an example, stearic (heptadecanoic) acid (1.6 equivalents) was reacted with TCNQ (0.006 equivalents) at 80 °C, followed by chlorosulfonic acid (0.05 equivalents) in a stream of chlorine gas (200 ml min^{-1}); the mixture was then heated at 150 °C for 1 hour with an increased flow rate (800 ml min^{-1}) to give 2-chlorostearic acid (88%).[112]

Alkanoyl chlorides ($R^1R^2CHCOCl$) may be similarly α-chlorinated by heating them with a mixture of a food grade antioxidant, oxygen, TCNQ, chlorine and chlorosulfonic acid at 100–120 °C.[113]

Aliphatic carboxylic acids may be similarly α-brominated in high yields (78–95%) by heating the acid with bromine and chlorosulfonic acid catalyst (0.05 equivalents) in 1,2-dichloroethane at 84 °C. No oxygen was required in the reaction. The kinetics of bromination were second order overall, first order in both bromine and the carboxylic acid, and the rate of reaction (v) is expressed by Equation 50. The rate constant (k) was proportional to the initial concentration of the chlorosulfonic acid catalyst at an early stage of the reaction. The rate of α-

bromination was found to be accelerated by the presence of electron-releasing groups in the substrate; consquently, the reactivity of the acids examined follows the order shown in Scheme 10. The bromination mechanism, like that of the analogous α-chlorination, resembles that of the Hell–Volhard–Zelinsky bromination reaction and probably involves enol and ketene intermediates.[114]

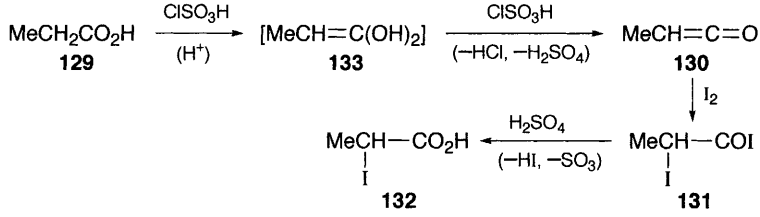
$$v = k\,[R^1R^2CHCO_2H][Br_2] \qquad (50)$$

$$Et_2CHCO_2H > Me_2CHCO_2H > Me_2CHCH_2CO_2H > MeCH_2CO_2H$$

decreasing reactivity of the acid →

Scheme 10

The kinetics of the α-iodination of propionic acid **129** by heating with iodine and chlorosulfonic acid catalyst in 1,2-dichloroethane at 80 °C were similar to those of the analogous bromination reaction and a ketene intermediate **130** was postulated.[115] The rate of iodination decreases with the progress of the reaction, probably due to gradual decomposition of the catalyst. The rate of iodination is less than that of the bromination reaction and it is proposed that iodine adds to the ketene intermediate **130** in the rate-determining stage to give the adduct **131** (Scheme 11). The iodine adduct **131** finally reacts with sulfuric acid to yield α-iodopropionic acid **132**. The initial enolic intermediate **133**, formed by acid-catalysed enolization of propionic acid **129**, would be unstable in the strongly acidic medium and loses water to give the ketene **130** (Scheme 11).



Scheme 11

The substituent effect and optimum conditions for the α-iodination of aliphatic acids in 1,2-dichloroethane were examined.[116] The substituent effect on the rate displays both polar and steric factors and the reaction mechanism involves the electrophilic addition of iodine to the ketene intermediate.

Carboxylic acids that are relatively unhindered at the α-carbon atom, except acetic acid, are α-iodinated at 80 °C in 80–100% yields.[116] As a model long chain aliphatic acid, caprylic (octanoic) acid (one equivalent) was heated with iodine (0.25 equivalents) and chlorosulfonic acid (one equivalent) in 1,2-dichloroethane at 80 °C for 2 hours to give a quantitative yield of 2-chlorooctanoic acid.

The stoichiometry and promotional role of chlorosulfonic and fuming sulfuric acids in the α-halogenation of aliphatic acids were examined. In α-bromination or iodination with bromine or iodine respectively, 1 mole of halogen produces 2 moles of the α-haloacid, whereas in the analogous chlorination 1 mole of chlorine

only yields 1 mole of the α-chloroacid. Fuming sulfuric acid was an effective catalyst for α-bromination but gave a lower product yield as compared with chlorosulfonic acid but this catalyst did not work for α-iodination.[117]

The general mechanism of the acid-catalysed α-halogenation of aliphatic carboxylic acids (**87**) may be summarized by Equations 51–53. The adduct (**131**; X = I) was found to regenerate iodine; consequently, 1 mole of iodine yields 2 moles of the α-iodoacid, a similar effect presumably occurs in bromination.

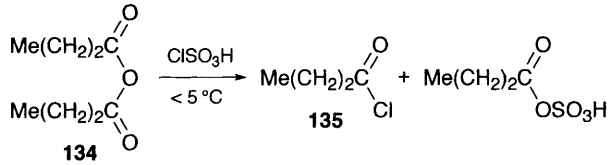
$$\underset{\mathbf{87}}{R^1R^2CHCO_2H} + ClSO_3H \underset{}{\overset{\text{fast}}{\rightleftharpoons}} \underset{\mathbf{130}}{R^1R^2C{=}C{=}O} + HCl + H_2SO_4 \qquad (51)$$

$$\underset{\mathbf{130}\ X = Cl, Br \text{ or } I}{R^1R^2C{=}C{=}O} + X_2 \overset{\text{slow}}{\rightleftharpoons} \underset{\mathbf{131}}{R^1R^2CXOX} \qquad (52)$$

$$\underset{\mathbf{131}}{R^1R^2CXOX} + H_2SO_4 \longrightarrow \underset{\mathbf{132}}{R^1R^2CXCO_2H} + HX + SO_3 \qquad (53)$$

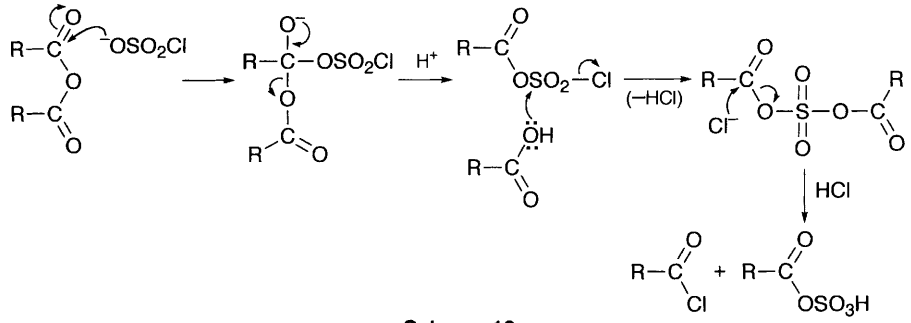
5.7 Aliphatic Acid Anhydrides

As mentioned in the Introduction (p 5), chlorosulfonic acid reacts easily with carboxylic acid anhydrides giving excellent yields of the corresponding alkanoyl chlorides, which provides a useful synthetic route to these compounds. For example, butanoic anhydride **134** by treatment with chlorosulfonic acid (0.8 equivalents) at −5 °C, followed by vacuum distillation, afforded butanoyl chloride **135** (95% yield) (Equation 54).[118]



(54)

The mechanism of reaction shown in Equation 54 presumably involves initial nucleophilic attack by the chlorosulfonate anion on the electrophilic carbonyl carbon atom of the acid anhydride, followed by the reaction sequence depicted in Scheme 12.

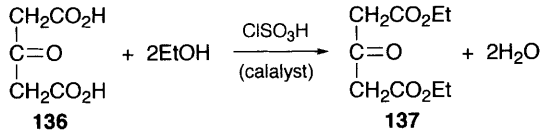


Scheme 12

5.8 Esterification of Aliphatic Acids

Chlorosulfonic acid, as well as catalysing the α-halogenation of aliphatic acids, also functions as an acidic dehydration catalyst which can be valuable in the esterification of carboxylic acids.

Thus, chlorosulfonic acid catalyses the esterification of acetonedicarboxylic acid **136** by ethanol yielding the diethyl ester **137** (Equation 55).[119]

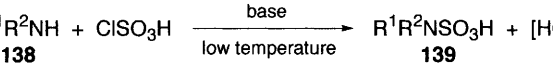


136 **137** (55)

The reaction was examined under various conditions and was optimized to yield diethyl acetonedicarboxylate **137** (93% purity) in 72% yield.

6 Aliphatic Amines

In the reaction of primary and secondary aromatic amines with chlorosulfonic acid, *C*-sulfonation probably occurs *via* the initially formed *N*-sulfonic acid (sulfamation), which on heating rearranges by migration of the sulfonic acid group into the aromatic nucleus to yield the aminoarylsulfonic acid (see Chapter 4, p 98). Such a rearrangement is obviously impossible with aliphatic primary or secondary amines **138** which therefore only undergo sulfamation (*N*-sulfonation) by reaction with the reagent, giving the corresponding *N*-sulfonic acid **139** (Equation 56).



138 **139** (56)

Sulfamation is not possible with tertiary amines which react with chlorosulfonic acid to form the corresponding amine–sulfur trioxide complex (see p 175).

The three classes of amines also react differently with organic sulfonyl chlorides; this is exploited in the Hinsberg separation of primary, secondary and tertiary amines.[7]

Many organic sulfamic acids are sweet, consequently a wide range of alkyl, alicyclic and aromatic derivatives has been synthesized in the search for new non-nutritive sweeteners.[7] One of the best synthetic routes to sulfamic acids involved treatment of the appropriate primary amine **140** (three equivalents) with chlorosulfonic acid (one equivalent) in an inert organic solvent such as chloroform, followed by neutralization with sodium hydroxide to yield the corresponding sodium sulfamate **141** and the amine for recovery and recycling (Equation 57).[120]

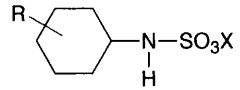
$$\underset{\mathbf{140}}{3RNH_2} + ClSO_3H \xrightarrow[0\,^\circ C]{CH_2Cl_2} \underbrace{RNHSO_3^-\,H_3\overset{+}{N}R + R\overset{+}{N}H_3Cl^-}_{\text{aq. NaOH}} \qquad (57)$$

$$\downarrow$$

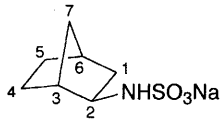
$$\underset{\mathbf{141}}{RNHSO_3^-\,Na^+} + 2RNH_2$$

Sodium *N*-cyclohexyl sulfamate (cyclamate, **141**; R = cyclohexyl) was introduced as a non-nutritive artificial sweetener in 1939. It is 30 times sweeter than sucrose, but was banned in the USA and Canada in 1970 because rats fed with large doses developed bladder cancer, although it is permitted in many other countries.[7] Cyclohexylammonium sulfamate, an intermediate in the manufacture of non-nutritive sweeteners, may be prepared by reaction of cyclohexylamine (two to three equivalents) with chlorosulfonic acid in trichloroethene at 60–75 °C; the presence of the excess amine avoids an acidic medium and side reactions.[121] *N*-Cyclohexylsulfamic acid has been obtained by treatment of cyclohexylamine with a mixture of sulfur trioxide and chlorosulfonic acid in trichloroethene at < 60 °C.[122] Cyclamate can also be manufactured by heating cyclohexylamine with sulfamic acid in xylene at 132–139 °C.[7,123] Benson and Spillane[123] discussed the use of sulfamates as sweeteners and their chemistry has been reviewed.[124]

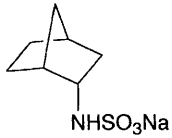
In *N*-substituted sulfamic acids, exceptional sweetness was discovered to be generally limited to those members containing a cyclohexyl ring which may be substituted, a free hydrogen atom attached to the nitrogen atom and almost any salt-forming group (X) as shown **142**.[120]



142



143



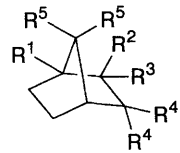
144

Eighteen sodium alicyclic and heterocyclic sulfamates (**141**, R = alicyclic or heterocyclic radical) were examined for sweetness. The sweetest was sodium *exo*-bicyclo[2.2.1]heptan-2-ylsulfamate **143** which was five times sweeter than cyclamate although the *endo* isomer **144** was tasteless.[125]

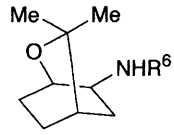
The terpenyl amines **145–147** reacted with chlorosulfonic acid to give the corresponding sulfamic acids (**145**; R = SO_3H), (**146**; R^2 or R^3 = $NHSO_3H$) and (**147**; R^6 = SO_3H).[126] The terpenoid sulfamic acids represented a new group of synthetic sweeteners.

Chlorosulfonic acid reacts with aliphatic and aromatic tertiary amines to form the corresponding amine–sulfur trioxide complexes **148** (Equation 58).[2,4,123] The dropwise addition of a solution of chlorosulfonic acid (one equivalent) in an inert organic solvent (*e.g.* chloroform or dichloromethane) to a stirred solution of the tertiary amine (two equivalents) in the same solvent at low temperature yields the complex (see Chapter 4, p 101). This procedure provides a convenient synthesis of the triethylamine–sulfur trioxide complex in 75% yield.[127] The complex is

145 R = H



146 $R^1 = R^4 = Me$, $R^2 = NH_2$, $R^3 = R^5 = H$;
$R^1 = R^5 = Me$, $R^2 = R^4 = H$, $R^3 = NH_2$;
$R^1 = R^5 = Me$, $R^2 = NH_2$, $R^3 = R^4 = H$;
$R^1 = R^3 = R^4 = R^5 = H$, $R^2 = NH_2$

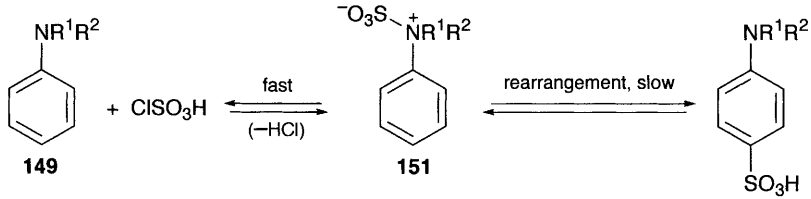


147 $R^6 = H$

$$2R_3N + ClSO_3H \longrightarrow \underset{\textbf{148}}{R_3N{\cdot}SO_3} + R_3\overset{+}{N}HCl^- \qquad (58)$$

claimed to be a superior reagent for the sulfation of sterols and polysaccharides; it gives purer products with a maximum degree of sulfation[127] (*cf.* Section 3).

The kinetics of the sulfonation of *N,N*-dialkylanilines **149** indicated that the reaction followed a first order rate equation yielding almost exclusively the *p*-aminobenzenesulfonic acid **150**.[128] The rate constants and activation energies of the sulfonation reaction were similar to those found for the rearrangement of *N,N*-dialkylaniline–sulfur trioxide complexes **151** to the corresponding *p*-aminobenzenesulfonic acids **150** (Scheme 13).[123,128] The reaction mechanism was therefore concluded to involve firstly the rapid formation of the amine–sulfur trioxide complex. The second step of the reaction is the slow rearrangement of the complex to form the *p*-aminobenzenesulfonic acid and this is the rate controlling stage of the reaction as shown in Scheme 13.



149 **151** **150**

Scheme 13

7 References

1 C.M. Suter, *The Organic Chemistry of Sulfur*, Wiley, New York, 1944, Reprinted edition by Intra-Science Research Foundation, Santa Monica, CA, 1969. Chapter 1 covers esters of sulfuric acid and Chapter 2 deals with aliphatic sulfonic acids (both chapters include the use of chlorosulfonic acid).

2 E.E. Gilbert, *Sulfonation and Related Reactions*, Interscience Publishers, New York, 1965.

3 K.E. Jackson, *Chem. Rev.*, 1939, **39**, 83 (deals with the early work on the action of chlorosulfonic acid on aliphatic alcohols, aldehydes, acids, acid chlorides and cyanoacetamides).

4 E.E. Gilbert, *Chem. Rev.*, 1962, **62**, 549 (this covers the sulfonation of organic

compounds by sulfur trioxide and its adducts which can be made by the reaction of chlorosulfonic acid with, for example, dioxan, pyridine and trimethylamine).

5 K.K. Andersen, 'Sulfonic Acid and Derivatives' in *Comprehensive Organic Chemistry*, D.H.R. Barton and W. Ollis (eds), Pergamon Press, Oxford, 1979, vol. 3, 331.

6 J. Hoyle, 'Preparation of Sulfonic Acids, Esters, Amides and Halides' in *Chemistry of Sulfonic Acids and Derivatives*, S. Patai and Z. Rappoport (eds), Wiley, Chichester, 1991, 354, 379.

7 R.J. Cremlyn, *An Introduction to Organosulfur Chemistry*, Wiley, Chichester, 1996.

8 A.F. Shepard and A.L. Henne, *Ind. Eng. Chem.*, 1930, **22**, 356.

9 A.F. Shepard, A.L. Henne and T. Midgley, *J. Am. Chem. Soc.*, 1931, **53**, 1948.

10 J.D. Baker, *Chem. Eng. News*, 1989, **67**, 2; *Chem. Abs.*, **112**, 76317.

11 S. Miron, *Chem. Eng. News*, 1990, **68**, 2; *Chem. Abs.*, **114**, 128162.

12 W.M. Mokhtar, H.M. Soliman, S.M. Abdel-Hamid and A.M. Badawi, *Tenside Surfactants, Deterg.*, 1992, **29**, 135; *Chem. Abs.*, **116**, 237810.

13 D.T. Roberts, J.A. Beckman, E. Lawrence and A.F. Halasa, US 944010 (1976); *Chem. Abs.*, **85**, 47337.

14 B.M. Lerman, Z.Ya. Aref'eva, A.R. Kuzyev and G.A. Tolstikov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1971, 894; *Chem. Abs.*, **75**, 140335.

15 G.A. Tolstikov, B.M. Lerman and Z.Ya. Aref'eva, *Tetrahedron Lett.*, 1972, 3191.

16 S.R. Sandler, Eur., EP 293672 (1988); *Chem. Abs.*, **110**, 192253; (a) B.H. Bakker and H. Cerfontain, *Eur. J. Org. Chem.*, 1999, **1**, 91; *Chem. Abs.*, **130**, 109876.

17 S. Miron and G.H. Richter, *J. Am. Chem. Soc.*, 1949, **71**, 453.

18 C.M. Suter and J.D. Malkemus, *J. Am. Chem. Soc.*, 1941, **63**, 978.

19 F.B. Downing and R.G. Clarkson, US 2016617; *Chem. Abs.*, **31**, 783.

20 P.C. Myhre and G.D. Andrews, *J. Am. Chem. Soc.*, 1970, **92**, 7596.

21 M.M. Tessler and D.V. Neigil, *Eur.*, EP 52294 (1982); *Chem. Abs.*, **97**, 91753.

22 Yu. Ol'dekop, R.V. Kaberdin and V.I. Potkin, *Zh. Org. Khim.*, 1983, **19**, 1648; *Chem. Abs.*, **99**, 212114.

23 M. Carrega, *Fr.*, FR 2094444 (1972); *Chem. Abs.*, **78**, 3695.

24 A.V. Folkin, A.I. Rapkin, V.I. Matveenko and O.V. Verenikin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1988, 2367; *Chem. Abs.*, **110**, 192217.

25 R.G. Pews, *Can. J. Chem.*, 1969, **47**, 1260; *Chem. Abs.*, **70**, 96212.

26 E.T. McBee and J.S. Newcomer, US 2516404 (1950); *Chem. Abs.*, **45**, 647.

27 J.S. Newcomer and E.T. McBee, *J. Am. Chem. Soc.*, 1949, **71**, 946.

28 R.A. Minns, US 4426505 (1984); *Chem. Abs.*, **100**, 140208.

29 V.D. Simonov, R.T. Gazizov and A.V. Ivanov, *Dokl. Neftekhim. Sekts. Bashkir. Respub. Pravl. Vses. Khim. Obshchest.*, 1972, 317; *Chem. Abs.*, **77**, 126069.

30 T. Oritani and K. Yamashita, *Jpn. Kokai*, JP 02258773 (1990); *Chem. Abs.*, **114**, 143747.

31 N.K. Balint, *Ger. Offen*, DE 2907466 (1979); *Chem. Abs.*, **91**, 175967.

32 J. Hradil and J. Stamberg, *Collect. Czech. Chem. Commun.*, 1972, **37**, 3868; *Chem. Abs.*, **78**, 137143.

33 L. Oniciu, O.H. Oprea, D.A. Lowy and I.A. Silberg, *Rom.*, RO 87994 (1985); *Chem. Abs.*, **105**, 135156.

34 D. Ostrovskii, M. Paronen, F. Sundholm and L.M. Torell, *Solid State Ionics*, Elsevier, Amsterdam, 1999, Vol. 116.

35 K.J. Ivin, D.T. Laverty, B.S. Reddy and J.J. Rooney, *Makromol. Chem., Rapid Commun.*, 1980, **1**, 467; *Chem. Abs.*, **94**, 4278.

36 M. Hauptschein and M. Braid, *J. Am. Chem. Soc.*, 1961, **83**, 2500.

37 P. Claesson, *J. Prakt. Chem.*, 1879, **19**, 231.

38 V.E. Kuban, D.A. Zhukov, B.A. Golovin and V.V. Suchkov, *USSR*, SU 682512 (1979); *Chem. Abs.*, **92**, 6060.
39 I.G. Reznikov, Z.P. Perel, V.P. Molokoedov, G.F. Anufrieva, A.I. Kasavchenko, A.M. Shiman, I.S. Sukhoterin and L.D. Bromberg, *USSR*, SU 372212 (1973); *Chem. Abs.*, **79**, 18073.
40 R.A.G. Carrington and H.C. Evans, *J. Chem. Soc.*, 1957, 1701.
41 T. Xie, *Faming Zhuanli Shenqing Gongkai Shuomingshu*, CN 85102990 (1986); *Chem. Abs.*, **108**, 55497.
42 M.A. Podustov, V.G. Pravdin, T.S. Morgunova and Z.V. Goncharova, *Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol.*, 1990, **33**, 103; *Chem. Abs.*, **114**, 8576.
43 Y. Hirakochi and M. Takahashi, *Jpn Kokai*, JP 61060643 (1986); *Chem. Abs.*, **105**, 135969.
44 P. Sosis and L.J. Dringoli, *J. Am. Oil Chem. Soc.*, 1970, **47**, 229; *Chem. Abs.*, **73**, 65958.
45 Nippon Shokubai Kagaku Kogyo Co. Ltd, Japan, *Jpn. Kokai*, JP 59175463 (1984); *Chem. Abs.*, **102**, 78364.
46 G.N. Burhardt, *J. Chem. Soc.*, 1930, 2387.
47 A.E. Sorbel and P.E. Spoerri, *J. Am. Chem. Soc.*, 1941, **63**, 1259.
48 R.D. Stayner, US 2802789 (1957); *Chem. Abs.*, **51**, 172207.
49 R.D. Guthrie, *Introduction to Carbohydrate Chemistry*, 4th edn, Clarendon Press, Oxford, 1974.
50 K. Tsubone, *Jpn. Kokai*, JP 05214363 (1992); *Chem. Abs.*, **120**, 86075.
51 N.V. Lazaridis, M.K. Park, Y. Sayed and J.M. Baloni, US, 88236167 (1988); *Chem. Abs.*, **114**, 49572.
52 E.C.V. Percival, *Quart. Rev. Chem. Soc. London*, 1949, **3**, 369.
53 L. Ahrgren, A.N. De Belder and T. Malson, *Carbohydr. Polym.*, 1991, **16**, 211; *Chem. Abs.*, **115**, 94736.
54 A.M. Salam, M. Mosihuzzaman and M. Ahmed, *J. Indian Chem. Soc.*, 1974, **51**, 433; *Chem. Abs.*, **81**, 123166.
55 T.C. Usher, N. Patel, T. Natu and C.G. Chhagan, US 5378828 (1993); *Chem. Abs.*, **123**, 12123.
56 J. Hamuro and Y. Yoshinari, *Ger. Offen*, DE 2433407 (1975); *Chem. Abs.*, **83**, 12702.
57 T. Ihara, S. Yano, K. Kita and Y. Fujikura, *Jpn. Kokai*, JP 07062102 (1993); *Chem. Abs.*, **123**, 84406.
58 E. Hayashi, K. Takita, H. Sato and Y. Nezu, *Ger. Offen*, DE 2452719 (1975); *Chem. Abs.*, **83**, 114822.
59 T. Okuyama, K. Sakurai, T. Yamaguchi and S. Kamohara, *Jpn. Kokai*, JP 50064267 (1975); *Chem. Abs.*, **83**, 114824.
60 A.M. Leone, P.L. Francis and B. McKenzie-Gray, *J. Pineal Res.*, 1988, **5**, 367; *Chem. Abs.*, **109**, 231493.
61 C.A. Street, W.L. Di, J.F. Peniston-Bird, P. Sadler and R.E. Silman, *J. Pineal Res.*, 1996, **20**, 98; *Chem. Abs.*, **124**, 279346.
62 A. Previero, M.A. Coletti-Previero and G. Rondouin, *Methods Pept. Protein Sequence Anal., Proc 3rd Int. Conf., 1979*, C. Birr (ed), Elsevier, Amsterdam, 1980, 349; *Chem. Abs.*, **95**, 7742.
63 B. Penke and L. Nyerges, *Pept. Res.*, 1991, **4**, 289; *Chem. Abs.*, **116**, 42032.
64 T. Ramdahl and S. Liaaen-Jensen, *Acta Chem. Scand. Ser., B*, 1980, **34**, 773; *Chem. Abs.*, **94**, 209009.
65 A. Behler, R. Wachter and H. Tesmann, *Ger. Offen*, DE 19642875 (1998); *Chem. Abs.*, **128**, 321808.

66 B. Fang and T. Jiang, *Peop. Rep. China Gongneng Gaofenzi Xuebao*, 1997, **10**, 527; *Chem. Abs.*, **128**, 193921.
67 A.I. Gamzazade and A.M. Sklyar, *Izobreteniya*, 1995, **32**, 188; *USSR*, RU 2048474 (1992); *Chem. Abs.*, **124**, 346440.
68 I.S. Sukhoterin, N.I. Solodova, A.A. Sukhoterina and L.V. Migutskii, *Neftepererab. Neftekhim. (Moscow)*, 1973, **11**, 57; *Chem. Abs.*, **80**, 110200.
69 M. Takashi, Y. Mizushima, H. Abe and T. Kabaru, *Jpn. Kokai*, JP 08283229 (1995); *Chem. Abs.*, **126**, 61863.
70 M. Takashi, Y. Mizushima, T. Kabaru and A. Fujio, *Jpn. Kokai*, JP 08283228 (1995); *Chem. Abs.*, **126**, 48620.
71 W.E. Truce and C.C. Alfieri, *J. Am. Chem. Soc.*, 1950, **72**, 2740.
72 W.E. Truce and P.T. Mori, *J. Org. Chem.*, 1953, **18**, 1655.
73 G. Serchi and A.R. Poggi, *Ann. Chim. (Rome)*, 1951, **41**, 723; *Chem. Abs.*, **47**, 10488.
74 J. Ueyanagi, *J. Pharm. Soc. Japan*, 1951, **71**, 613; *Chem. Abs.*, **46**, 949.
75 F.H. Allen and D. Rogers, *Chem. Commun.*, 1966, 837.
76 P.D. Stanley, R.J. Cremlyn, J. Nangle and F.J. Swinbourne, *Magn. Reson. Chem.*, 1988, **26**, 14.
77 R.J. Cremlyn, M. Bartlett and L. Wu, *Phosphorus and Sulfur*, 1988, **39**, 173.
78 R.J. Cremlyn, L. Wu, C.R. Theocharis and W. Jones, *J. Chem. Soc. Pak.*, 1987, **9**, 167.
79 R.J. Cremlyn and L. Wu, *Phosphorus and Sulfur*, 1988, **39**, 165.
80 S.R. Sandler, *Eur.*, EP 289952 (1988); *Chem. Abs.*, **110**, 114307.
81 S.R. Sandler, *Eur.*, EP 419796 (1991); *Chem. Abs.*, **115**, 28698.
82 E. Gudriniece, E. Dreimanis and G. Vanags, *Dokl. Acad. Nauk SSSR*, 1956, **110**, 786; *Chem. Abs.*, **51**, 8052.
83 A. Strakov, E. Gudriniece, A. Ievins and G. Vanags, *Zh. Obshch. Khim.*, 1960, **30**, 3967; *Chem. Abs.*, **55**, 22251.
84 S.L. Brown, *Eur.*, EP 418081 (1991); *Chem. Abs.*, **114**, 186409.
85 D.L. Klass, *J. Org. Chem.*, 1964, **29**, 2666.
86 J.L. Smith, US 2805228 (1957); *Chem. Abs.*, **52**, 5455.
87 N.N. Vorozhtzov and E.N. Yuruigina, *Zh. Obshch. Khim. Khim., Ser. 1*, 1931, 49; *Chem. Abs.*, **25**, 4521.
88 K. Fuchs and E.E. Katscher, *Chem. Ber.*, 1929, **62**, 2381; *Chem. Abs.*, **24**, 828.
89 J. Balint, M. Szarvas and F. Fabian, *Hung. Teljes.*, HU 11887 (1976); *Chem. Abs.*, **85**, 176874; (a) A. Le Berre, A. Etienne, J. Coquelin and C. Jacquot, *Bull. Soc. Chim. Fr.*, 1973, **1**(2), 210; *Chem. Abs.*, **78**, 123952.
90 M. Fild and H.P. Rieck, *Chem. Ztg.*, 1976, **100**, 391; *Chem. Abs.*, **85**, 159332.
91 J.K. Weil, A.J. Stirton, R.G. Bistline and W.C. Ault, *J. Am. Oil Chem. Soc.*, 1960, **37**, 679.
92 A.J. Stirton, *J. Am. Oil Chem. Soc.*, 1962, **39**, 490.
93 L. Bert, V. Blinoff and M. Prokofieff, *Fr.*, FR 984456 (1951); *Chem. Abs.*, **50**, 5018.
94 L. Bert and M. Prokofieff, US 2441865 (1948); *Chem. Abs.*, **42**, 6375.
95 R. Andreasch, *Monatsh. Chem.*, 1886, **7**, 158.
96 Z. Csuros, R. Soos, L. Szeghy, B. Losonczi and I. Szergenyi, *Hung. Teljes.*, HU 9674 (1975); *Chem. Abs.*, **84**, 4495.
97 W.J. Middleton, *J. Org. Chem.*, 1979, **44**, 2291.
98 W.H. Brugmann, US 2694084 (1954); *Chem. Abs.*, **49**, 10617.
99 K.H. Bauer and J. Stockhausen, *J. Prakt. Chem.*, 1931, **130**, 35; *Chem. Abs.*, **25**, 3314.
100 K.G. Naik and M.B. Amin, *J. Indian Chem. Soc.*, 1928, **5**, 579; *Chem. Abs.*, **23**, 3205.
101 K.G. Naik and C.H. Shah, *J. Indian Chem. Soc.*, 1930, **7**, 111; *Chem. Abs.*, **24**, 4508.

102 R.J. Cremlyn, F.J. Swinbourne, J.G. Bloy, K. Pathak and O. Shode, *J. Chem. Soc. Pak.*, 1985, **7**, 111.
103 M. Periasamy, *Ger. Offen.*, DE 2942105 (1980); *Chem. Abs.*, **93**, 167647.
104 R.G. Bistline, W.R. Noble, F.D. Smith and W.M. Linfield, *J. Am. Oil Chem. Soc.*, 1977, **54**, 371; *Chem. Abs.*, **87**, 169552.
105 M.A. Kira and Y.M. Shaker, *Egypt. J. Chem.*, 1973, **16**, 551; *Chem. Abs.*, **82**, 169982.
106 Y. Ogata, T. Harada, K. Matsuyama and T. Ikejiri, *J. Org. Chem.*, 1975, **40**, 2960.
107 Y. Ogata and T. Ikejiri, *Nippon Kagaku Kaishi*, 1975, **9**, 1517; *Chem. Abs.*, **83**, 178239.
108 Y. Ogata, T. Sugimoto and M. Inaishi, *Org. Synth.*, 1980, **59**, 20.
109 P. Maki-Arvela, T. Salmi, E. Paatero and R. Sjoholm, *Ind. Eng. Chem. Res.*, 1995, **34**, 1976; *Chem. Abs.*, **122**, 317340.
110 T. Salmi, E. Paatero and K. Fagerstolt, *Chem. Eng. Sci.*, 1993, **48**, 735; *Chem. Abs.*, **118**, 254178.
111 E. Paatero, T. Salmi and K. Fagerstolt, *Ind. Eng. Chem. Res.*, 1992, **31**, 2425; *Chem. Abs.*, **117**, 21170.
112 R.J. Crawford, *J. Org. Chem.*, 1983, **48**, 1364.
113 J.E. Thompson, *Eur.*, EP 167202 (1986); *Chem. Abs.*, **104**, 206227.
114 Y. Ogata and T. Sugimoto, *J. Org. Chem.*, 1978, **43**, 3684.
115 Y. Ogata and S. Watanabe, *J. Org. Chem.*, 1979, **44**, 2768.
116 Y. Ogata and S. Watanabe, *J. Org. Chem.*, 1980, **45**, 2831.
117 Y. Ogata and S. Watanabe, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 2417; *Chem. Abs.*, **94**, 15150.
118 L.F. Fieser and M. Fieser, *Reagents for Organic Synthesis*, Wiley, New York, 1967, Vol. 1, 139.
119 L. Xuarez, Z. Rodriguez, R. Gonzalez, M. Mesa and R. Pellon, *Rev. Cenic., Cienc. Quim.*, 1994–1995 (Pub. 1995), **25–26**(1–3); *Chem. Abs.*, **127**, 247835.
120 L.F. Audrieth and M. Sveda, *J. Org. Chem.*, 1944, **9**, 89.
121 M. Zbirovsky and Z. Janu, *Czech.*, CS 146237 (1972); *Chem. Abstr.*, **78**, 110694.
122 H. Stopsach, M. Schmidt and D. Bartel, *Ger.*, DE 79487 (1971); *Chem. Abstr.*, **76**, 13924.
123 G.A. Benson and W.J. Spillane, 'Sulfamic Acid and Derivatives' in *The Chemistry of Sulfonic Acids, Esters and their Derivatives*, S. Patai and Z. Rappoport (eds), Wiley, Chichester, 1991, 954, 965.
124 K.A. Andersen, 'Sulfamic Acids and their Derivatives' in *Comprehensive Organic Chemistry*, D.N. Jones (ed.), Pergamon Press, Oxford, 1979, Vol. 3, 363.
125 M. De Nardo, C. Runti and F. Ulian, *Farmaco, Ed. Sci.*, 1984, **39**, 125; *Chem. Abstr.*, **100**, 137568.
126 F. Evangelisti, A. Bargagna and P. Schenone, *Riv. Soc. Ital. Sci. Aliment.*, 1980, **9**, 435; *Chem. Abstr.*, **95**, 115755.
127 V. Nair and S. Bernstein, *Org. Prep. Proced. Int.*, 1987, **19**, 466.
128 R.N. Khelevin, *Zh. Org. Khim.*, 1987, **23**, 1925; *Chem. Abstr.*, **108**, 166776.

CHAPTER 6

Reactions of Chlorosulfonic Acid with Heterocyclic Compounds

Heterocyclic compounds are derived from the parent carbocycle by replacement of one or more carbon atoms by heteroatoms. In saturated heterocyclic compounds, the presence of the heteroatoms makes comparatively little difference to the chemical properties. The saturated cyclic ethers, sulfides and amines thus have very similar chemical and physical properties to those of the analogous dialkyl ethers, sulfides and di- and trialkylamines. A similar argument is also valid for the partially unsaturated heterocyclic compounds. In contrast, the chemical properties of aromatic heterocyclic molecules are often substantially altered by the introduction of the heteroatom. The chemistry of heteroaromatic compounds is of great importance in studies of organic reaction mechanisms and because most biologically-active molecules are heterocyclic compounds. There are many books and reviews dealing with heterocyclic chemistry;[1–3] the chemical behaviour of many heteroaromatic compounds can be explained on the basis of two different types of aromatic ring systems: (a) those derived from the cyclopentadienyl anion by replacement of one or more methylene groups by a heteroatom, and (b) those obtained by substitution of one or more of the methylene groups in benzene by the heteroatom.[1–3]

Type (a) leads to the formation of five-membered π-excessive heterocyclic compounds **1** in which the heteroatom X donates electrons into the aromatic nucleus so facilitating electrophilic substitution reactions, *e.g.* sulfonation. Type (b) leads to the formation of the six-membered π-deficient heterocyclic compounds **2** in which the heteroatom X functions as an electron sink, withdrawing electrons from the aromatic nucleus making the molecule more resistant to electrophilic substitutions.

1

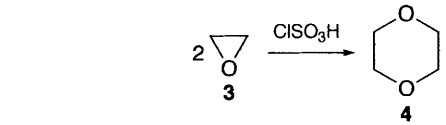
2

Saturated heterocyclic compounds may, in certain cases, react with chlorosulfonic acid. The nitrogen heterocycles containing NH groups, like the analogous

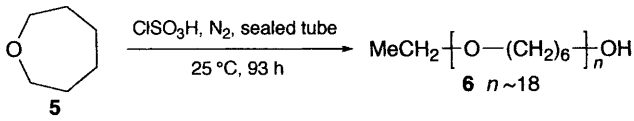
amines, are sulfonated by treatment with chlorosulfonic acid, while the tertiary nitrogen heterocycles form the corresponding amine–sulfur trioxide complexes which are sometimes useful as mild sulfonating reagents[4] (also see Chapter 4, p 101). The saturated oxygen heterocycles, THF and dioxan, also react with chlorosulfonic acid to yield the corresponding THF or dioxan–sulfur trioxide complexes.[4] The sterically strained three- and four-membered saturated heterocycles possess special reactivity due to the ease with which they undergo ring-opening reactions.

Oxo-alcohol ether sulfates useful as detergents can be synthesised by sulfation of a mixture of ethylene oxide (two equivalents) and undecyl alcohol (one equivalent) with chlorosulfonic acid or sulfur trioxide.[5]

Ethylene oxide **3** may be cyclodimerized to 1,4-dioxan **4** in the presence of superacids, like chlorosulfonic or perchloric acid (Equation 1). The reaction was accelerated by aprotic dipolar solvents, but was retarded by less polar solvents.[6] Chlorosulfonic acid also catalysed ring-opening polymerization of the saturated oxygen heterocycle oxepine **5** to the polymer **6** (Equation 2).[7]



3 **4** (1)



5 **6** $n \sim 18$ (2)

THF may also be polymerized in the presence of 30% oleum, chlorosulfonic acid and silver salts (*e.g.* silver carbonate but not silver halides) to give a good yield of polytetramethylene glycol.[8] Chlorosulfonic acid also catalysed the polymerization of 3-methyltetrahydrofuran at 0 °C to give a low molecular weight polymer, demonstrating that, in spite of the hindrance of the methyl group, polymerization was still possible.[9]

The sulfonation of aromatic heterocyclic compounds has been dealt with in several books; for instance, those by Suter,[10] Cerfontain[11] and Gilbert.[12] In addition, the chlorosulfonation of aromatic and heteroaromatic compounds was reviewed by Bassin, Cremlyn and Swinbourne.[13]

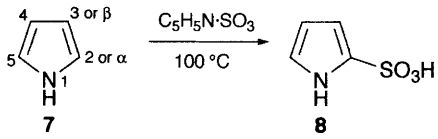
1 Aromatic Nitrogen Heterocycles

1.1 Compounds Containing One Hetero Nitrogen Atom

1.1.1 Pyrrole

Pyrrole (**7**) is readily decomposed by acids, consequently sulfonation cannot be accomplished by reaction with sulfuric or chlorosulfonic acid. However, heating

pyrrole with sulfur trioxide–dioxan, or better with pyridine–sulfur trioxide complex, yields the 2-sulfonic acid **8** (Equation 3).

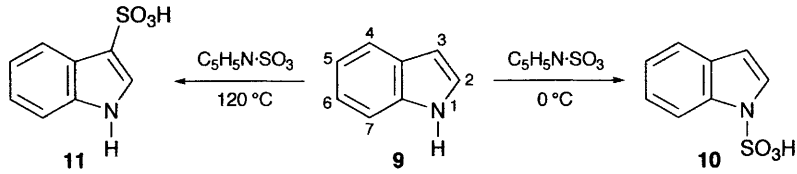


(3)

Prolonged reaction with pyridine–sulfur trioxide complex can yield the 2,5-disulfonic acid, and if both the α-positions are blocked sulfonation can occur in the β- or 3-position.[1–4] In pyrrole, electron donation from the heteroatom favours electrophilic attack in the 2- and 5-positions since these are the sites of maximum π-electron density. It is found that pyrroles containing electron-withdrawing substituents are stabilized relative to the parent heterocycle and may consequently be sulfonated by chlorosulfonic acid or oleum.[3]

1.1.2 Indole

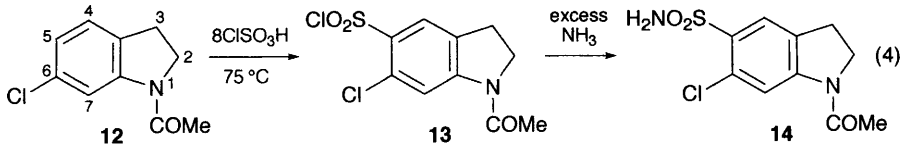
Indole (benzopyrrole) **9** is sulfonated by treatment with the pyridine–sulfur trioxide adduct to avoid acid-catalysed polymerization. If the reaction is conducted at low temperature, *N*-sulfonation occurs to give the 1-sulfonic acid **10**, whereas at 120 °C, the reaction gave indole-3-sulfonic acid **11** (Scheme 1).[1–4]



Scheme 1

In indole, the 3-position appears more reactive towards sulfonation than with the 2-position; the reactivity of the 3-position is also shown in the reaction of 2-phenylindole with pyridine–sulfur trioxide complex which yields 2-phenylindole-3-sulfonic acid in which sulfonation occurs in the 3-position of the indole ring in preference to the phenyl ring.[4]

1-Acetyl-6-chloroindoline **12**, by heating with excess chlorosulfonic acid (eight equivalents) for 4 hours, afforded the 5-sulfonyl chloride **13**, 48%, which by condensation with ammonia gave the 5-sulfonamide **14** (Equation 4).[14] Sulfonation occurs in the expected 5-position, which is *para* with respect to the electron-donating nitrogen atom and is different from indole which sulfonates in the 3-position. The sulfonamide **14** was the intermediate in the synthesis of a range of 1-substituted-6-chloro-5-indolinesulfonamides with diuretic activity.[14]



1.1.3 Carbazole

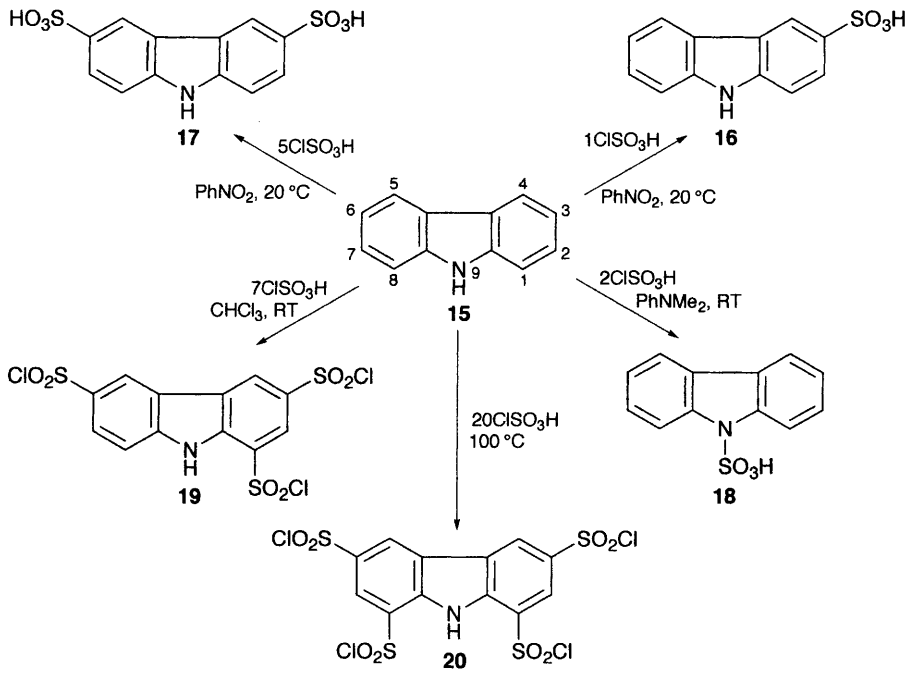
The sulfonation of carbazole (dibenzopyrrole, **15**) has been extensively studied[10–12] and was reviewed by Katritzky and Taylor.[15] The favoured sites for sulfonation are the 3- and 6-positions which are in agreement with the π-electron density pattern of the heterocycle and are *para* to the electron-donating hetero nitrogen atom. The orientation of sulfonation resembles that shown in the sulfonation of diphenylamine (see Chapter 4, p 100). The reaction of chlorosulfonic acid on carbazole in organic solvents has been examined under various conditions:[16] at 20 °C, using the reagent (one equivalent) in nitrobenzene, the major product was carbazole-3-sulfonic acid **16**, 85%.[1,16] With more chlorosulfonic acid (four to five equivalents), the 3,6-disulfonic acid **17**, 90%, was isolated (Scheme 2).[16] On the other hand, sulfonation by chlorosulfonic acid (two equivalents) in the presence of excess dimethylaminobenzene at room temperature (2 hours) afforded the 9-sulfonic acid **18**, 86%.[16] In this reaction, the effective reagent is the dimethylaminobenzene–sulfur trioxide complex accounting for the different orientation of sulfonation, since the 9-sulfonic acid is unstable in acidic media and migrates to the adjacent 1- and 8-positions.

Attempts to prepare carbazolesulfonyl chlorides by reacting carbazole **15** with chlorosulfonic acid (one or two equivalents) in thionyl chloride were unsuccessful and appear to yield polychlorinated products.[17] On the other hand, treatment of carbazole with boiling excess chlorosulfonic acid in the presence of varying proportions of phosphorus pentachloride was claimed[18] to yield carbazolesulfonyl chlorides. Carbazole **15** reacted with excess chlorosulfonic acid (seven equivalents) in chloroform solution at room temperature (1 hour) to give the 1,3,6-trisulfonyl chloride **19**, 72% (Scheme 2).[17]

Reaction of carbazole with a very large excess of the reagent (20 equivalents) at room temperature gave a mixture of the 1,3,6-trisulfonyl chloride **19** and the 1,3,6,8-tetrasulfonyl chloride **20**. However, when the reaction mixture was heated at 100 °C for 1 hour, it afforded a low yield of the 1,3,6,8-tetrasulfonyl chloride **20**, 27%. If heating was continued for 6 hours, the yield of the tetrasulfonyl chloride was increased (55%), but the product appeared to be contaminated with the 2,3,6,8-isomer.[17]

The chlorosulfonation of dinitrocarbazoles by reaction with chlorosulfonic acid has also been studied.

3,6-Dinitrocarbazole, by heating at 100 °C with a large excess of chlorosulfonic acid (8–18 equivalents) and phosphorus pentachloride (3–5 equivalents) afforded a mixture of the corresponding mono- (5.1–21.5%) and disulfonyl chlorides (78.5–94.9%) in 77.3–94.4% overall yields.[19]



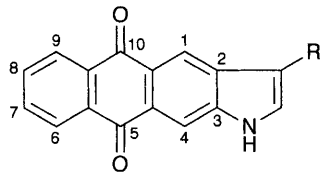
Scheme 2

Heating 3,6-dinitrocarbazole with a very large excess of chlorosulfonic acid (20–30 equivalents) in carbon tetrachloride at 77 °C gave a mixture of the sulfonyl chloride (95.2–98.9%) and the sulfonic acid (4.8–1.1%) in 98% overall yield. At 100 °C, the reaction afforded the sulfonyl chloride (73.3%) and the sulfonic acid (26.7%). 1,6-Dinitrocarbazole, by heating with excess chlorosulfonic acid (8, 12 and 18 equivalents) and phosphorus pentachloride (three equivalents) at 100 °C gave a mixture of the mono- (37.9, 6.2, 92.2%) and disulfonyl chlorides (62.1, 93.8 and 7.8%) respectively. The chlorosulfonation of dinitrocarbazoles was also effected by treatment with chlorosulfonic acid in the presence of phosphorus pentoxide and phosphoryl chloride.[19]

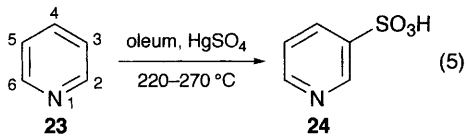
Naphtho[2,3*f*]indole-5,10-dione **21** reacted with excess chlorosulfonic acid in dioxan containing sodium sulfate to give the sulfonyl chloride **22** in 63% yield.[20] In this indole derivative sulfonation again occurs in the expected 3-position.

1.1.4 Pyridine

Pyridine is an important example of a π-deficient six-membered nitrogen heterocycle in which the heteroatom acts as an electron-withdrawing site so electrophilic substitutions are difficult. For example, pyridine **23** may be sulfonated only under drastic conditions, *e.g.* by heating with oleum at 220–270 °C in the presence of mercury(II) sulfate catalyst to give the 3-sulfonic acid **24** (Equation 5).[1–3,10]



21 R = H
22 R = SO_2Cl

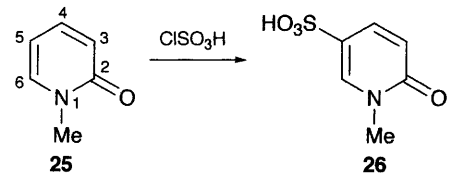


23 **24** (5)

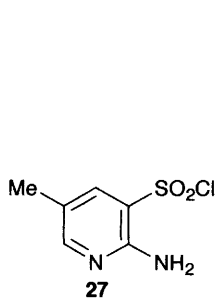
Pyridine **23** (two equivalents) reacts with chlorosulfonic acid in an inert organic solvent, *e.g.* carbon tetrachloride, to yield equimolar quantities of the pyridine–sulfur trioxide complex and pyridinium chloride; this behaviour is typical of the reaction of a tertiary amine with the reagent (see Chapter 4, p 101).[4,10–12] The potentiometric curve for the neutralization of chlorosulfonic acid by pyridine in nitromethane has been determined and showed two steps.[21] Pyridine 1-oxonium chloride similarly yields the pyridine–sulfur trioxide adduct on treatment with chlorosulfonic acid.[11,22]

In pyridine derivatives containing electron-donating groups, electrophilic substitution reactions are facilitated; thus 3-aminopyridine reacts with chlorosulfonic acid to give the corresponding 2- or 6-sulfonic acid (sulfonation *o*/*p* to the electron-donating amino group) since removal of the amino group yields pyridine-2-sulfonic acid.[10] *N*-Substituted 2-pyridones also reacted with chlorosulfonic acid giving the corresponding 5-sulfonic acids; thus 1-methyl-2-pyridone **25** was converted into the 5-sulfonic acid **26** (Equation 6).[23]

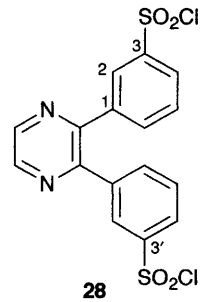
2-Amino-5-methylpyridine reacts with excess chlorosulfonic acid under forcing conditions to give the 3-sulfonyl chloride **27**,[14,24] whereas 2,3-diphenylpyrazine with chlorosulfonic acid (six equivalents) at 170 °C afforded the corresponding 3,3′-disulfonyl chloride **28**.[25]



25 **26** (6)



27

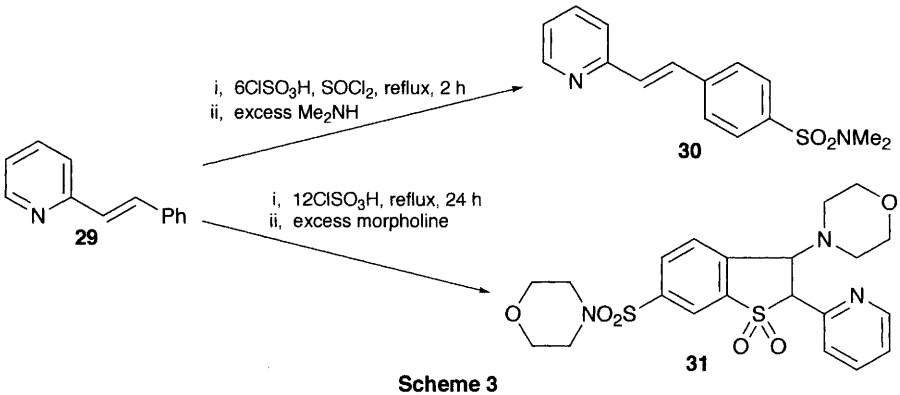


28

These reactions illustrate the significant deactivation caused by the –M electronic effect of the hetero nitrogen atoms, especially under acidic conditions,

and the latter reaction further demonstrates the transmission of the –M electronic effect into the phenyl rings.[14]

Recent research[26] showed that styrylpyridine **29** reacts with chlorosulfonic acid (six equivalents) in boiling excess thionyl chloride to yield the corresponding *p*-sulfonyl chloride which was characterized as the dimethylsulfonamide derivative **30** (Scheme 3).

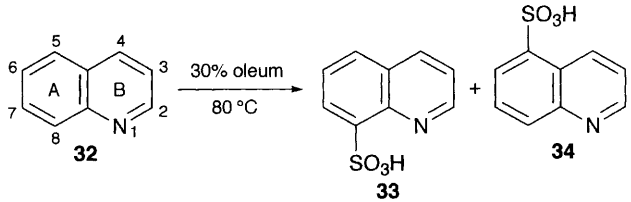


Scheme 3

It was discovered that when styrylpyridine **29** was refluxed with more chlorosulfonic acid (12 equivalents) for 24 hours, a further cyclization of the substrate occurred and treatment of the initial product with excess morpholine afforded the morpholinosulfonylmorpholidate **31**. The postulated mechanism for the conversion of **29**→**31** is reported.[26] In the reaction, it was surprising, even under the drastic conditions used, that polymerization of styrylpyridine was not observed, indicative of the stabilizing effect of the 2-pyridyl moiety on the alkenic double bond.

1.1.5 Quinoline

Quinoline **32** is sulfonated more readily than pyridine, but the heterocycle is still considerably less reactive than naphthalene due to the presence of the electron-withdrawing hetero nitrogen atom. Sulfonation of quinoline **32** with 30% oleum at 80 °C yields mainly the 8-sulfonic acid (**33**, 54%) together with some of the 5-isomer **34** (Equation 7).[10–12]



(7)

In quinoline **32**, the homocyclic ring A is more reactive towards electrophilic substitution than ring B due to the deactivating effect of the heteroatom; hence

substitution occurs preferentially in ring A, also as in naphthalene (Chapter 4, p 43) the α-positions of quinoline are more reactive than the β-positions.

When the sulfonation was carried out in the presence of mercury(II) sulfate catalyst, quinoline-8-sulfonic acid **33** was the only isolated product.[10,11]

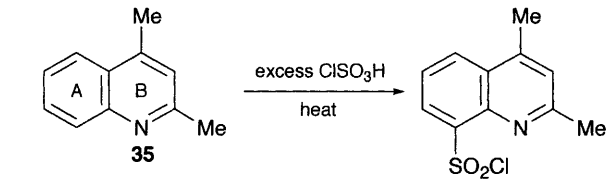
8-Ethoxyquinoline reacted with chlorosulfonic acid at 70 °C to give, as expected, the corresponding 5-sulfonic acid (sulfonation in ring A and *para* to the electron-donor ethoxy group).[27]

8-Methoxyquinoline reacts with a large excess of chlorosulfonic acid (10 equivalents) at 0–15 °C to give the 5-sulfonyl chloride. 8-Methoxy-5-quinoline-sulfonyl chloride is used as an analytical fluorogenic reagent for the chromatographic determination of amines, amino acids and peptides.[28]

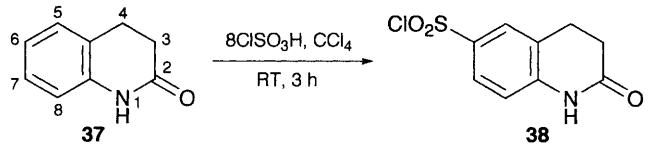
Quinolinesulfonyl hydrazides, useful as blood serum amine monooxidase inhibitors, are synthesised from the parent substituted quinolines *via* chlorosulfonation, achieved by treatment with excess chlorosulfonic acid and subsequent condensation of the sulfonyl chloride with hydrazine.[29]

2,4-Dimethylquinoline **35**, with hot excess chlorosulfonic acid, yields the corresponding 8-sulfonyl chloride **36** (Equation 8).[30] In this substrate, ring B has been somewhat activated by the two electron-donating (+I electronic effect) methyl groups, but not sufficiently to overcome the deactivating effect of the hetero nitrogen atom and induce sulfonation in ring B.

3,4-Dihydrocarbostyril **37** reacted with excess chlorosulfonic acid (eight equivalents) in carbon tetrachloride solution at room temperature (3 hours) forming the 6-sulfonyl chloride **38**, 80% (Equation 9).[31] The orientation of sulfonation in the 6-position is to be expected, since it is *para* to the electron-donating NH group.



(8)

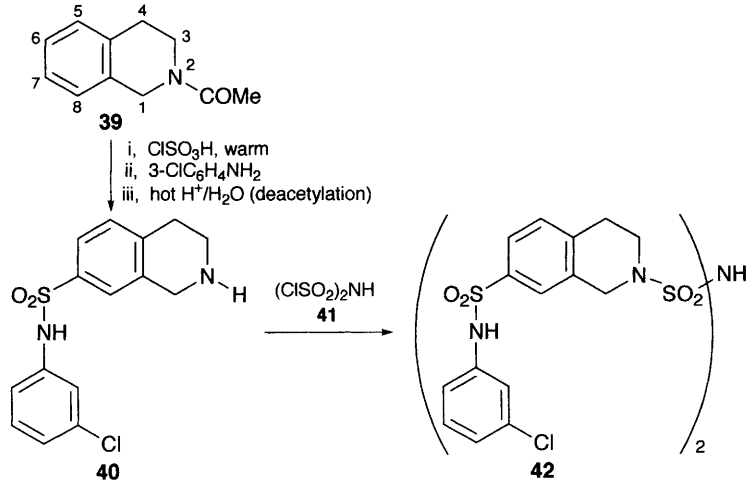


(9)

The sulfonyl chloride **38** was reduced to the corresponding thiol and condensed with haloesters giving compounds possessing anti-inflammatory and anticoagulating properties.[31] A similar reaction sequence was also carried out starting from carbostyril (2-quinolone) to give the analogous compounds containing the 3,4-double bond.[31]

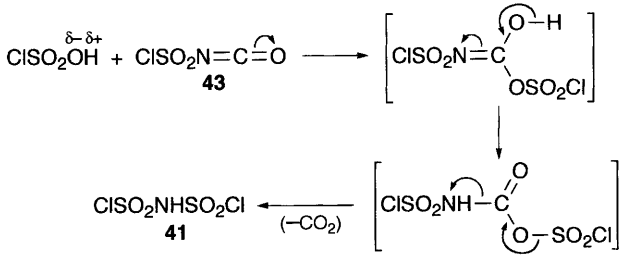
1.1.6 Isoquinoline

Isoquinoline (two equivalents) reacts with chlorosulfonic acid (one equivalent) in an inert organic solvent to give an equimolar mixture of the isoquinoline–sulfur trioxide complex and isoquinolinium chloride.[4,11] Sulfonation of isoquinoline with 40–50% oleum at room temperature affords the 5-sulfonic acid.[2,3,11,12] *N*-Acetyl-1,2,3,4-tetrahydroisoquinoline **39** reacted with excess chlorosulfonic acid to give the 7-sulfonyl chloride which, by condensation with 3-chloroaniline and deacetylation, formed the 7-(3-chlorobenzenesulfonamide) derivative **40** and subsequent reaction with dichlorosulfonylimine **41** gave the antiallergic agent **42** (Scheme 4).[32]



Scheme 4

Dichlorosulfonylimine **41** was obtained by reaction of chlorosulfonylisocyanate **43**[33] with chlorosulfonic acid; the probable mechanism for this reaction is shown in Scheme 5.

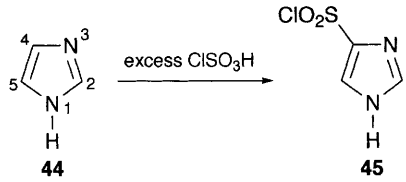


Scheme 5

1.2 Compounds Containing Two or More Hetero Nitrogen Atoms

1.2.1 Imidazole

Imidazole **44** reacts with excess chlorosulfonic acid to give an excellent yield of the 4-sulfonyl chloride **45** (Equation 10);[14,34] the chlorosulfonation was also achieved by heating the heterocycle **44** with chlorosulfonic acid (1.5 equivalents) in excess thionyl chloride (Equation 10).[34]

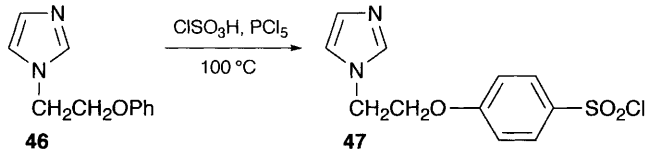


(10)

The action of chlorosulfonic acid on 2-(4-chlorophenyl)imidazole also gave the 4-sulfonyl chloride with preferential substitution occurring in the imidazole ring rather than in the phenyl nucleus – presumably the orientation is as a result of favourable stereoelectric factors.[35]

2-Methylimidazole, by heating with excess chlorosulfonic acid (eight equivalents) at 150 °C for 3 hours followed by addition of thionyl chloride and further heating at 100 °C (3 hours), afforded the 4-sulfonyl chloride (50%).[36,37] 1,2-Dimethylimidazole, by heating with chlorosulfonic acid–thionyl chloride, similarly gave the corresponding 4-sulfonyl chloride.[36] 4-Bromoimidazole by heating with excess chlorosulfonic acid (10 equivalents) at 190–200 °C afforded the 5-sulfonyl chloride (51% yield).[38]

Treatment of 4- and 5-chloro-1-methylimidazole with boiling chlorosulfonic acid yields the 5- and 4-sulfonyl chlorides respectively.[3,39] 1-(2-Phenoxyethyl)imidazole **46** reacts with a mixture of chlorosulfonic acid (two equivalents) and phosphorus pentachloride (one equivalent) at 100 °C (10 minutes) to give the *p*-sulfonyl chloride **47** (Equation 11).[14,40]



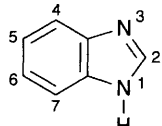
(11)

In the substrate **46**, the phenoxy nucleus is strongly activated towards electrophilic attack by the oxygen atom (+M electronic effect) accounting for the observed orientation of sulfonation.

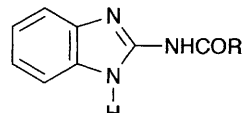
In agreement with this argument, 2-(4-nitrophenyl)imidazole was chlorosulfonated in the imidazole ring yielding the 4-sulfonyl chloride.[14,41] The phenyl nucleus is now deactivated by the presence of the electron-withdrawing nitro group, so sulfonation occurs in the imidazole ring.

1.2.2 Benzimidazole

In benzimidazole **48**, molecular orbital calculations indicate that the maximum π-electron density is in the 5-position (*para* to the NH moiety) and in agreement this is found to be the preferred site of sulfonation.[11]

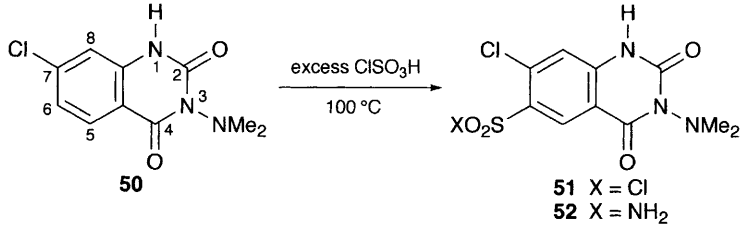


48



49

Benzimidazole derivatives with electrophilic substituents (*e.g.* phenyl, *p*-nitrophenyl, *etc.*) in the 2-position, on treatment with excess chlorosulfonic acid, gave the corresponding 5-sulfonyl chlorides, but other 2-substituted benzimidazoles formed the 5-sulfonic acids. Thus, benzimidazole **48** and the 2-methyl derivative by heating with excess chlorosulfonic acid (six equivalents) at 105–110 °C (30 minutes) gave 5-benzimidazolesulfonic acid (65%). A range of benzimidazol-2-yl carbamates (**49**; R = C_1–C_4 alkyl radicals), reacted with excess chlorosulfonic acid at 40 °C to yield the corresponding 5-sulfonyl chlorides.[14,42] The major factors affecting the yield and quality of the product were the reaction temperature and the purity of the starting materials.[42a]



(12)

50

51 X = Cl
52 X = NH_2

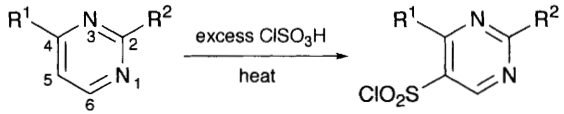
7-Chloro-3-(dimethylamino)-2,4-(1*H*,3*H*)-quinazolinedione **50** by heating with excess chlorosulfonic acid at 100 °C afforded the 6-sulfonyl chloride **51**, which on subsequent reaction with ammonia gave the sulfonamide **52** (Equation 12).[43] Some of the substituted derivatives of type **52** showed diuretic properties.[43]

1.2.3 Pyrimidine

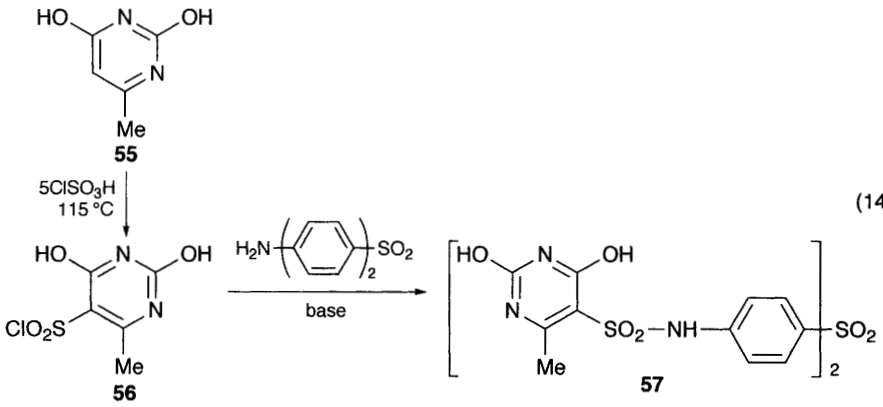
Pyrimidine (**53**; $R^1 = R^2 = H$) has not been sulfonated due to the strongly deactivating effect of the two nitrogen atoms.[11,12] However, pyrimidines containing electron-donating substituents in the 2-, 4- or 6-positions activate the π-deficient system sufficiently to allow sulfonation in the 5-position (*meta* to the deactivating hetero nitrogen atoms).[11] For instance, uracil (2,4-dihydroxypyrimidine, **53**; $R^1 = R^2 = OH$), by heating with excess chlorosulfonic acid (nine equivalents) at 90–100 °C, afforded the 5-sulfonyl chloride (**54**; $R^1 = R^2 = OH$) (Equation 13).[44–46]

6-Methyluracil **55** with hot excess chlorosulfonic acid (five equivalents) at 115 °C gives the 5-sulfonyl chloride **56**,[46,47] which by condensation with 4,4′-

diaminodiphenylsulfone gave the disulfonamidosulfone **57**, useful in the treatment of rheumatoid arthritis (Equation 14).[48] 6-Amino-1,3-dimethyluracil similarly reacted with chlorosulfonic acid (100 °C, 2 hours) to yield the 5-sulfonyl chloride.[49]



53 **54** (13)

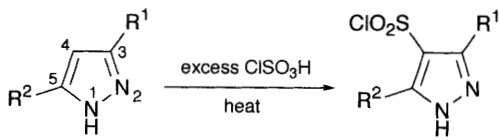


55 **56** **57** (14)

Other pyrimidine derivatives sulfonated in the 5-position by treatment with chlorosulfonic acid at the temperatures shown in brackets included: 2-chloro- and 2,4-dichloro;[50] 2-amino, by boiling chlorosulfonic acid (10 equivalents, 8 hours);[51] 4-methyl-2-amino (110 °C);[52] 6-methyl-2,4-diamino (110 °C);[52] 4-hydroxy-2-amino (110 °C);[52] 6-methyl-4-hydroxy-2-amino (110 °C);[52] 4-hydroxy-2,6-diamino (100 °C);[49] 2-hydroxy-4,6-diamino (100 °C);[49] 2-methylthio-4,6-diamino (100 °C);[49] 2-methyl-4-hydroxy-6-amino (100°C);[49] 2-hydroxy (110 °C);[11] 2-hydroxy-4-amino (110 °C);[46] 6-methyl-2-hydroxy-4-amino (110 °C);[46] 6-amino-2,4-dihydroxy (90 °C);[45] 4-amino-6-hydroxy (100 °C);[49] 2,4-diamino-6-chloro, by boiling chlorosulfonic acid (eight equivalents, 1 hour).[49]

1.2.4 Pyrazole

Pyrazole (**58**; $R^1 = R^2 = H$) by heating with 20% oleum at 90 °C yields the 4-sulfonic acid and 3,5-dimethylpyrazole (**58**; $R^1 = R^2 = Me$) reacts with excess chlorosulfonic acid at 90 °C to give a good yield of the 4-sulfonyl chloride (**59**; $R^1 = R^2 = Me$) (Equation 15).[53]



58 **59** (15)

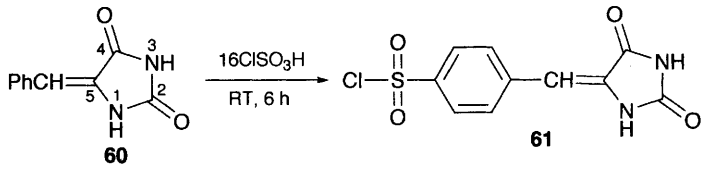
1.2.5 Hydantoins and Barbiturates

5-(Benzylidene)hydantoin **60**, by treatment with a very large excess of chlorosulfonic acid (16 equivalents) at room temperature (6 hours), gave the *p*-sulfonyl chloride **61**, 87% (Equation 16).[54]

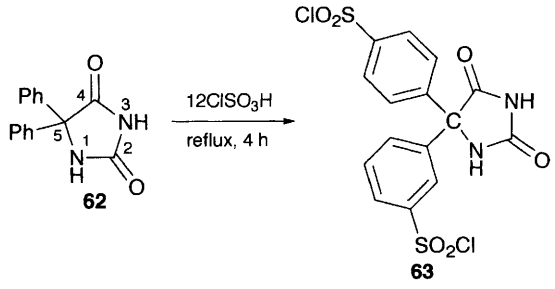
5,5-Diphenylhydantoin **62**, by boiling with the reagent (12 equivalents) for 4 hours, afforded the disulfonyl chloride **63**, 82% (Equation 17).[55]

Repetition of the experiment under the same conditions, except that at the end of the reaction excess thionyl chloride was added to the mixture which was then left at room temperature for 5 days, gave the same product **63** in a slightly higher yield (88%).[55] The NMR spectrum of the bisdimethylsulfonamide derivative of **63** indicated a *m,p*-orientation of sulfonation as shown in the structure **63**.[55]

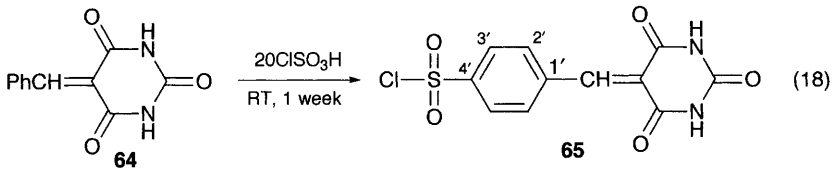
5-(Benzylidene)barbituric acid **64** reacted smoothly with a very large excess of chlorosulfonic acid (20 equivalents) at room temperature (1 week) yielding the *p*-sulfonyl chloride **65**, 85% (Equation 18).[56] The chlorosulfonation may also be effected by treatment of 5-(benzylidene)barbituric acid **64** with a mixture of chlorosulfonic acid (six equivalents) in excess thionyl chloride at room temperature for one week to give the sulfonyl chloride **65**, 80% yield. This appeared to be the purest product and these were concluded to be the optimum conditions for chlorosulfonation of this substrate. The *p*-sulfonation of benzylidenebarbituric acid **64** would be expected, in view of the strongly electron-donating character of alkylidene double bond, as was observed in sulfonation of 5-benzylidenehydantoin. The chlorosulfonation of other 5-arylidenebarbituric acids was studied and appeared to be successful with the *p*-methoxybenzylidene, cinnamylidene and 2-thienylidene derivatives.[55]



(16)

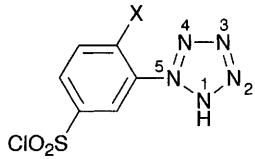


(17)



1.2.6 Tetrazoles

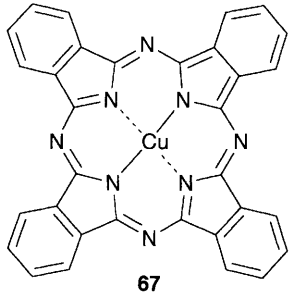
A variety of substituted 5-aryltetrazoles reacted with excess chlorosulfonic acid yielding the corresponding *para* sulfonyl chlorides (**66**; X = Me, Br, Cl). In these compounds, it was observed that sulfonation always occurred *para* to the substituent group.[56]



66 X = Me, Br, Cl

1.2.7 Phthalocyanines (Tetrabenzotetraazaporphines)

Copper phthalocyanine **67** is an important example of a group of blue to green organic pigments. Phthalocyanines may be made water soluble by sulfonation, and the soluble phthalocyanine sulfates are important as direct dyes in the dyestuffs industry.



67

Phthalocyanines may be regarded as benzopyrrole derivatives, and heating with excess chlorosulfonic acid at 125–130 °C converts them into sulfonyl chlorides.[10,57] Heating copper phthalocyanine **67** with a mixture of thionyl chloride and chlorosulfonic acid followed by condensation of the resultant product with 3-methoxypropylamine and di(*o*-methylphenylamino)imine afforded a blue dye used for blue inks in ballpoint pens.[58] Copper phthalocyanine **67**, with chlorosulfonic acid and 3-(dimethylamino)propylamine, gave a precipitate which, on dissolution in an aqueous mixture of ethylene glycol–urea and treatment with aluminium sulfate, dyed paper a clear turquoise blue.[59] Crude alpha-type

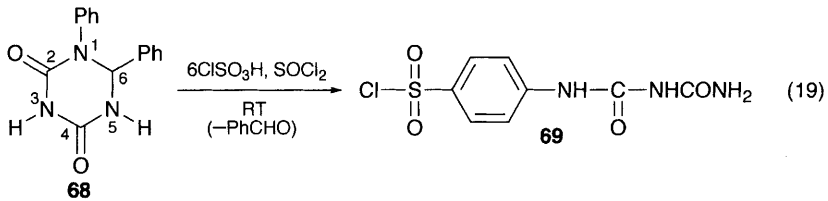
phthalocyanine pigments are manufactured by mixing copper phthalocyanine **67** with chlorosulfonic acid followed by neutralization by treatment with an aqueous base in the presence of crystalline sodium sulfate. The resultant pigments are used in printing inks, coating materials and plastic mouldings.[60] Reactive copper phthalocyanine dyes may also be obtained by chlorosulfonation of copper phthalocyanine **67** with chlorosulfonic acid and reaction of the intermediate with ammonium chloride and 4-fluoro-5-chloro-6-(3-aminophenyl)aminopyrimidine. The resultant compound dyed cotton fabrics shades of turquoise blue.[61]

Metal phthalocyanines, by heating with chlorosulfonic acid in solvents at 80–150 °C, gave tetrachlorosulfonate salts which can be converted into the corresponding sulfonic acids. For instance, copper phthalocyanine **67** with chlorosulfonic acid (four equivalents) in acetic acid at 85–95 °C (2 hours) gave the tetrachlorosulfonate salt (90%).[62]

Tetrabenzotriazaporphine reactive dyes are obtained by treating copper tetrabenzotriazaporphine with chlorosulfonic acid and condensation of the resultant chlorosulfonyl derivative with an aqueous solution of β-sulfatoethyl-(4-aminophenyl)sulfone. The product dyed cotton a fast green colour.[63]

1.2.8 1,6-Diphenyl-2,4-dioxohexahydro-s-triazine

1,6-Diphenyl-2,4-dioxohexahydro-s-triazine **68**, by treatment with excess chlorosulfonic acid (six equivalents) in thionyl chloride for 3 days at room temperature gave *N*-(*p*-chlorosulfonylphenyl)-*N'*-carbamoylurea **69** by a novel ring opening reaction (Equation 19).[64] In the conversion of **68** to **69**, benzaldehyde was formed as a by-product and the suggested reaction mechanism is shown in Scheme 6.[65]

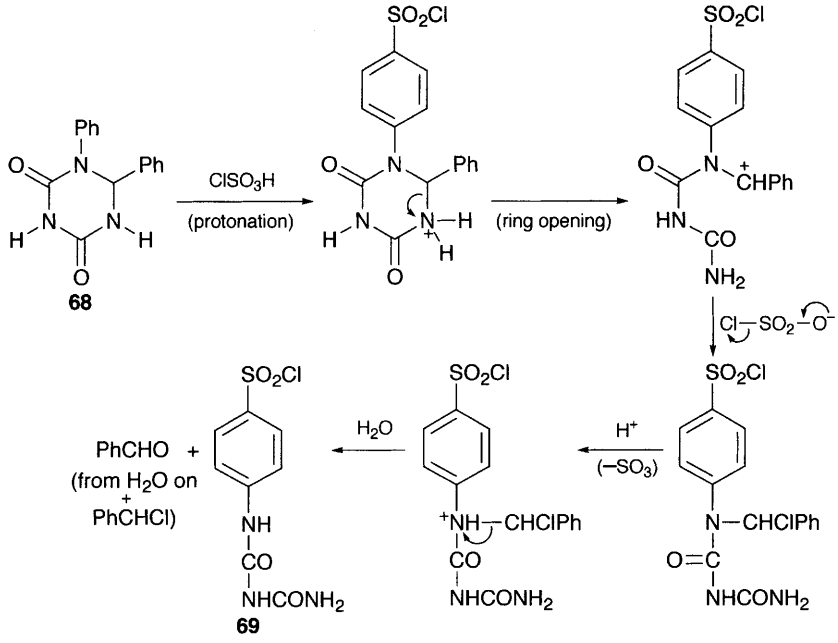


68 **69** (19)

Surprisingly, the carbamoylurea **69** was not isolated by heating the triazine **68** with concentrated hydrochloric acid, so possibly the presence of the chlorosulfonyl group on the *N*-phenyl ring may play a subtle role in the ring-opening reaction by chlorosulfonic acid. The sulfonyl chloride **69** was converted into sulfonamides, several of which showed high *in vivo* fungicidal activity against barley powdery mildew (*Erysiphe graminis*).[64]

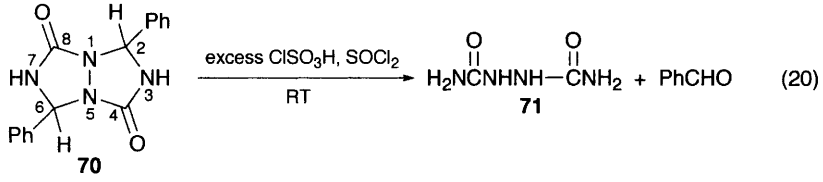
1.2.9 3,7-Dihydro-2,6-diphenyl-1,3,5,7-tetraazabicyclo[3.3.0]octane-4,8-dione

3,7-Dihydro-2,6-diphenyl-1,3,5,7-tetraazabicyclo[3.3.0]octane-4,8-dione **70** reacted with excess chlorosulfonic acid in thionyl chloride at RT (1 week) to yield hydrazinodicarbonamide **71** and benzaldehyde by a similar type of ring-opening



Scheme 6

reaction involving a stabilized benzylic carbocation intermediate (Equation 20).[65] Repetition of the reaction under various conditions gave similar results and the identical product **71** was also obtained when the octanedione **70** was heated with concentrated hydrochloric acid.



(20)

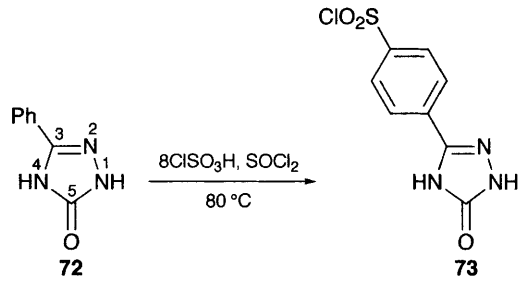
1.2.10 3-Phenyl-1,2,4-triazolen-5-one

3-Phenyl-1,2,4-triazolen-5-one **72** did not react with excess chlorosulfonic acid at RT, but by heating with the reagent (eight equivalents) in thionyl chloride at 80 °C for 2 hours, the reaction afforded the *p*-sulfonyl chloride **73**, 68% (Equation 21).[66]

1.2.11 Criss-cross Adducts from Isocyanates and Diaryl Azines

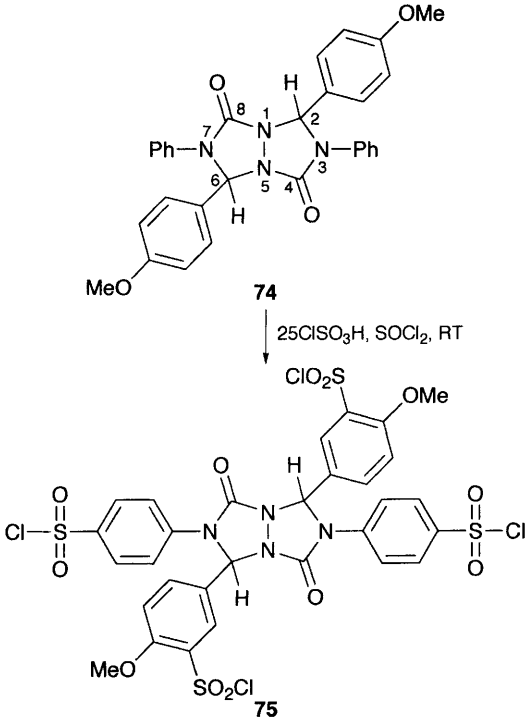
The criss-cross cycloadducts from the reaction of isocyanates and diaryl azines have been chlorosulfonated by treatment with a mixture of chlorosulfonic acid and thionyl chloride.[66]

The cycloadduct [3,7-diphenyl-2,6-di(4-methoxyphenyl)-1,3,5,7-tetrazabicy-



72 73 (21)

clo[3.3.0]octane-4,8-dione, **74**], obtained from phenylisocyanate and *p*-methoxybenzaldehyde, reacted with a very large excess of chlorosulfonic acid (25 equivalents) in thionyl chloride at RT (1 week) to give the tetrasulfonyl chloride **75**, 82% (Equation 22).[66] On the other hand, attempted chlorosulfonation of the analogous less reactive cycloadduct from benzaldehyde azine and phenylisocyanate was unsatisfactory giving a complex mixture of products.[65]



(22)

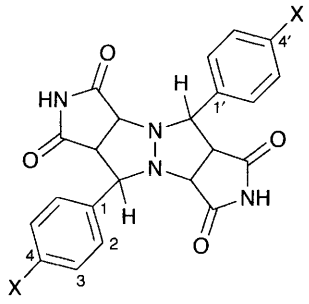
An alternative synthetic route to these sulfonyl criss-cross cycloadducts involved performing the cycloaddition reaction using sulfonyl aryl azines obtained by chlorosulfonation of the appropriate diaryl azine as described in Chapter 4, p 119.

1.2.12 Criss-cross Adducts from Diaryl Azines and Maleimides or Maleic Anhydride

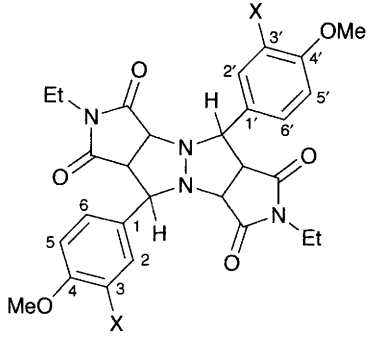
Criss-cross cycloadducts may also be prepared by reaction of diaryl azines with either maleimides or maleic anhydride and these may also be chlorosulfonated by treatment with chlorosulfonic acid.[67] The cycloadduct **76** (from the reaction of benzaldehyde azine and maleimide) reacts with chlorosulfonic acid at RT (1 week) to give the corresponding 4,4′-disulfonyl chloride **77**, 70%.[67]

Similarly, the cycloadduct (**78**, from 4-methoxybenzaldehyde azine and *N*-ethylmaleimide) by treatment with a large excess of the reagent (eight equivalents) in thionyl chloride at RT (1 week) afforded the corresponding 3,3′-disulfonyl chloride **79**, 86% yield. The analogous cycloadduct from 2-methoxybenzaldehyde azine and *N*-ethylmaleimide was also chlorosulfonated by chlorosulfonic acid–thionyl chloride to give the corresponding 5,5′-disulfonyl chloride (67%).[67] In both cases, as expected, sulfonation occurred *para* to the strongly electron-donating methoxy group.

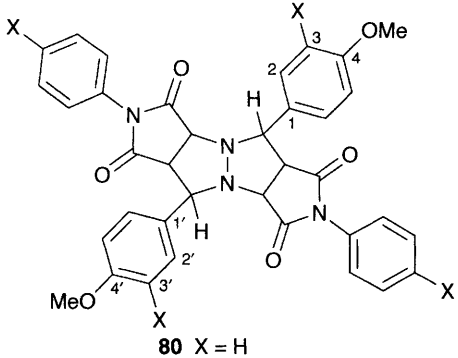
The cycloadduct from 4-methoxybenzaldehyde azine and *N*-phenylmaleimide **80**, by reaction with a very large excess of chlorosulfonic acid (24 equivalents) – thionyl chloride (1 week) afforded the tetrasulfonyl chloride **81**, 86% yield.



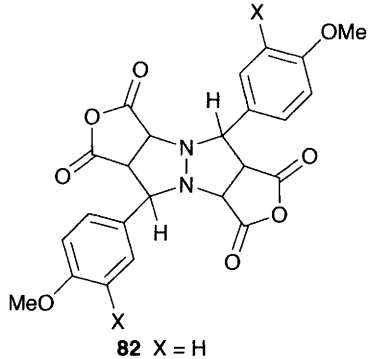
76 X = H
77 X = SO_2Cl



78 X = H
79 X = SO_2Cl



80 X = H
81 X = SO_2Cl



82 X = H
83 X = SO_2Cl

The cycloadduct **82** (from the reaction of 4-methoxybenzaldehyde azine and maleic anhydride), by treatment with chlorosulfonic acid (12 equivalents) in thionyl chloride at room temperature for 1 week afforded the corresponding 3,3′-disulfonyl chloride, **83**, (55%).[67] The yield was appreciably lower than the 86% yield obtained in the chlorosulfonation of the analogous cycloadduct **78** from *N*-ethyl maleimide. The decreased yield is probably due to competing ring-opening reactions suffered by the anhydride adduct **82** under the acidic conditions.

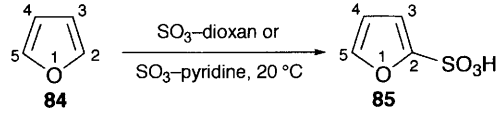
2 Heterocyclic Oxygen Compounds

2.1 Furan

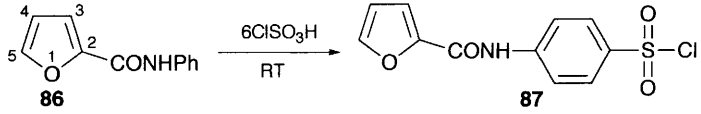
Furan **84** is a five-membered π-excessive aromatic heterocycle containing one hetero oxygen atom. It is unstable in acids, forming tars, so like pyrrole (Chapter 6, p 182) the substrate cannot be sulfonated by sulfuric or chlorosulfonic acid. However, again like pyrrole, treatment of furan **84** with sulfur trioxide in either dioxan or pyridine yields the 2-sulfonic acid **85** (Equation 23). [1-4,10,12]

More prolonged reaction gives furan-2,5-disulfonic acid. In furan **84**, the 2- and 5-positions are the sites of maximum π-electron density as a result of electron donation from the heteroatom and consequently they are the favoured positions for the electrophilic substitutions.

The furan nucleus is stabilized by the presence of electron-withdrawing substituents and so sulfonation of such furan derivatives may be achieved by the use of acidic reagents like sulfuric or chlorosulfonic acid. Thus: furan-2-carboxaldehyde (furfural) is converted into the corresponding 5-sulfonic acid by treatment with oleum;[1] furan-2-carboxylic acid with excess chlorosulfonic acid gives a mixture of the 4-and 5-sulfonyl chlorides; and furan-2-carboxamide is reported[53]to react with excess reagent to yield the 4-sulfonyl chloride. In contrast, furan-2-carboxanilide **86** reacted with chlorosulfonic acid (six equivalents) at RT (1 hour) to give the *p*-sulfonyl chloride **87**, 60% (Equation 24).[68]



84 **85** (23)



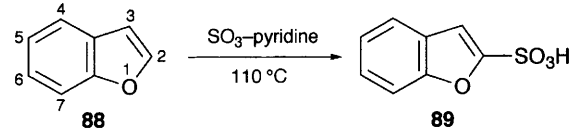
86 **87** (24)

It was rather surprising that sulfonation of the anilide **86** did not occur in the reactive furan nucleus, although if the *para* position of the phenyl ring was blocked, then sulfonation did take place in the 4-position of the furan ring[68] (see Chapter 4, p 108).

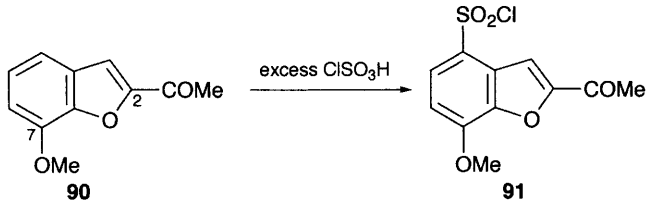
2.2 Benzofuran

Benzofuran **88** is, like furan, decomposed by strong acids, but by heating with pyridine–sulfur trioxide complex at 110 °C, it yields the 2-sulfonic acid **89** (Equation 25).[1,11]

Several substituted benzofuransulfonyl derivatives are useful medicinal agents. 2-Acetyl-7-methoxybenzofuran **90** reacts with excess chlorosulfonic acid to yield the corresponding 4-sulfonyl chloride **91** (Equation 26).[69] In this substrate, the 2-position of the benzofuran nucleus is blocked and hence sulfonation would be expected to occur in the 4-position of the phenyl ring as it is *para* to the electron-donating methoxy group. The sulfonyl chloride **91** is an intermediate in the synthesis of compounds which were useful in the treatment of diabetes.[69]



88 **89** (25)



90 **91** (26)

Several 2,3-dihydrobenzofuran-5-sulfamido derivatives possess diuretic and antihypertensive properties. As an example, 6,7-dichloro-2,3-dihydrobenzofuran-2-ethylcarboxylate **92** reacted with chlorosulfonic acid to give the corresponding 5-sulfonyl chloride **93** which, after condensation with dimethylamine and hydrolysis, gave the dimethylsulfonamide derivative **94** which had diuretic activity (Equation 27).[70]

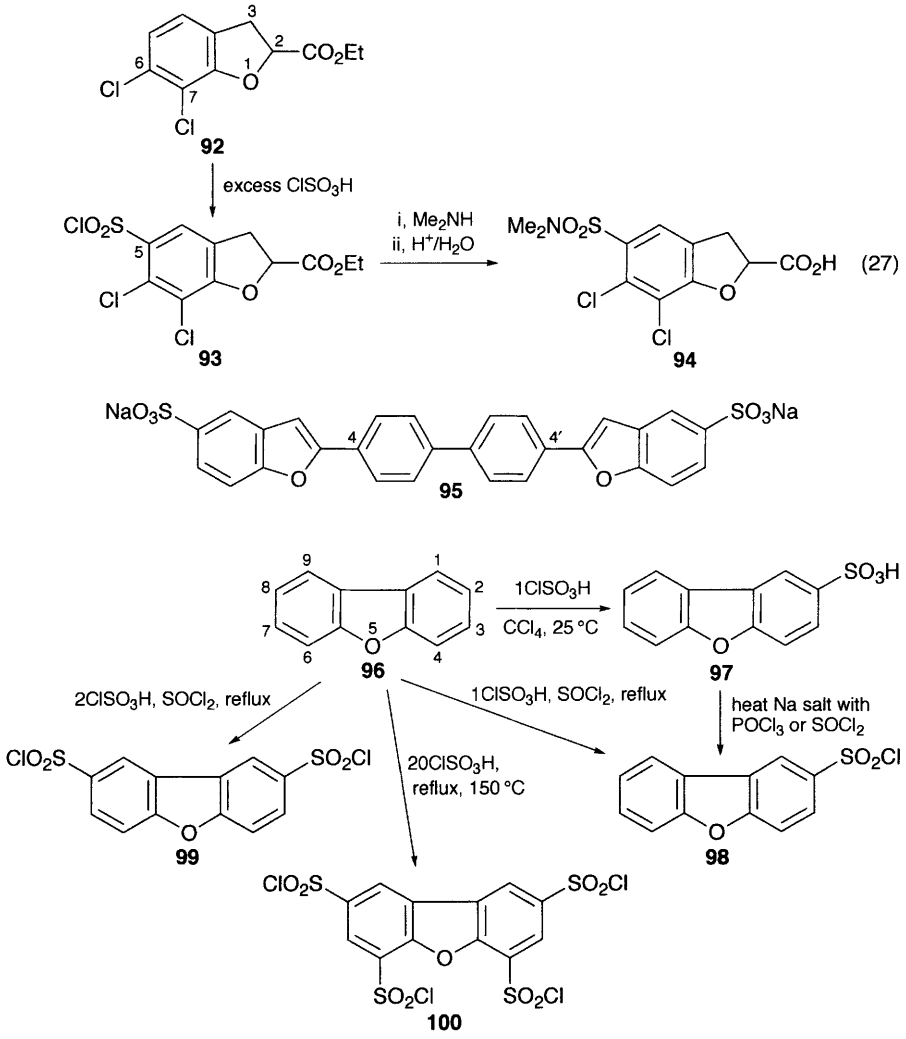
Sulfonation of **92** occurs as expected in the 5-position of the phenyl ring which is *para* to the electron-donating hetero oxygen atom.

4,4′-bis (2-Benzofuranyl) biphenyl is sulfonated by treatment with chlorosulfonic acid (two equivalents) and the product is neutralized with sodium hydroxide to yield the 5,5′-disodium sulfonate **95**. Sulfonation is again *para* to the hetero oxygen atom and such compounds are useful as fluorescent brighteners.[71]

2.3 Dibenzofuran

In dibenzofuran **96**, the preferred sites of sulfonation are the 2- and 2,8- positions which are *para* to the heteroatom.

Dibenzofuran **96** reacts with an equimolar quantity of chlorosulfonic acid in carbon tetrachloride solution at 25 °C for 1 hour to give the 2-sulfonic acid **97**, 89%, isolated as the sodium salt (Scheme 7).[72] Dibenzofuran-2-sulfonyl chloride **98** could be prepared in 82% yield by heating the 2-sodium sulfonate with phosphorus oxychloride[72] or thionyl chloride. Later work showed that the sulfonyl



Scheme 7

chloride **98** was also conveniently obtained by refluxing dibenzofuran **96** with chlorosulfonic acid (one equivalent) in excess thionyl chloride for 3 hours.[17]

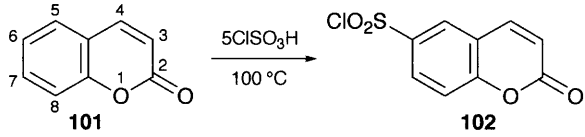
Dibenzofuran by refluxing with chlorosulfonic acid (two equivalents) in thionyl chloride (3 hours) gave the 2,8-disulfonyl chloride **99**, 89% yield; also reaction with the reagent (six equivalents) in carbon tetrachloride at RT and at 50 °C afforded the same product **99** in lower yields (50 and 45% respectively).[17] Treatment of the substrate **96** with a very large excess of chlorosulfonic acid (20 equivalents) at RT gave a mixture of the di- and trisulfonyl chlorides; however when the same reaction mixture was refluxed at 150 °C (4 hours) the 2,4,6,8-tetrasulfonyl chloride **100** was isolated (52% yield) (Scheme 7).

The various dibenzofuransulfonyl chlorides were characterized as their

dimethylsulfonamide derivatives and the orientation of sulfonation was confirmed by NMR spectral analysis.[17]

2.4 Coumarins (2-Ketobenzopyrans)

Coumarin **101** by heating with excess chlorosulfonic acid (five equivalents) at 100 °C for 4 hours afforded the 6-sulfonyl chloride **102**, 58% (Equation 28).[73]



(28)

Repetition of the chlorosulfonation of coumarin gave the same product **102** in a slightly higher yield (64%); but when the reaction was attempted at RT, there was only a 10% conversion after 7 days.[74]

In coumarin **101**[2,3,10,11]studies have shown that sulfonation generally occurs in the 3- and 6- positions which is in agreement with the polar mesomeric structures of **101**; also the presence of a 4-methyl group appears to inhibit 3-sulfonation probably as a result of steric hindrance. The 6-position would be expected to be the most favoured site for sulfonation since it is *para* to the electron-donating hetero oxygen atom. Coumarin **101** with chlorosulfonic acid (two equivalents) at 100 °C (2 hours) yields a mixture of the 6-sulfonic acid and the 6-sulfonyl chloride **102**, while at 130–140 °C (3 hours), the reaction gives the 3,6-disulfonic acid and the 3,6-disulfonyl chloride.[11,75]

Table 1 lists substituted coumarins that have been sulfonated by treatment with chlorosulfonic acid. 7-Hydroxy-4-methyl-8-acetylcoumarin **103**, by heating with an equimolar quantity of chlorosulfonic acid at 100 °C for 3 hours, gave the 6-sulfonic acid **104**.

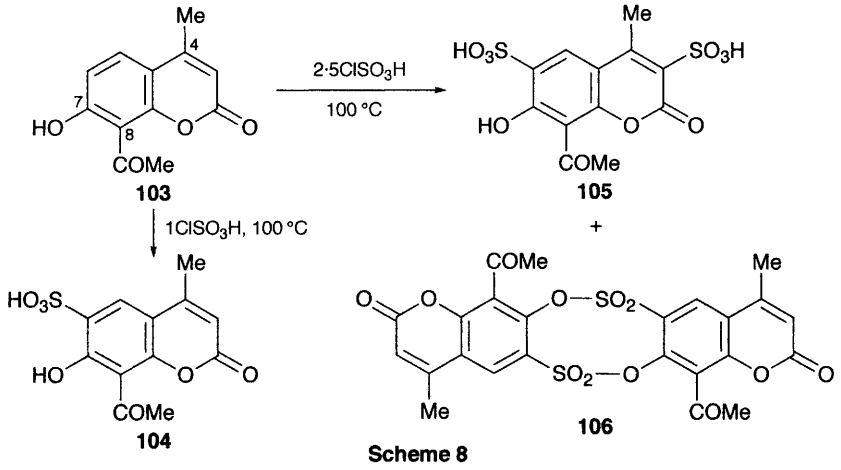
When the acetylcoumarin **103** was heated with excess reagent (2.5 equivalents) at 100 °C for 2 hours, the reaction gave the 3,6-disulfonic acid **105** together with a neutral compound, probably the 6-sulfonylide **106** (Scheme 8).[79]

The yield of the sulfonylide **106** increased with the amount of chlorosulfonic acid used and with a large excess of the reagent (10 equivalents), it was almost the only reaction product. 7-Methoxy-4-methyl-8-acetylcoumarin could not be sulfonated with chlorosulfonic acid (one or two equivalents) at 60 °C, while at higher temperatures, sulfonation occurred with some demethylation. Compounds analogous to the sulfonylide **106** are known to be formed in the sulfonation of substituted phenols[10] (see Chapter 4, p 62).

In the sulfonation of 7-hydroxy- and 7-methoxycoumarins, the 6-position was more reactive than the 3- or 8-positions and for coumarins generally the 6-position was the favoured site of sulfonation. The 8-position appeared unfavourable for the formation of sulfonyl chlorides, probably because the 7-sulfonic acid is stabilized by O–H···O hydrogen bonding between the sulfonic acid group and the hetero oxygen atom.

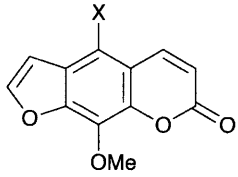
Table 1 *Sulfonation conditions of substituted coumarins*

Coumarin	*Equivalents of reagent*	*Reaction time (h)*	*Reaction temperature (°C)*	*Products*	*Ref.*
6-nitro	10	4	130–140	3-SO_3H+3-SO_2Cl	75
7-hydroxy-4-methyl	4	2	100	6-SO_3H + 6SO_2Cl	75
	4	4	130–140	6,8-diSO_3H	75
	8	4	140	3,6,8-triSO_3H	75
	excess	2	100	6-SO_2Cl (used as a fluorescence labelling reagent for determination of amino acids)	76
7-hydroxy-3,4-dimethyl	4	3	80	6-SO_3H + 6-SO_2Cl	77
	8	6	130–140	6,8-diSO_3H	77
7-hydroxy-6-ethyl-3,4-dimethyl	excess	2	100	8-SO_3H	77
	excess	2	> 100	8-SO_2Cl	77
7-hydroxy-6-bromo-3,4-dimethyl	excess	2	100	8-SO_3H	77
7-hydroxy-4-methyl-6-ethyl	2	2	100	8-SO_3H	77
7-hydroxy-3,8,dibromo-4-methyl	7.5	2	100	6-SO_3H + 6-SO_2Cl	75
7-hydroxy-3,6-dibromo-4-methyl	10	2	100	8-SO_3H	75
7-hydroxy-6-carboxy-4-methyl	4	2	100	3,8-diSO_3H	75
7-hydroxy-6-carbomethoxy-4-methyl	1	2	60($CHCl_3$)	8-SO_3H (of the carboxy derivative [demethylation has occurred])	75
7-methoxy-4-methyl	8	8	60($CHCl_3$)	3,6-diSO_3H + 3,6-diSO_2Cl	75
	4	2	100	6-SO_3H + 6-SO_2Cl	75
7-methoxy-4-methyl-6-ethyl	4	2	100	3-SO_3H + 3-SO_2Cl	77
7-methoxy-3,4-dimethyl	4	2	100	6-SO_3H + 6-SO_2Cl	77
7-methoxy-3-bromo-4-methyl	4	2	100	6-SO_3H + 6-SO_2Cl	75
5-hydroxy-4-methyl	8	2	100	6,8-diSO_3H	78
	8	6	140	3,6,8-triSO_3H	78
5-hydroxy-4,7-dimethyl	excess	2	100	6-SO_3H + 6-SO_2Cl	78
5-hydroxy-6-carboxy-4-methyl	2.5	2	100	8-SO_2Cl	78
	10	6	140	triSO_3H	78
5-methoxy-4-methyl	1	1.5	60($CHCl_3$)	mono-SO_3H	78
5-hydroxy-6-carbomethoxy-4-methyl	2.5	2	100	8-SO_3H + 8-SO_2Cl	78
	10	6	140	triSO_3H	78



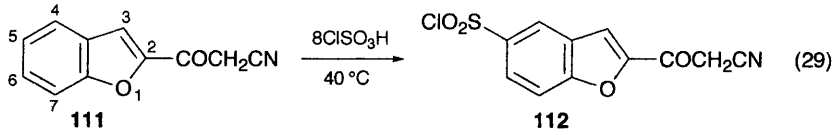
Scheme 8

Xanthotoxin **107** reacted with chlorosulfonic acid to give a mixture of the monosulfonyl chloride **108** and the corresponding sulfonic acid **109**.[80] In xanthotoxin **107**, the orientation of sulfonation is *para* with respect to the electron-donating methoxy group and the ratio of the products (**108** and **109**) was dependent on the reaction conditions. Some of the xanthotoxin sulfonamide derivatives, *e.g.* **110**, were active as skin photosentizers.[80]



107 X = H
108 X = SO_2Cl
109 X = SO_3H
110 X = SO_2NH_2

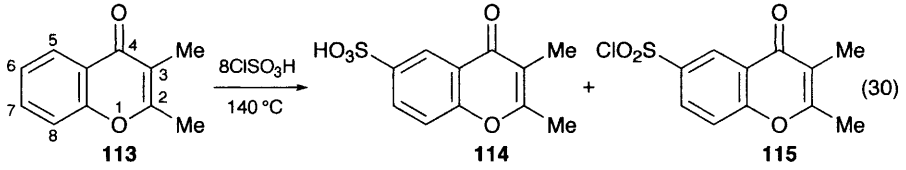
Treatment of 2-(cyanoacetyl)benzofuran **111** with excess chlorosulfonic acid (eight equivalents) at 40 °C (5 hours) afforded 2-(cyanoacetyl)-5-benzofuransulfonyl chloride **112**, 78% yield) (Equation 29).[81]



(29)

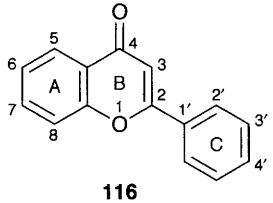
2.5 Chromones (4-Ketobenzopyrans)

Several substituted chromones have been successfully sulfonated by treatment with chlorosulfonic acid. For instance, 2,3-dimethylchromone **113** by heating with excess reagent (eight equivalents) at 140 °C for 4 hours gave a mixture of the 6-sulfonic acid **114** and the corresponding sulfonyl chloride **115** (Equation 30).[82]

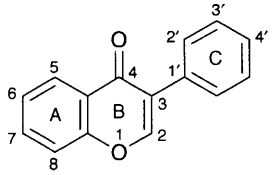


113 **114** **115**

In chromones, the favoured sites for sulfonation are 6- and 8- positions which are respectively *para* and adjacent to the electron-donating hetero oxygen atom. Table 2 lists substituted chromones that have been sulfonated by treatment with chlorosulfonic acid. The 5-hydroxychromones were more easily sulfonated than the corresponding 7-hydroxy derivatives and when sulfonation of 5-methoxy-2-methylchromone was attempted under more drastic conditions than those reported here, the sulfonation was accompanied by demethylation of the substrate. Flavones and isoflavones are 2- and 3-phenylchromones (**116** and **117**) respectively.



116



117

Recent studies[83] showed that flavone **116** and 4′-methoxyflavone react with excess chlorosulfonic acid to give selective sulfonation in the phenyl ring C, because ring A is relatively deactivated by protonation of the α,β-unsaturated carbonyl group. Thus, flavone **116**, by heating with excess reagent (six equivalents) at 70 °C for 3 days, gave a mixture of the 3′- and 4′-sulfonyl chlorides (ratio 3:1) and in an overall yield of 62%. 4′-Methoxyflavone, by treatment with excess chlorosulfonic acid (six equivalents) at RT (2 days), afforded an excellent yield of the corresponding 3′-sulfonyl chloride (78%).[83] The high yield and mild conditions required for the chlorosulfonation of this substrate reflect the activating influence of the 4′-methoxy group. In contrast, Table 3 shows 5- and 7-hydroxyflavones and isoflavones sulfonated by chlorosulfonic acid in ring A due to the activating effect of the hydroxy substituent group.

7-Hydroxyflavone-6,8-disulfonic acid, by heating with excess chlorosulfonic acid (four equivalents) at 140 °C for 2 hours, was converted into the corresponding 6,8,2′-trisulfonic acid.[82]

Similarly, 5-hydroxyflavone-6,8-disulfonyl chloride with hot chlorosulfonic acid (four equivalents, 140 °C, 2 hours) gave the corresponding 6,8,2′-trisulfonic acid.[82]

The isoflavones were more easily sulfonated than the corresponding flavones and, as with chromones, the 5-hydroxyflavones were more reactive towards sulfonation than the 7-hydroxy analogues. A solution of chlorosulfonic acid in chloroform (4:1) is used as a spray reagent in TLC for detection of coumarins and flavanoids in silica gel G plates.[84]

Table 2 *Sulfonation conditions of substituted chromones*

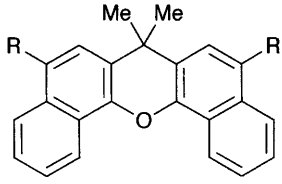
Chromone	*Equivalents of reagent*	*Reaction time (h)*	*Reaction temperature (°C)*	*Products*	*Ref.*
7-hydroxy-2-methyl	4	2	100	8-SO_3H	82
	8	6	140	6,8-diSO_3H	82
7-methoxy-2-methyl	4	2.5	100	8-SO_3H	82
5-hydroxy-2-methyl	1	2	60($CHCl_3$)	8-SO_3H	82
	5	2	100	6,8-diSO_3H	82
5-methoxy-2-methyl	1	1	60($CHCl_3$)	8-SO_3H	82

Table 3 *Sulfonation conditions of substituted flavones*

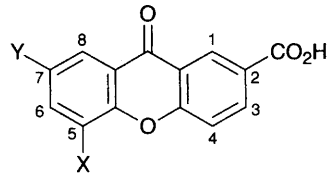
Flavone	*Equivalents of reagent*	*Reaction time (h)*	*Reaction temperature* (°C)	*Products*	*Ref.*
7-hydroxyflavone	4	4	60($CHCl_3$)	8-SO_3H	82
	6	6	140	6,8-diSO_3H	82
	15	4.5	140	6,8,2′-triSO_3H	82
5-hydroxyflavone	1	1.5	60($CHCl_3$)	8-SO_3H	82
	6	6	140	6,8-diSO_3H	82
	10	6	140	6,8-diSO_2Cl	82
	15	4.5	140	6,8,2′triSO_3H	82
7-hydroxy-2-methylisoflavone	2	4	100	8-SO_3H	82
	6	6	140	6-8-diSO_3H + 6,8-diSO_2Cl	82
	10	6	140	triSO_3H	82
7-hydroxy-2-phenylisoflavone	2	2	60($CHCl_3$)	6,8-diSO_3H	82
	10	6	140	6,8-diSO_3H + triSO_3H	82

2.6 Xanthenes

7,7-Dimethyl-7*H*-dibenzoxanthene **118** reacts with excess chlorosulfonic acid and potassium hydroxide to give the dipotassium sulfonate which, by refluxing with phosphorus oxychloride, afforded the disulfonyl chloride **119**.[85]



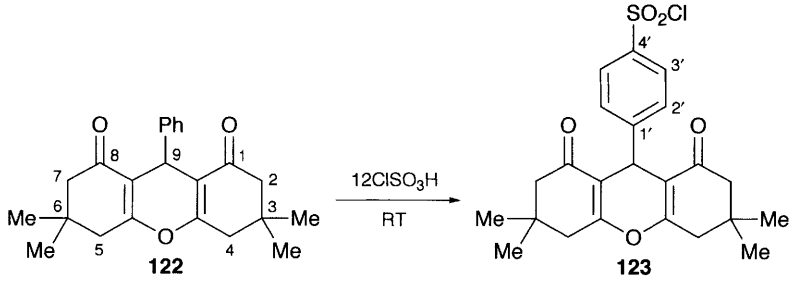
118 R = H
119 R = SO_2Cl



120 X = Me, Et, Me_2CHO, Me_2CH, n-C_8H_{17}, MeO, EtO, n-C_3H_7O; Y = H
121 X = Me, Et, Me_2CHO, Me_2CH, n-C_8H_{17}, MeO, EtO, n-C_3H_7O; Y = SO_2Cl

Sulfonation occurred, as expected *para* to the electron-donating hetero oxygen atom. 5-Substituted xanthone-2-carboxylic acid derivatives **120** reacted with excess chlorosulfonic acid under forcing conditions to give the corresponding 7-sulfonyl chlorides **121**.[86]

A series of 9-aryl-3,3,6,6-tetramethyloctahydroxanthen-1,8-diones has been chlorosulfonated by treatment with a large excess of chlorosulfonic acid (12 equivalents) at RT for 2–7 days.[87] The chlorosulfonation may also be carried out using a mixture of chlorosulfonic acid (six equivalents) in thionyl chloride under similar conditions; in each case sulfonation occurred in the aryl ring. For instance, the 9-phenyl derivative **122** gave the corresponding *p*-sulfonyl chloride **123** (Equation 31).[87]



(31)

In the 9-(3′-methoxyphenyl) derivative, chlorosulfonation afforded the corresponding 4′,6′-disulfonyl chloride (sulfonation *o/p* to the methoxy group) and in the 2′-methyl and 2′-methoxy derivatives reaction with excess chlorosulfonic acid afforded the corresponding 5′-sulfonyl chlorides. On the other hand, in the 2′- and 3′-chloro derivatives, chlorosulfonation occurred in the 4′-position which is *para* to the electron-donating alkyl moiety. With the 9- (2′- and 3′-thienyl) derivatives, sulfonation occurs in the 5′-position (adjacent to the electron-donating hetero sulfur atom).[87]

Preliminary studies[88] indicated that the analogous 9-aryloctahydroxanthen-1,8-diones may be similarly chlorosulfonated with chlorosulfonic acid; although the

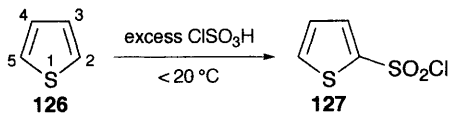
starting materials appeared rather less crystalline and the products were more difficult to characterize as their dimethylsulfonamide derivatives. 1,4-Benzodioxan-5-carboxylic acid **124** reacts with excess chlorosulfonic acid and dimethylamine to give the 7-dimethylsulfonamide derivative **125**, an intermediate in the synthesis of antidepressant drugs (Equation 32).[89]

124 **125** (32)

3 Sulfur Heterocycles

3.1 Thiophene

Thiophene **126** is a π-excessive sulfur heterocycle and, like the other five-membered heterocyclic compounds, sulfonation occurs preferentially in the 2- and 5- positions when these are available[1–3,10–12] However, unlike furan and pyrrole, thiophene is reasonably stable in strong acids and accordingly it can be sulfonated by treatment with sulfuric or chlorosulfonic acid. Thiophene is easily chlorosulfonated by reaction with excess chlorosulfonic acid (two to three equivalents) at relatively low temperatures (< 20 °C) to give the 2-sulfonyl chloride **127** (Equation 33).[13,90–94] The chlorosulfonation of thiophene may also be carried out using an inert solvent such as chloroform at −10 °C.[94]



126 **127** (33)

When thiophene is heated with a large excess of chlorosulfonic acid (six equivalents) at 100 °C (1.5 hours), the reaction yields 2,4-thiophenedisulfonyl chloride (38%).[93]

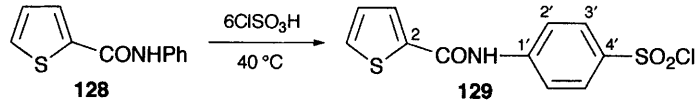
The sulfonation of 2-substituted thiophene derivatives containing electron-withdrawing groups normally occurs mainly or exclusively in the 5-position. On the other hand, with electron-donating substituents in the 2-position, sulfonation is less selective and often occurs in both the 4- and 5- positions of the thiophene ring.[2,3]

Table 4 shows thiophene derivatives that have been sulfonated by treatment with excess chlorosulfonic acid.

Thiophene-2-carboxanilide **128** reacted with excess chlorosulfonic acid (six equivalents) at 40 °C (45 minutes) to give an excellent yield of the 4′-sulfonyl chloride **129**, 80% (Equation 34).[68]

Table 4 *Sulfonation conditions of thiophene derivatives*

Thiophene	*Equivalents of reagent*	*Reaction temperature* (°C)	*Products*	*Ref.*
2-methyl	2	< −10	5-SO_2Cl	95
2-chloro	2	< −5	5-SO_2Cl	93
	2	−10	5-SO_2Cl	96
	6	100	3,5-diSO_2Cl	93
2-bromo	2	−15	5-SO_2Cl	97
	$ClSO_3H$ + 33% oleum	30	3,5-diSO_2Cl	97
2-iodo	2	−15	5-SO_2Cl	97
2,3-dichloro	2	−10	5-SO_2Cl	96, 98
2,5-dichloro	1.3	10	3-SO_2H	99
	10	100	3-SO_2Cl (46%) and 3,4-diSO_2Cl (17%)	93
2,3-dibromo	2	20	5-SO_2Cl	97
2,4-dibromo	2	10	5-SO_2Cl	97
	6	100	3,5-diSO_2Cl	93
3,4-dibromo	2	10	2-SO_2Cl	97
2,3,4-trichloro	2	−5	5-SO_2Cl	96
2,3,5-trichloro	2	−5	4-SO_2Cl	96
2-nitro	2.7	60($CHCl_3$)	4-SO_2Cl (74%)	93, 100
2-carboxamido	6	40	4-SO_2Cl	101
2-chlorosulfonyl	6	60	2,4- and 2,5-diSO_2Cl (2:1 mixture)	101
2-acetamido	6	20–50	5-SO_2Cl (37%)	102
	8	90	3,5-diSO_2Cl (31%)	100
	2	0–5	3,5-diSO_3H	100
2-*N*-methylcarbamoyl-5-chloro	2	0	4-SO_2Cl (48%)	93
2-phthalimido	6	50	5-SO_2Cl (76%)	102
	8	−5	5-SO_2Cl (55%)	103
2-succinimido	3.5	−5	5-SO_2Cl (30%)	104



128 **129** (34)

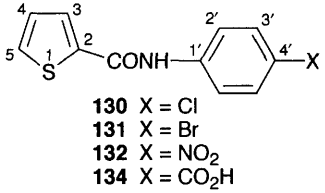
In this compound, sulfonation occurs preferentially in the electron rich phenyl ring and there was no attack on the thiophene nucleus in contrast to thiophene-2-carboxamide which sulfonates in the 4-position of the thiophene ring.[101]

If the 4′-position in thiophene-2-carboxanilide **128** is blocked, then sulfonation does occur in the thiophene ring; thus thiophene-2-(4′-chlorocarboxanilide) **130** by warming with chlorosulfonic acid (six equivalents) at 50 °C (3 hours) gave mainly the 4-sulfonyl chloride and a little of the 5-isomer. The analogous

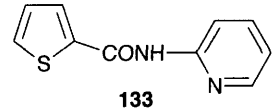
4′-bromocarboxanilide **131** with chlorosulfonic acid under the same conditions afforded the 4-sulfonyl chloride (75%).[68] The 4′-nitrocarboxanilide **132** gave a lower yield of the 4-sulfonyl chloride as did the *N*-(2-pyridyl) derivative **133**, while the 4′-carboxanilide **134** with excess reagent (six equivalents) at RT afforded only thiophene-2-carboxylic acid. Chlorosulfonation of thiophene-2-carboxanilides containing the electron-withdrawing nitro and pyridyl groups gave lower yields of the corresponding sulfonyl chlorides, probably because these groups weaken the amide bond, facilitating carbon–nitrogen bond cleavage. In the carboxy derivative **134**, this effect becomes so pronounced that only carbon–nitrogen bond cleavage was observed leading to the formation of thiophene-2-carboxylic acid.[68]

Several thiophenesulfonamido derivatives are fungicidal.[105] For instance, 5-dialkylamino-4-nitrosulfonamidothiophenes, such as the haloalkyl derivative **135**, are synthesized from 5-chlorothiophene-2-sulfonyl chloride (obtained by the action of chlorosulfonic acid on 2-chlorothiophene).[106]

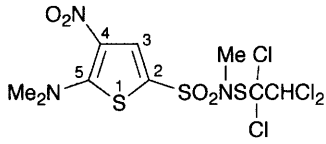
2-(*N*-Haloalkylthiosulfonamido)thiophenes **136** also show useful fungicidal activity.[107]



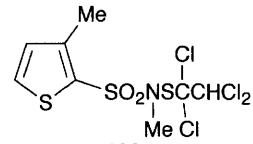
130 X = Cl
131 X = Br
132 X = NO_2
134 X = CO_2H



133



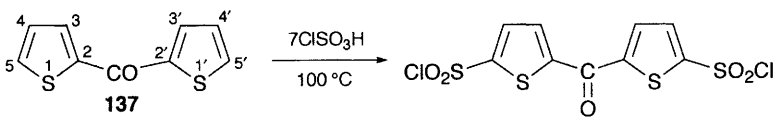
135



136

3-(*β*-Trifluoroethoxymethyl) thiophene reacts with chlorosulfonic acid to give the 2-sulfonyl chloride;[108] it is possible that initial attack at the ether oxygen atom may direct the course of this sulfonation.[13]

2,2′-Dithienylketone **137**, by heating with a large excess of chlorosulfonic acid (seven equivalents, 100 °C, 3 hours) afforded the 5,5′-disulfonyl chloride **138** (Equation 35).[93] The rather more drastic conditions needed for the chlorosulfonation of the ketone **137** probably result from the deactivating influence of the carbonyl group as was observed in the chlorosulfonation of other diaryl ketones (see Chapter 4, p 78).

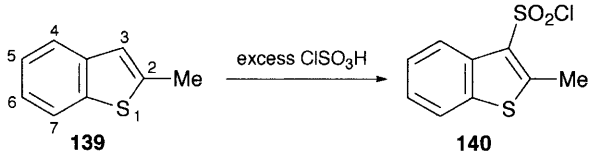


137 **138** (35)

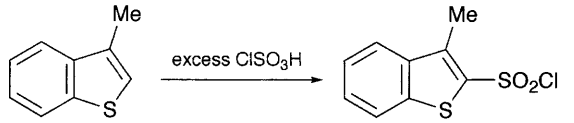
The kinetics of the reaction of 5-substituted thiophene-2-sulfonyl chlorides with aniline in methanolic solution has been studied and has been demonstrated to be a second order process.[109]

3.2 Benzo[*b*]thiophene

Benzo[*b*]thiophene (thionaphthene) reacts with concentrated sulfuric acid in acetic anhydride at 10 °C to give an excellent yield of the monosulfonic acid, probably mainly the 3-sulfonic acid with a little of the 2-isomer.[11] In benzo[*b*]thiophene, the calculated π-electron density pattern would predict the relative order of reactivity for electrophilic substitution to be $3 > 2 > 6 \sim 5$.[11] In agreement, 2- and 3-methylbenzothiophene (**139**, **141**) react with excess chlorosulfonic acid to give the 3- and 2- sulfonyl chlorides (**140**, **142**) respectively (Equations 36 and 37).[2,110] However, more recent attempts to chlorosulfonate benzo[*b*]thiophene by treatment with chlorosulfonic acid (one equivalent) in excess thionyl chloride at RT failed to give a pure product.[17]



139 **140** (36)



141 **142** (37)

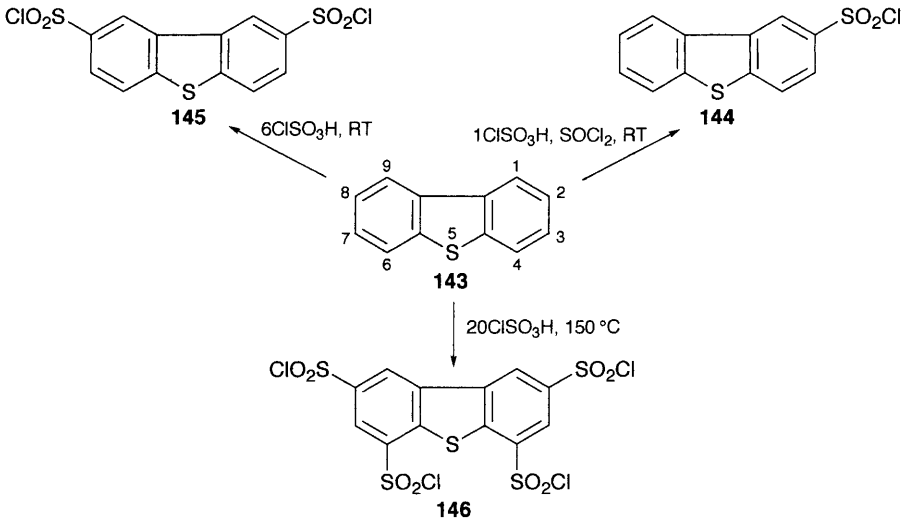
3.3 Dibenzothiophene

Dibenzothiophene **143**, like dibenzofuran, sulfonates successively in the 2- and 8-positions which are *para* with respect to the electron-donating hetero sulfur atom and the observed order of sulfonation is in agreement with the calculated π-electron density pattern for the heterocycle.[11] The pattern of sulfonation resembles that exhibited by diphenyl sulfide (see Chapter 4, p 76).

Dibenzothiophene reacts with chlorosulfonic acid (1.1 equivalents) in thionyl chloride for 10 days at RT to yield the 2-sulfonyl chloride **144**; 62%.[17]

When the heterocycle **143** was treated with more of the reagent (six equivalents, or two equivalents in thionyl chloride) for 10 days at RT, the 2,8-disulfonyl chloride **145**; 87%) was isolated. (Scheme 9).

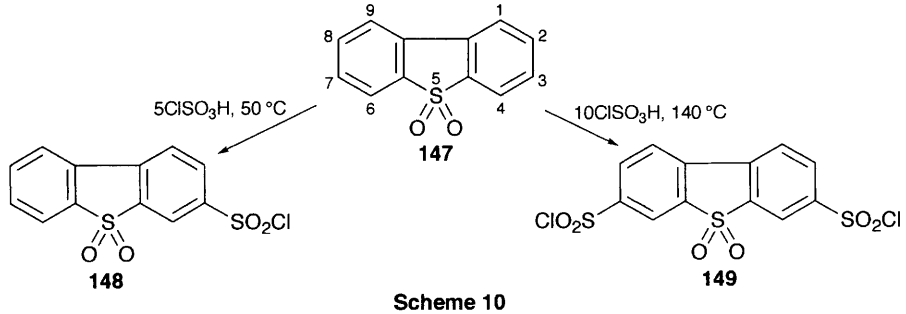
Dibenzothiophene **143**, by refluxing with a very large excess of chlorosulfonic acid (20 equivalents) for 4 hours, gave the 2,4,6,8-tetrasulfonyl chloride **146**; 45% (Scheme 9).[17]



Scheme 9

3.4 Dibenzothiophene-5,5-dioxide

Dibenzothiophene-5,5-dioxide **147** reacts with chlorosulfonic acid (five equivalents) for 2 hours at 50 °C to yield the 3-sulfonyl chloride **148**; 65% (Scheme 10).[17] On the other hand, when the dioxide **147** was strongly heated with a large excess of the reagent (10 equivalents) at 140 °C for 4 hours, the reaction afforded the 3,7-disulfonyl chloride **149**; 70% (Scheme 10).[17]



Scheme 10

The electron-withdrawing property of the sulfonyl moiety in dibenzothiophene-5,5-dioxide **147** is reflected in the more drastic conditions required for the chlorosulfonation of this substrate as compared with those needed for dibenzothiophene **143**. It also accounts for the observed orientation of sulfonation in the 3- and 3,7-positions, since these are both *meta* to the deactivating sulfonyl group and *para* to the activating bridge bond. The pattern to sulfonation shown by the dioxide **147** is similar to that of biphenyl (see Chapter 4, p 42).

4 Heterocyclic Compounds with Two or More Different Heteroatoms

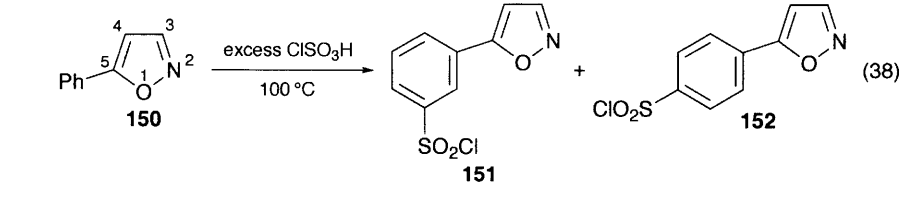
4.1 Nitrogen and Oxygen Heterocycles

4.1.1 Isoxazole and Derivatives

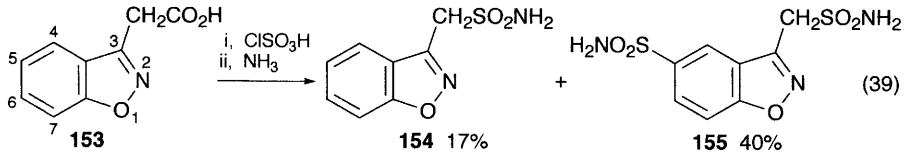
Isoxazole reacts with 20% oleum at 90 °C to give a low yield of the 4-sulfonic acid (17%).[2,11] The isoxazole ring is found to be rather resistant to sulfonation with the 4-position the most favoured site of attack.[2] The action of boiling excess chlorosulfonic acid on 3- and 5-methylisoxazole gave a mixture of the 4-sulfonic acid and the 4-sulfonyl chloride, whereas 3,5-dimethylisoxazole on similar treatment afforded only the 4-sulfonic acid derivative.[10,11,111] However, 3,5-dimethylisoxazole, by dropwise treatment with chlorosulfonic acid at 80 °C, heating at 110 °C (2 hours), followed by further heating with thionyl chloride at 60–110 °C for 2 hours, afforded an excellent yield of the 4-sulfonyl chloride (81.7%).[111a]

5-Phenylisoxazole **150** by prolonged heating with chlorosulfonic acid at 100 °C (30 hours) yields a mixture of the *m*- and *p*-chlorosulfonyl derivatives **151** and **152** in a ratio of 2:1; in this substrate only the phenyl ring is attacked (Equation 38).[11,112,113]

3-Phenyl-1,2-benzisoxazole is reported[114] to react with 40% oleum to give a disulfonic acid of unknown structure and 1,2-benzisoxazole-3-acetic acid **153** with excess chlorosulfonic acid, followed by treatment with ammonia afforded a mixture of the sulfonamides **154** and **155** (Equation 39).[2] In this reaction, the major sulfonation occurred in the 5-position of the benzisoxazole nucleus, which is *para* to the electron-donating hetero oxygen atom leading to the formation of the disulfonamide **155**.



150 **151** **152**



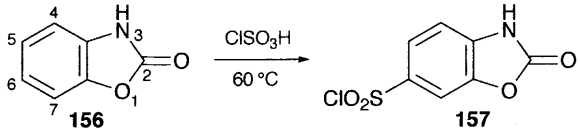
153 **154** 17% **155** 40%

4.1.2 Oxazoles

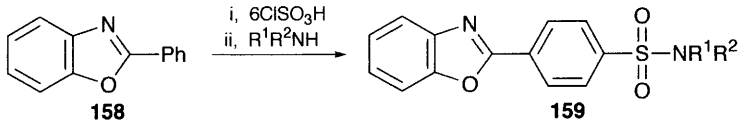
Benzoxazolone **156**, by warming with excess chlorosulfonic acid (2.5 equivalents) at 60 °C for 2 hours, yields the 6-sulfonyl chloride **157** (50–60%) (Equation 40).[115]

2-Phenylbenzoxazole **158** reacted with chlorosulfonic acid (six equivalents) at

100 °C for 3 hours, followed by refluxing with thionyl chloride–DMF (catalyst) for 2 hours and treatment with amines to give the corresponding *para*-sulfonamides **159** (39–68%) (Equation 41).[116] In this reaction, the conversion of the initially formed sulfonic acid into the sulfonyl chloride was comparatively slow and the sulfonyl chloride was not isolated, but was immediately converted into the corresponding sulfonamides. 2-Styrylbenzoxazole **160** similarly reacted with excess chlorosulfonic acid (six equivalents) at RT (1week) to give the *p*-sulfonyl chloride which was again not isolated, but was converted into the sulfonamides **161**, 41–68% (Equation 42).[116]

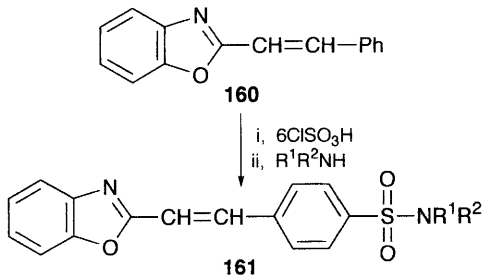


156 **157** (40)

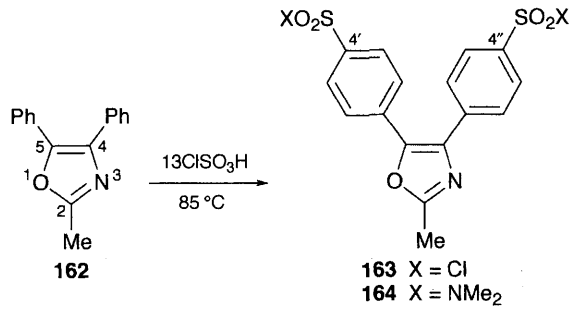


158 **159** (41)

The milder conditions needed for the sulfonation of the styryl derivative **160** as compared with 2-phenylbenzoxazole **158** are a reflection of the activating effect of the alkenic double bond. 2-Methyl-4,5-diphenyloxazole **162** with a large excess of chlorosulfonic acid (13 equivalents) at 85 °C for 13 hours afforded the 4′,4″-disulfonyl chloride **163** (Equation 43).[25] The *para*-sulfonation was shown by NMR spectral analysis of the bis-*N,N*′-dimethylsulfonamide derivative **164** (Equation 43).



160 **161** (42)

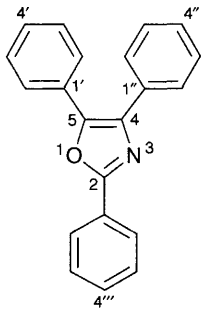


162

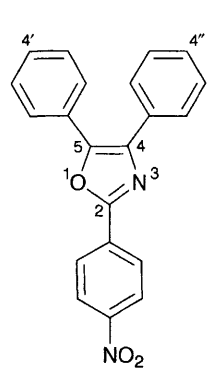
163 X = Cl
164 X = NMe_2

(43)

2,4,5-Triphenyloxazole **165** was treated with chlorosulfonic acid under various conditions. With excess of the reagent (12 equivalents) in thionyl chloride at RT (3 hours), the product of the reaction was the 4′-sulfonyl chloride (45%). The use of a very large excess of the reagent (20 equivalents) at RT (1 week) afforded an excellent yield of the 4′,4″-disulfonyl chloride (83%), while the same reaction at 90 °C for 5 hours resulted in the formation of a mixture of the 4′,4″-disulfonyl chloride and the 4′,4″,4‴-trisulfonyl chloride in an overall yield of 87%.[117]



165



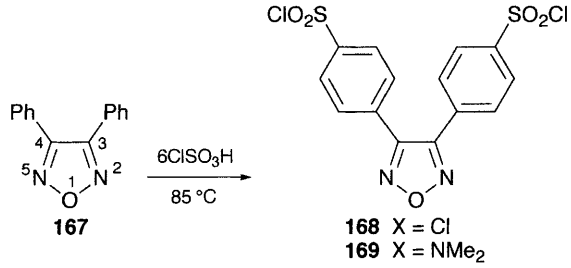
166

2-(*p*-Nitrophenyl)-4,5-diphenyloxazole **166**, by heating with excess chlorosulfonic acid (12 equivalents) at 90 °C for 3 hours, gave the 4′,4″-disulfonyl chloride (48%). The remaining phenyl ring being relatively deactivated by the strongly electron-withdrawing nitro group was not attacked. At RT, the reaction afforded a mixture of the mono- and disulfonyl chlorides.

4.1.3 Furazans

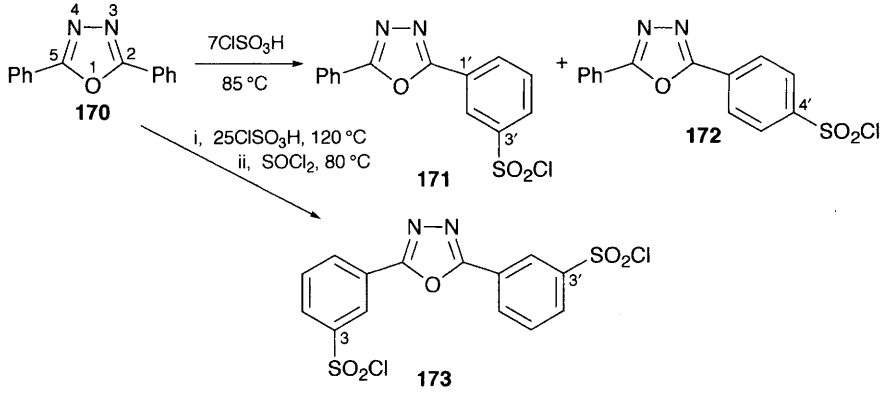
3,4-Diphenylfurazan **167** reacts with excess chlorosulfonic acid (six equivalents) at 85 °C (3 hours) to give the 4′,4″-disulfonyl chloride (**168**; X = Cl) (Equation 44). The NMR spectrum of the bisdimethylsulfonamide derivative (**169**; X = NMe_2) confirmed the *para*-disulfonation.[118] This orientation is contrary to our previous report[119] which suggested that chlorosulfonation occurred in the 3,3′-positions and the revised orientation is indicative of the dominance of the +M

electronic effect of the hetero oxygen atom over the −M effect of the imino part of the ring.



167 **168** X = Cl; **169** X = NMe_2 (44)

2,5-Diphenylfurazan **170** with chlorosulfonic acid (seven equivalents) at 85 °C (3 hours) and 110 °C ($1^1/_2$ hours) afforded a mixture of the 3′- and 4′-sulfonyl chlorides **171** and **172** respectively (Scheme 11).

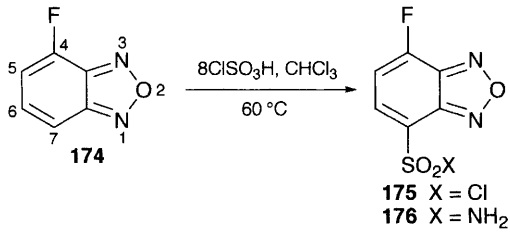


Scheme 11

On the other hand, when 2,5-diphenylfurazan **170** was treated with a large excess of chlorosulfonic acid (25 equivalents) at 120 °C for 14 hours, followed by heating with thionyl chloride for 3 hours, the major reaction product appeared to be the 3,3′-disulfonyl chloride **173** (Scheme 11).[118]

4.1.4 4-Fluoro-2,1,3-benzoxadiazole

4-Fluoro-2,1,3-benzoxadiazole **174**, by reaction with chlorosulfonic acid (eight equivalents) in boiling chloroform for 2 hours afforded the 7-sulfonyl chloride **175**, 78% (Equation 45).[120]



(45)

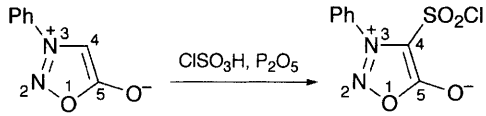
174

By treatment with ammonia, the sulfonyl chloride **175** was converted into 7-(aminosulfonyl)-4-fluoro-2,1,3-benzoxadiazole **176**, which is used as a new fluorogenic reagent for thiols in HPLC.[120]

4.1.5 Sydnones

Sydnones contain the 1,2,3-oxadiazole ring; they can be represented by a mesomeric betaine structure and 3-substituted sydnones may be sulfonated in the 4-position by treatment with sulfur trioxide–dioxan complex in dichloromethane at 20–40 °C.[2,121]

3-Phenylsydnone **177** reacts with chlorosulfonic acid in presence of phosphorus pentoxide to give the 4-sulfonyl chloride **178**, 77% (Equation 46).[122] The sulfonyl chloride was successfully converted into a range of amides and esters.



(46)

177 178

4.2 Nitrogen and Sulfur Heterocycles

4.2.1 Thiazole and Derivatives

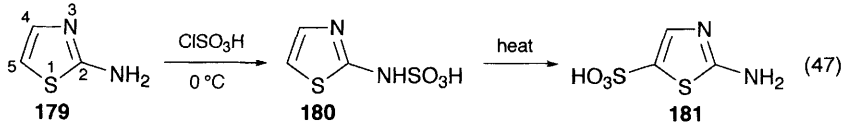
Thiazole is only sulfonated under forcing conditions due to the presence of the electron-withdrawing hetero nitrogen atom; thus heating the heterocycle with oleum at 250 °C in the presence of mercury(II) sulfate catalyst yields the 5-sulfonic acid (65%).[2]

2-Aminothiazole **179**, with chlorosulfonic acid, gives the sulfamic acid **180** which on heating rearranges to 2-aminothiazole-5-sulfonic acid **181** (Equation 47).[2]

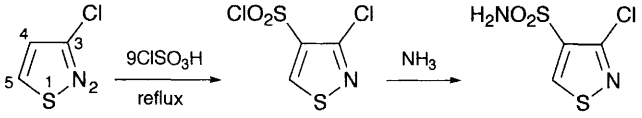
Isothiazole is also sulfonated by oleum to yield the 4-sulfonic acid derivative;[2] in both thiazole and isothiazole the orientation of sulfonation is in agreement with the calculated π-electron density patterns of the parent heterocycles.[11]

3-Chloroisothiazole **182**, by refluxing with excess chlorosulfonic acid (nine equivalents) for 2 days, yields the 4-sulfonyl chloride **183** which, by subsequent

treatment with ammonia, afforded 3-chloro-4-isothiazolesulfonamide **184** (Equation 48).[123]



179 **180** **181** (47)



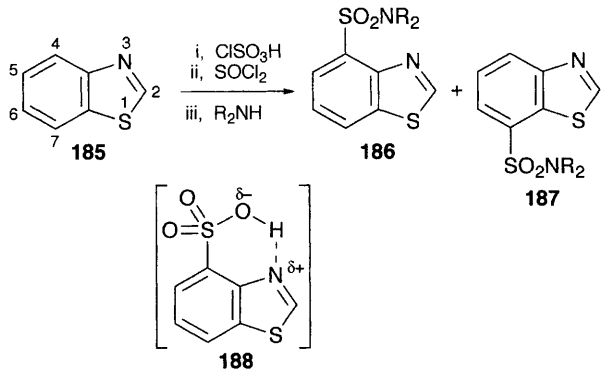
182 **183** **184** (48)

The sulfonamide **184** is an intermediate in the synthesis of herbicidal *N*-(pyrimidine aminocarbonyl) thiazolesulfonamides.[123] In addition, several sulfonyl derivatives of isoxazole, pyrazole and thiazole have shown antifungal activity.[105]

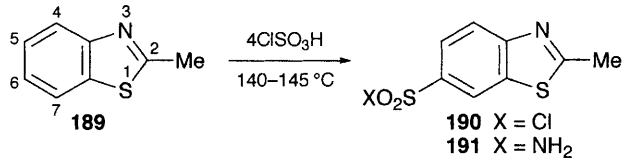
Benzothiazole **185** is reported[124] to react with chlorosulfonic acid to only give a salt; later repetition[117] of the reaction with chlorosulfonic acid at both RT and 100 °C confirmed this result. On the other hand, when benzothiazole **185** was heated with excess chlorosulfonic acid (six equivalents) at 150 °C ($4\frac{1}{2}$ hours), followed by boiling with thionyl chloride (2 hours), the reaction gave the sulfonyl chloride as a gum. Subsequent treatment with amines afforded a mixture of the 4- and 7-sulfonamides **186** and **187** respectively (Equation 49).[117]

The NMR spectra of the dimethylamide derivatives **186**; R = Me and **187**; R = Me, indicated that the product mixture contained 80% of the 4-sulfonamide and 20% of 7-isomer.[117] The failure of the action of chlorosulfonic acid alone on benzothiazole to yield the sulfonyl chloride may be due to the 4-sulfonic acid existing as the stabilized hydrogen-bonded structure **188** which requires a more powerful chlorinating agent (thionyl chloride) to convert it into the sulfonyl chloride. This is analogous to the situation previously observed in the chlorosulfonation of diarylureas (see Chapter 4, p 112)

2-Methylbenzothiazole **189** reacts with chlorosulfonic acid (four equivalents) at 140 °C (4 hours) to give mainly the 6-sulfonyl chloride **190** together with some of the 5-isomer. Subsequent reaction with ammonia and purification of the crude product, afforded the pure 6-sulfonamide **191** (Equation 50).[125] The yield of the sulfonyl chloride **190** was low (~20%); however when the chlorosulfonation was repeated in the presence of thionyl chloride, the yield of the chloride **191** was increased to 45%.[117] In the reaction of 2-methylbenzothiazole **189** with chlorosulfonic acid no salt formation was observed, in contrast to the analogous reaction with benzothiazole **185**. Salt formation is possibly inhibited in 2-methylbenzothiazole by the steric effect of the 2-methyl group and consequently the orientation of sulfonation is now governed by electron donation from the nitrogen lone pair of electrons leading to preferential 6-attack, since this position is *para* to the hetero nitrogen atom.[117]

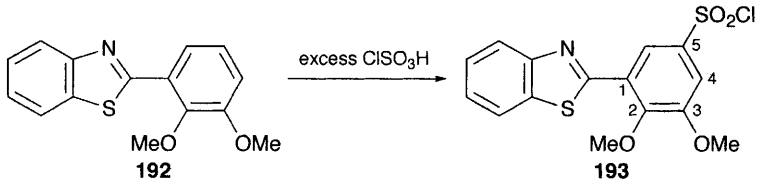


(49)



(50)

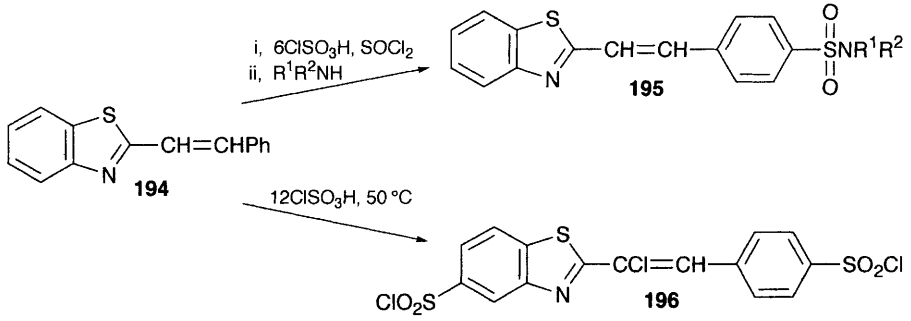
2-(2,3-Dimethoxyphenyl)benzothiazole **192** reacts with excess chlorosulfonic acid to give the 5-sulfonyl chloride **193**; in this reaction sulfonation has occurred in the least hindered *para*-position with respect to the electron-donating methoxy group (Equation 51).[13,126]



(51)

Treatment of the sulfonyl chloride **193** with ammonia afforded the corresponding 5-sulfonamide, which functioned as a moderator of calcium-induced smooth muscle contraction.[126]

2-Styrylbenzothiazole **194**, by treatment with excess chlorosulfonic acid (six equivalents) at RT (1 week), gave mainly the sulfonic acid, but when the product was reacted with thionyl chloride and subsequently with amines, the sulfonamides **195**, 20–45%, were isolated.[116] Under these conditions, sulfonation occurs exclusively on the styryl moiety and there is no attack on the benzothiazole ring, since this demands prolonged heating with excess chlorosulfonic acid.[117]



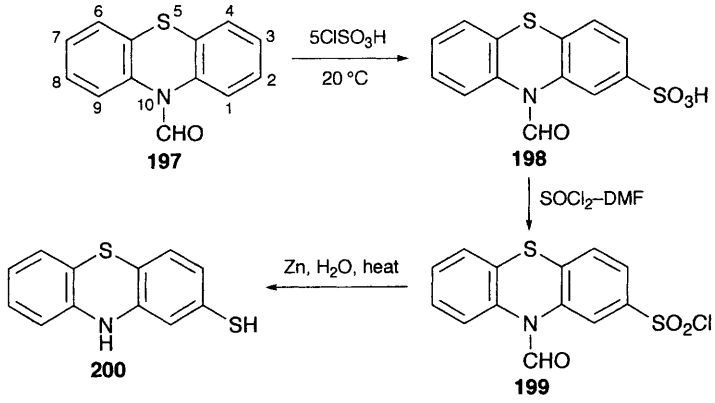
Scheme 12

When 2-styrylbenzothiazole **194** was heated with a larger excess of the reagent (12 equivalents) at 50 °C for 5 hours, the chlorinated disulfonyl chloride **196** was isolated (Scheme 12).[116]

The disulfonyl chloride **196** was characterized by formation of the dimorpholidate derivative and examination of its NMR spectrum. In particular, the position of the chlorine atom was determined by a study of the fully proton-coupled ^{13}C NMR spectrum.[116]

4.2.2 N-Formylphenothiazine

A process for the direct regioselective functionalization of phenothiazine in the 2-position by the thiol group is outlined in Scheme 13. It involves firstly reaction of *N*-formylphenothiazine **197** with chlorosulfonic acid (five equivalents) at 20 °C (3 hours) to give *N*-formyl-2-phenothiazinesulfonic acid **198**; 75%, which with thionyl chloride–DMF (catalyst) in dichloromethane afforded the sulfonyl chloride **199**; 96% and finally the sulfonyl chloride, by heating with zinc, gave 2-mercaptophenothiazine **200** (Scheme 13).[127]



Scheme 13

5 References

1 G.R. Newkome and W.W. Paudler, *Contemporary Heterocyclic Chemistry*, Wiley, New York, 1982.

2 A.R. Katritzky and C.W. Rees (eds), *Comprehensive Heterocyclic Chemistry*, Pergamon Press, Oxford, 1984, (8 vols.).

3 'Heterocyclic Compounds', in *Comprehensive Organic Chemistry*, P.G. Sammes (ed), Pergamon Press, Oxford, 1979, Vol. 4.

4 E.E. Gilbert, *Chem. Rev.*, 1962, **62**, 549 (reviews the sulfonation of organic compounds by sulfur trioxide and its adducts with, for example, dioxan, pyridine, triethylamine).

5 T. Kanekiyo and S. Ochi, *Jpn. Kokai*, JP 04046149 (1992); *Chem. Abs.*, **117**, 10295.

6 S. Kobayashi, K. Morikawa and T. Saegusa, *Macromolecules*, 1975, **8**, 952; *Chem. Abs.*, **83**, 206657.

7 S. Kobayashi, N. Tsuchida, K. Morikawa and T. Saegusa, *Macromolecules*, 1975, **8**, 942; *Chem. Abs.*, **83**, 206655.

8 Mitsui Toatsu Chemicals Inc, Japan, *Jpn. Kokai*, JP 55165919 (1980); *Chem. Abs.*, **94**, 175852.

9 R. Chiang and J.H. Rhodes, *J. Polym. Sci., Part B*, 1969, **7**, 643; *Chem. Abs.*, **71**, 125029.

10 C.M. Suter, *The Organic Chemistry of Sulfur*, Wiley, New York, 1944. Reprinted edition by Intra-Science Research Foundation, Santa Monica, CA, 1969. The early work on the sulfonation of heterocyclic compounds is covered in Chapter 3, 315 *et seq.*

11 H. Cerfontain, *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*, Interscience Publishers, New York, 1968, Ch. 10, 137 *et seq.*

12 E.E. Gilbert, *Sulfonation and Related Reactions*, Interscience Publishers, New York, 1965.

13 J.P. Bassin, R.J. Cremlyn and F.J. Swinbourne, *Phosphorus, Sulfur, Silicon*, 1991, **56**, 245.

14 E.J. Glamkowski and P.A. Reitano, *J. Med. Chem.*, 1979, **22**, 106; *Chem. Abs.*, **90**, 48260.

15 A.R. Katritzky and R. Taylor, *Advances in Heterocyclic Chemistry*, Interscience Publishers, New York, 1990, Vol. 47, 239.

16 V.F. Borodkin, *J. Appl. Chem. USSR* (Engl. Transl.), 1950, **23**, 803; *Chem. Abs.*, **46**, 8089.

17 J.P. Bassin, R.J. Cremlyn and F.J. Swinbourne, *Phosphorus, Sulfur, Silicon*, 1992, **72**, 157.

18 T.I. Proshechkina, V.I. Shishkina and G.M. Novikova, *USSR*, SU 270729 (1970); *Chem. Abs.*, **73**, 98795.

19 G.M. Novikova, V.I. Shishkina and N.T. Igonina, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.*, 1974, **17**, 1360; *Chem. Abs.*, **82**, 72722.

20 S.L. Vorb'eva, V.N. Buyanov, I.I. Levina and N.N. Suvorov, *Zh. Vses. Khim. Ova im D.I. Mendeleeva*, 1989, **34**, 129; *Chem. Abs.*, **111**, 173943.

21 J.C. Fischer, Y. Auger and M. Wartel, *C.R. Acad. Sci. Ser. C*, 1972, **274**, 1446; *Chem. Abs.*, **77**, 75103.

22 P. Baumgarten and H. Erbe, *Chem. Ber.*, 1938, **71**, 2603.

23 O.V. Schickh, *Ger.*, DE 601896 (1934); *Chem. Abs.*, **28**, 7267.

24 Y. Morisawa, M. Katoake, K. Kihano and K. Kusano, *Jpn. Kokai*, 7821171 (1978); *Chem. Abs.*, **89**, 6238.

25 R.J. Cremlyn, F.J. Swinbourne and O.O. Shode, *J. Heterocycl. Chem.*, 1985, **22**, 1211.
26 J.P. Bassin, R.J. Cremlyn and S. Graham, *Phosphorus, Sulfur, Silicon*, 1998, **142**, 83.
27 J. Kawahata, H. Koibuchi, T. Ito and S. Toyoshima, *Chem. Pharm. Bull. (Tokyo)*, 1960, **8**, 788; *Chem. Abs.*, **55**, 26996.
28 I.R. Kovel'man and S.I. Kirillova, *USSR*, SU 1074869 (1984); *Chem. Abs.*, **100**, 220924.
29 I.N. Gracheva, L.I. Gridneva, A.I. Tochilkin and V.Z. Gorkin, *Khim.-Farm. Zh.*, 1988, **22**, 1336; *Chem. Abs.*, **110**, 165944.
30 A. Sturis, V. Purmale, T.I. Dichko, J. Asaks, P.I. Brusilovskii and A.Yu. Bankovskii, *Latv. PSR Zinet. Akad. Vestis., Kim. Ser.*, 1979, **2**, 181; *Chem. Abs.*, **91**, 39289.
31 T. Nishi, T. Ueda and K. Nakagawa, *Jpn. Kokai*, JP 53021175 (1978); *Chem. Abs.*, **89**, 43145.
32 E.F. Ali, *Eur.*, EP38177 (1981); *Chem. Abs.*, **96**, 68845; US 4315935 (1982); *Chem. Abs.*, **97**, 6172.
33 R.J. Cremlyn, *An Introduction to Organosulfur Chemistry*, Wiley, Chichester, 1996.
34 R.L. Ellis, US 3932444 (1976); *Chem. Abs.*, **84**, 136515.
35 J.E. Baldwin and F.C. Novello, US 4110456 (1978); *Chem. Abs.*, **90**, 87462.
36 A. Shaffiee, T. Akharzadeh, A. Foroumadi and F. Hadizadeh, *J. Heterocycl. Chem.*, 1998, **35**, 141.
37 R. Graeve, I. Okyayuz-Baklouti and D. Seiffge, *Ger. Offen.*, DE 4004061 (1990); *Chem. Abs.*, **115**, 232247.
38 L.L. Bennett and H.T. Baker, *J. Am. Chem. Soc.*, 1957, **79**, 2188.
39 M.H. Fisher, W.H. Nicholson and R.S. Stuart, *Can. J. Chem.*, 1961, **39**, 1336.
40 P.E. Cross, R.P. Dickinson, M.J. Parry and M.J. Randall, *J. Med. Chem.*, 1985, **28**, 1427.
41 V.G. Sayapin, A.M. Simonov and V.V. Kuz'nenko, *Khim. Geterosikl. Soedin.*, 1970, **5**, 681; *Chem. Abs.*, **73**, 45409.
42 F. Sperber, C. Huszar, A. Nemeth, E. Somfai and I. Pali, *Ger. Offen.*, DE 3826036 (1989); *Chem. Abs.*, **111**, 57733; (a) T. Sadikov, D.V. Khakimova, R.Kh. Nuriddinov and N.Kh. Aripov, *Uzb. Khim. Zh.*, 1999, (**5–6**), 40; *Chem. Abs.*, **132**, 334399.
43 R. Callendret, *Eur.*, EP 12051 (1980); *Chem. Abs.*, **93**, 239451.
44 R.R. Herr, T. Enkoji and T.J. Bardos, *J. Am. Chem. Soc.*, 1956, **78**, 401.
45 G.R. Barker, N.G. Luthy and M.M. Dhar, *J. Chem. Soc.*, 1954, 4206.
46 N.V. Khromov-Borisov and R.A. Karlinskaya, *J. Gen. Chem. USSR* (Engl. Transl.), 1957, **27**, 2576.
47 R.C. Elderfield and R.N. Prasad, *J. Org. Chem.*, 1961, **26**, 3863.
48 N.M. Goloshchapov, A.Ya. Sigidin, E.S. Tsvetkova, I.L. Bilich, V.S. Reznik, N.G. Pashkurov, G.F. Zaika and A.A. Muslinkin, *Fr. Demande*, FR 2408348 (1979); *Chem. Abs.*, **92**, 41976.
49 M. Gilow and J. Jacobus, *J. Org. Chem.*, 1963, **28**, 1994.
50 K. Seitz, US 3086020 (1963); *Chem. Abs.*, **59**, 10084.
51 T. Caldwell and G.E. Jaffe, *J. Am. Chem. Soc.*, 1959, **81**, 5166.
52 V. Khromov-Borisov and R.A. Karlinskaya, *Zh. Obshch. Khim.*, 1954, **24**, 2212; *Chem. Abs.*, **50**, 355.
53 R.J. Cremlyn, F.J. Swinbourne and K.M. Yung, *J. Heterocycl. Chem.*, 1981, **18**, 997; *Chem. Abs.*, **96**, 52222.
54 R.J. Cremlyn, S. Jethwa, G. Joiner and D. White, *Phosphorus, Sulfur*, 1988, **36**, 99.
55 R.J. Cremlyn, J.P. Bassin, F. Ahmed, M. Hastings, I. Hunt and T. Mattu, *Phosphorus, Sulfur, Silicon*, 1992, **73**, 161.
56 G.F. Holland, US 3894003 (1975); *Chem. Abs.*, **83**, 206282.

57 F. Nadler, H. Hoyer and O. Bayer, US 2219330 (1941); *Chem. Abs.*, **35**, 1072.
58 H. von Tobel, *Ger. Offen.*, DE 2404069 (1974); *Chem. Abs.*, **82**, 32587.
59 M. Hiraki, Y. Shimizu and M. Kojima, *Jpn. Kokai*, JP 01297468 (1989); *Chem. Abs.*, **112**, 120615.
60 Y. Kuwahara, *Jpn. Kokai*, JP 49075647, JP 49075648 (1974); *Chem. Abs.*, **82**, 18753, 18754.
61 H. Schuendehuette, M. Groll and J.W. Stawitz, *Eur.*, EP 371332 (1990); *Chem. Abs.*, **114**, 124554.
62 T. Sekiguchi, M. Tanaka and T. Shimura, *Jpn. Kokai*, JP 53120739 (1978); *Chem. Abs.*, **90**, 88749.
63 H. Jaeger and B. Kaletta, *Ger. Offen.*, DE 3902053 (1990); *Chem. Abs.*, **114**, 64259.
64 R.J. Cremlyn, R.M. Ellam and S. Farouk, *Pestic. Sci.*, 1998, **52**, 70.
65 S. Farouk, PhD Thesis, University of Hertfordshire, 1994.
66 R.J. Cremlyn, R.M. Ellam and S. Farouk, *Phosphorus, Sulfur Silicon*, 2000, **161**, 213.
67 R.J. Cremlyn, R.M. Ellam, S. Farouk, S. Graham and A. Williams, *Phosphorus, Sulfur, Silicon*, 1997, **122**, 87.
68 R.J. Cremlyn, F.J. Swinbourne and O.O. Shode, *J. Chem. Soc. Pak.*, 1986 **8**, 323.
69 Y. Ohishi, M. Nagahara, W. Kajikawa, M. Yajima, K. Nogimori and S. Kurokawa, *Eur.*, EP 187387 (1986); *Chem. Abs.*, **106**, 4857.
70 H. Harada, Y. Matsushita, M. Nakamura and Y. Yonetani, *Eur.*, EP 173899 (1986); *Chem. Abs.*, **105**, 114890.
71 K. Weber, H.R. Meyer, J. Krashig and C. Eckhardt, *Eur.*, EP 344776(1989); *Chem. Abs.*, **113**, 25560.
72 H. Gilman, E.W. Smith and J.H. Oatfield, *J. Am. Chem. Soc.*, 1934, **56**, 1412.
73 M.V. Rubtsov and V.M. Fedosova, *J. Gen. Chem. USSR* (Engl. Transl.), 1944, **14**, 848; *Chem. Abs.*, **40**, 1804.
74 R.J. Cremlyn and S. Clowes, *J. Chem. Soc. Pak.*, 1988, **10**, 97.
75 J.R. Merchant and R.C. Shah, *J. Indian. Chem. Soc.*, 1957, **34**, 35; *Chem. Abs.*, **51**, 16448.
76 Q. Cao and Q. Xu, *Fenxi Huaxue*, 1993, **21**, 1472; *Chem. Abs.*, **120**, 289113.
77 J.R. Merchant and R.C. Shah, *J. Org. Chem.*, 1957, **22**, 884.
78 J.R. Merchant and R.C. Shah, *J. Indian Chem. Soc.*, 1957, **34**, 45; *Chem. Abs.*, **51**, 16449.
79 J.R. Merchant and R.C. Shah, *J. Org. Chem.*, 1957, **22**, 1104.
80 M.A. Loutby and H.A. Abu-Shady, *Pharmazie*, 1977, **32**, 240; *Chem. Abs.*, **87**, 68200.
81 I.A. Solov'ena and G.I. Arbuzov, *Zh. Obshch. Khim.*, 1951, **21**, 765, *Chem. Abs.*, **45**, 9524.
82 D.V. Joshi, J.R. Merchant and R.C. Shah, *J. Org. Chem.*, 1956, **21**, 1104.
83 A.M.G. Silva, A.C. Tomé, A.M.S. Silva and J.A.S. Cavaleiro, *Phosphorus, Sulfur, Silica*, 1998, **140**, 113.
84 P. Ghosh, P. Sil and S. Thakur, *J. Chromatogr.*, 1987, **403**, 285; *Chem. Abs.*, **107**, 194376.
85 F.D. Hamb and J.C. Wilson, US 3902904 (1975); *Chem. Abs.*, **84**, 45190.
86 J.R. Pfister, I.T. Harrison and J.H. Fried, US 3902904 (1976); *Chem. Abs.*, **86**, 72443; US 3989721 (1976); *Chem. Abs.*, **86**, 72444.
87 R.J. Cremlyn and D. Saunders, *Phosphorus, Sulfur, Silicon*, 1993, **81**, 73.
88 R.J. Cremlyn, unpublished observations, University of Hertfordshire, 1993.
89 Societe d'Etudes Scientifiques et Industrielles de I'le-de-France, *Fr. Demande*, FR 239675 (1979); *Chem. Abs.*, **92**, 163975.
90 W. Steinkopf and T. Höpner, *Liebigs Ann. Chem.*, 1933, **501**, 174; *Chem. Abs.*, **27**, 2443.

91 W.H. Houff and R.D. Schuetz, *J. Am. Chem. Soc.*, 1953, **75**, 6316.
92 A.H. Blatt, S. Bach and L.W. Kresch, *J. Org. Chem.*, 1957, **22**, 1693
93 A. Buzas and J. Teste, *Bull. Soc. Chim Fr.*, 1960, 793; *Chem. Abs.*, **55**, 5455.
94 W.E. Truce, B. Van Gemert and W.W. Brand, *J. Org. Chem.*, 1978, **43**, 101.
95 C. Sone and Y. Matsuki, *Nippon Kagaku Zasshi,* 1962, **83**, 496; *Chem Abs.*, **59**, 3861.
96 W. Steinkopf and W. Köhler, *Liebigs Ann. Chem.*, 1937, **532**, 250; *Chem. Abs.*, **32**, 3391.
97 W. Steinkopf, H. Jacob and H. Penz, *Liebigs Ann. Chem.*, 1934, **512**, 136; *Chem. Abs.*, **29**, 779.
98 E. Profft and G. Solf, *Liebigs Ann. Chem.,* 1961, **649**, 100.
99 W.E. Truce and F.J. Lotspeich, *J. Am. Chem. Soc.*, 1955, **70**, 3410.
100 H.Y. Lew and C.R. Noller, *J. Am. Chem. Soc.*, 1950, **72**, 5715.
101 R.J. Cremlyn, K.H. Goulding, F.J. Swinbourne and K.-M. Yung, *Phosphorus, Sulfur*, 1981, **10**, 111; *Chem. Abs.*, **95**, 150313.
102 J. Cymerman and D.F. Faiers, *J. Chem. Soc.*, 1952, 165.
103 J. Cymerman-Craig and D. Willis, *J. Chem. Soc.*, 1955, 1071.
104 J. Cymerman-Craig, G.N. Vaughan and W.K. Warburton, *J. Chem. Soc.*, 1956, 4114.
105 K.H. Goulding, K.-M. Yung, A.M. Hall and R.J. Cremlyn, *Pestic. Sci.*, 1983, **14**, 158.
106 L.H. Edwards, US 3996243 (1976); *Chem. Abs.*, **86**, 106359.
107 L.H. Edwards, US 3991081 (1976); *Chem. Abs.*, **86**, 72424.
108 F. Kimura, T. Haga, K. Maeda, K. Hayashi, M. Ikeguchi and Y. Yoshida, *Braz. Pedido*, P1 BR 8602648 (1987); *Chem. Abs.*, **108**, 37636.
109 E. Maccarone, G. Musumarra and G.A. Tomaselli, *Ann. Chim.* (Rome), 1973, **63**, 861; *Chem. Abs.,* **83**, 8686.
110 M. Pailer and E. Romberger, *Monatsh. Chem.*, 1961, **92**, 677; *Chem. Abs.*, **56**, 439.
111 A. Quilico and R. Justoni, *Gazz. Chim. Ital.*, 1940, **70**, 1, 11; (a) B. Gallenkemp and L. Rohe, *Ger. Offen.*, DE 19747625, (1999); *Chem Abs.*, **130**, 311786.
112 N.K. Kochetkov and S.P. Sokolov, *Adv. Heterocycl. Chem.*, 1963, **2**, 365.
113 R.B. Woodward, R. Olofson and H. Mayer, *J. Am. Chem. Soc.*, 1961, **83**, 1010.
114 K.-H. Wünsch and A.J. Boulton, *Adv. Heterocycl. Chem.*, 1967, **8**, 277.
115 J.V. Scudi and R.P. Buhs, *J. Am. Chem. Soc.*, 1941, **63**, 879.
116 R.J. Cremlyn, S. Graham and D. Saunders, *Phosphorus Sulfur, Silicon*, 1994, **92**, 65.
117 R.J. Cremlyn, J.P. Bassin, S. Farouk, M. Potterton and T. Mattu, *Phosphorus, Sulfur, Silicon*, 1992, **73**, 107.
118 R.J. Cremlyn, R. Sheppard and F.J. Swinbourne, *Phosphorus, Sulfur, Silicon*, 1990, **54**, 117.
119 R.J. Cremlyn, F.J. Swinbourne and O.O. Shode, *J. Chem. Soc. Perkin Trans. 1*, 1983, 2181.
120 T. Toyo'oka and K. Imai, *Anal. Chem.*, 1984, **56**, 2461; *Chem. Abs.*, **101**, 166558.
121 V.F. Vasil'eva and V.G. Yashunskii, *Khim. Nauka i Prom.*, 1958, **3**, 282; *Chem. Abs.*, **52**, 20013.
122 B.G. Ugarkar, B.V. Badami and G.S. Puranik, *Arch. Pharm.* (Weinheim, Ger.), 1979, **312**, 977; *Chem. Abs.*, **92**, 181092.
123 R. Shapiro, US 4604130 (1986); *Chem. Abs.*, **106**, 45722.
124 C.F.H. Allen, A. Bell and C.V. Wilson, *J. Am. Chem. Soc.*, 1944, **66**, 835.
125 A.I. Kiprianov and I.K. Ushenko, *J. Gen. Chem.* (USSR), 1945, **15**, 207; *Chem. Abs.*, **40**, 2309.
126 T. Tanaka, H. Umekawa, M. Saitoh, T. Ishikawa, T. Shin, M. Ito, H. Itoh, Y. Kawamatsu, H. Sugihara and H. Hidaka, *Mol. Pharmacol.*, 1986, **29**, 264; *Chem. Abs.,* **104**, 184072.
127 M. Meneghin, *Eur.*, EP 451675 (1991); *Chem. Abs.,* **116**, 106306.

CHAPTER 7

Reaction of Chlorosulfonic Acid with Elements and Inorganic Compounds

The early work in this area was summarized by Jackson in his review.[1]

1 Elements

As mentioned in the Introduction (Chapter 1) chlorosulfonic acid acts as a chlorinating agent with sulfur, which by warming with the reagent yields a mixture of sulfur dichloride, sulfur dioxide and hydrogen chloride. Conductometric and spectrophotometric measurements on the red solutions of sulfur in chlorosulfonic acid indicated the formation of the S_{16}^{2+} cationic species, which is unstable and gradually converts to the stable yellow S_4^{2+} cation.[1,2]

With arsenic and antimony, chlorosulfonic acid yields the corresponding trichlorides; thus on warming finely powdered arsenic with the reagent, gaseous sulfur dioxide is evolved and arsenic trichloride distils off leaving a residue of arsenious oxide. Antimony behaves similarly, while tin reacts in the cold with chlorosulfonic acid to give tin tetrachloride (Equation 1).[1]

$$Sn + 4ClSO_3H \longrightarrow SnCl_4 + H_2SO_4 + 2SO_2 \quad (1)$$

With phosphorus, the reagent reacts violently on warming with evolution of sulfur dioxide and hydrogen chloride. The reaction using amorphous (red) phosphorus is less vigorous and yields phosphoric acid and phosphorus oxychloride.

By warming chlorosulfonic acid with charcoal, it is decomposed to a mixture of sulfur dioxide, carbon dioxide and hydrogen chloride.[1] Anthracite can be oxidized to mellitic acid (benzenehexacarboxylic acid, 24% yield) by heating with a mixture of nitric and chlorosulfonic acid in a stream of air at 130 °C.[3] The kinetics of the oxidation were examined and the presence of nitric acid was found to be essential.

Chlorosulfonic acid does not form intercalation compounds with graphite in the presence of an oxidant.[4]

The kinetics of the reactions of chlorosulfonic acid with iron powder in pyridine and in 2-, 3- and 4-methylpyridines at 30–65 °C have been studied.[5]

The electrochemical behaviour of silver, mercury, gold, platinum and vitreous carbon electrodes was examined in chlorosulfonic acid; the experiments showed that only the latter material was not attacked; the oxidizing properties of chlorosulfonic acid were mainly due to the presence of sulfur trioxide.[6] As mentioned in Chapter 1, chlorosulfonic acid reacts with powdered selenium or tellurium with the formation of moss-green or cherry-red colours respectively, which may be used as spot tests for the reagent.[1]

Conductometric and UV–visible spectroscopic studies of solutions of tellurium in chlorosulfonic acid indicated that the red colour of the solution is due to the formation of the Te_4^{2+} cation. In the presence of oxidizing agents, *e.g.* potassium persulfate, the red (Te_4^{2+}) cation is converted into the yellow Te_4^{4+} cationic species and with excess oxidant tellurium oxide (TeO_2) is formed.[7] Other workers[8] isolated the compounds $Te_4(SO_3Cl)_2$ and $Te_2(SO_3Cl)_2$, which on dissolution in chlorosulfonic acid afforded the Te_4^{2+} and Te_2^{2+} cations. Experiments demonstrate that solutions of selenium and tellurium in chlorosulfonic acid in the presence of chlorine and bromine form the halocations $SeCl_3^+$, $SeBr_3^+$, $TeCl_3^+$ and $TeBr_3^+$ respectively.[9]

Selenium dissolves in chlorosulfonic acid giving a green solution, which after a few hours turns yellow. Conductometric and spectrophotometric studies indicated that the green and yellow colours are due to the formation of the Se_8^{2+} and Se_4^{2+} cations respectively (Equations 2 and 3).[10]

$$8Se + 4ClSO_3H \longrightarrow Se_8^{2+} + 2ClSO_3^- + H_2SO_4 + 2HCl + SO_2 \quad (2)$$

$$4Se + 4ClSO_3H \longrightarrow Se_4^{2+} + 2ClSO_3^- + H_2SO_4 + 2HCl + SO_2 \quad (3)$$

The green and yellow solids, namely $Se_8(SO_3Cl)_2$ and $Se_4(SO_3Cl)_2$, have been isolated and their IR spectra determined; both compounds dissolved in chlorosulfonic acid to give highly conducting solutions.[11]

Iodine dissolves slowly in chlorosulfonic acid at 25 °C to give a reddish-brown conducting solution (Equation 4).

$$5I_2 + 4ClSO_3H \longrightarrow 2I_5^+ + 2ClSO_3^- + H_2SO_4 + SO_2 \quad (4)$$

The solution was studied by UV–visible spectrometry and conductometric redox titrations of iodine in mixtures of potassium persulfate and chlorosulfonic acid.[12] Similar studies of the bromine oxidation of iodine, potassium iodide and iodic acid in chlorosulfonic acid indicated the formation of the dibromoiodine cation (Br_2I^+) as a stable entity in solution.[13]

2 Inorganic Compounds

With water, chlorosulfonic acid reacts violently producing hydrogen chloride and sulfuric acid in a highly exothermic reaction (Equation 5).

$$ClSO_3H + H_2O \longrightarrow H_2SO_4 + HCl \quad (5)$$

Chlorosulfonic acid reacts violently with silver nitrate giving silver chloride and nitroxychlorosulfonate ($NO-O-SO_2Cl$) and with potassium chromate, it yields chromyl chloride.[1] Later studies[14] showed that potassium chromate and potassium dichromate dissolved in chlorosulfonic acid forming reddish-orange solutions, which on concentration afforded chromyl chlorosulfonate [$CrO_2(SO_3Cl)_2$], a moss-green solid at RT. Chlorosulfonic acid has been extensively studied as a polar non-aqueous solvent.[15] Conductometric and spectral studies of various inorganic and organic acid anhydrides in chlorosulfonic acid at 25 °C indicate that NO and N_2O behave as non-electrolytes while N_2O_3, N_2O_4 and N_2O_5 form NO^+ and NO_2^+ cations (Equations 6–8).[15–17]

$$N_2O_3 + 3ClSO_3H \longrightarrow 2NO^+ + 2ClSO_3^- + H_2SO_4 + HCl \quad (6)$$

$$N_2O_4 + 3ClSO_3H \longrightarrow NO_2^+ + NO^+ + 2ClSO_3^- + H_2SO_4 + HCl \quad (7)$$

$$N_2O_5 + 3ClSO_3H \longrightarrow 2NO_2^+ + 2ClSO_3^- + H_2SO_4 + HCl \quad (8)$$

Phosphorus pentoxide with chlorosulfonic acid yields a mixture of sulfur oxychlorides which act as non-electrolytes. As_2O_3, Sb_2O_3 and Bi_2O_3 undergo solvolysis, but B_2O_3 yields $B(SO_3Cl)_3$. Organic acid anhydrides function as weak bases in chlorosulfonic acid and the extent of their protonation shows that chlorosulfonic acid is a stronger acid than sulfuric acid.[16,17]

The solvolysis of vanadium(V) and chromium(VI) compounds in chlorosulfonic acid showed that V_2O_5, $VOCl_3$ and NH_4VO_3 were solvolysed to the non-electrolyte $H[VO(SO_3Cl)_4]$, whereas CrO_2Cl_2, $K_2Cr_2O_7$, K_2CrO_4 and CrO_3 were converted into $CrO_2(SO_3Cl)_2$.[18]

When a small amount of fused potassium nitrate was treated with chlorosulfonic acid, chlorine gas was evolved and on heating, a large amount of nitrogen dioxide was produced.[1] Sodium chloride dissolves in chlorosulfonic acid with evolution of hydrogen chloride and formation of sodium chlorosulfonate.[1] The addition of sodium chloride to chlorosulfonic acid may sometimes enhance its effectiveness in the chlorosulfonation of organic compounds (see Chapter 2, p 13).

Selenium and tellurium oxychlorosulfonates were prepared and characterized by dissolving Na_2SeO_3 or Na_2TeO_3 in chlorosulfonic acid to give yellow, highly conducting solutions containing $SeO(SO_3Cl)_2$ and $TeO(SO_3Cl)_2$ respectively.[19]

Mercury(II) salts rapidly catalyse the decomposition of boiling chlorosulfonic acid quantitatively into sulfuryl chloride and sulfuric acid (see Chapter 1). With other salts, the reaction is similar but slower. When chlorosulfonic acid (50 g) was boiled with the appropriate salt (1 g) for 1 hour, the yields of sulfuryl chloride

produced by each salt are as shown in brackets: $HgCl_2$ (13.0 g), $HgSO_4$ (13.0 g), $SbCl_5$ (7.5 g), $SbCl_3$ (7.5 g), $SnCl_4$ (5.8 g), $BiCl_3$ (3.3 g), $PtCl_4$ (2.5 g), VO_2Cl_2 (1.7 g), $AuCl_3$ (1.2 g), $CuSO_4$ (0.8 g), WCl_3 (0.8 g), $PbCl_5$ (0.7 g), $CoSO_4$ (0.5 g), $MgCl_2$ (0.5 g). The chlorides of aluminium, calcium, iron, and zinc did not react with chlorosulfonic acid.

The quantitative decomposition of the reagent by mercury(II) salts may be used for the manufacture of sulfuryl chloride.[1]

By heating chlorosulfonic acid with powerful dehydrating agents, like phosphorus pentoxide or oxychloride, it is converted into its anhydride, namely pyrosulfuryl chloride, $[(ClSO_2O)_2O]$.

The electrical conductivities of arsenic, antimony, bismuth, vanadium, selenium and tellurium oxides and of antimony, bismuth and vanadium oxyhalides have been determined in chlorosulfonic acid. Arsenic, antimony and bismuth oxides in chlorosulfonic acid yield the corresponding oxychlorosulfonates as shown (Equation 9).

$$M_2O_3 + 3ClSO_3H \longrightarrow 2MOSO_3Cl + H_2SO_4 + HCl \quad (9)$$
(M = As, Sb, Bi)

Vanadium pentoxide and vanadium oxychloride are weak electrolytes and appear to form $H[VO(SO_3Cl)_4]$, while selenium and tellurium dioxides are protonated in chlorosulfonic acid yielding SeO_2H^+ and TeO_2H^+ respectively.[20]

The chemistry of some cerium(IV), thorium(IV) and lanthanum(III) compounds in chlorosulfonic acid has been examined.[21] Cerium(IV) oxide, sulfate, perchlorate, acetate, nitrate and chloride are all solvolysed to the $Ce(SO_3Cl)_4$ species, which behaves as a nonelectrolyte. Thorium(IV) oxide, nitrate, acetate and chloride are solvolysed to $H_2[Th(SO_3Cl)_6]$, a weak acid. Lanthanum(III) oxide, sulfate, acetate and chloride form $H[La(SO_3Cl)_4]$, a very weak acid.[21]

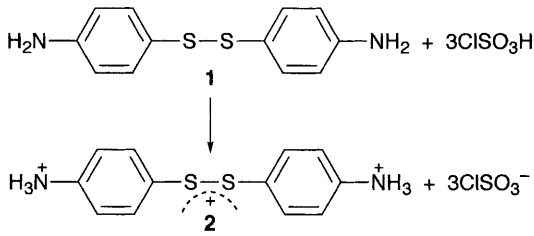
Selenium and tellurium tetrabromides dissolve in chlorosulfonic acid to form $SeBr_3^+$ and $TeBr_3^+$ cations and solutions of selenium chloride (SeCl) in chlorosulfonic acid contain both $SeCl_3^+$ and Se_4^{2+} ions.[22] Phosphorus pentachloride yields PCl_4^+ ions, while phosphorus trichloride behaves as a very weak base.[22] Phosphorus tri- and pentabromide are oxidized in chlorosulfonic acid to give phosphoryl bromide, which is further protonated at the oxygen atom by the acid.[22] The reactions of phosphorus(V) halides and oxyhalides in strongly acid solvents have been examined by ^{31}P NMR spectroscopy.[23] Analogous studies were also carried out with the monophenyl organophosphorus compounds phenylphosphoric acid and phenylphosphorodichloridate[24] and with phosphorus trihalides (PX_3; X = Cl, Br, I).[25] Studies of the solvolysis of various niobium(V), tantalum(V), molybdenum(V) and molybdenum(VI) compounds in chlorosulfonic acid showed that the pentoxides (M_2O_5; M = Nb, Ta), oxychlorides ($MOCl_3$), pentahalides (MX_5; X = Cl, Br), and NH_4MO_3 yield $H[Nb(SO_3Cl)_4]$ and $H[Ta(SO_3Cl)_4]$ which behave as nonelectrolytes.[26] K_2MoO_4 and Mo_2O_5 also solvolyse in chlorosulfonic acid to yield an orange solid $MoO_2(SO_3Cl)_2$, while $MoCl_5$ yields $H_2[Mo(SO_3Cl)_8]$ which functions as a nonelectrolyte in this medium.[26]

The solvolytic behaviour of 25 lead(IV), tin(IV) and silicon(IV) compounds in chlorosulfonic acid has been examined conductometrically.[27]

Conductometric and spectral studies of some uranium(IV) and (VI) compounds in chlorosulfonic acid showed that solvolysis of UO_3, UO_2SO_4, UO_2Cl_2, $UO_2(C_2O_4)_2$, $UO_2(HCOO)_2$ and $UO_2(OCOMe)_2$ gave $UO_2(SO_3Cl)_2$; UCl_6 forms $H[U(SO_3Cl)_7]$ or $H_2[U(SO_3Cl)_8]$ which function as nonelectrolytes in chlorosulfonic acid, while $U(OCOMe)_4$ yields the very weak acid $H_2[U(SO_3Cl)_6]$.[28]

The basicity of sulfides, sulfones and sulfoxides in chlorosulfonic acid has been studied conductometrically and the acid strengths of $ClSO_3H$, FSO_3H, $H_2S_2O_7$ and H_2SO_4 were compared.[29] Dimethyl sulfoxide behaved as a fully protonated base in chlorosulfonic acid, but the nitro derivatives were weak bases, similarly dimethyl and diethyl sulfones were weak bases. Diphenyl sulfone, unlike diphenyl sulfoxide, was a weakly ionized base and the introduction of nitro groups further reduced the basicity of the sulfones. Diphenyl sulfide was a strong base, whereas the nitro derivatives were weak bases in chlorosulfonic acid. The protonation studies showed that chlorosulfonic acid was a stronger acid than sulfuric acid.[29]

4,4′–Diaminodiphenyl disulfide **1** is believed to give a unique cation **2** containing three positive charges on treatment with chlorosulfonic acid (Equation 10).[15]



(10)

Conductometric studies demonstrated that alkyl selenoxides and selenones are completely ionized bases in chlorosulfonic acid, whereas the corresponding phenyl compounds and their nitro derivatives are only weakly basic. The selenones were found to be stronger bases than the corresponding sulfones.[30]

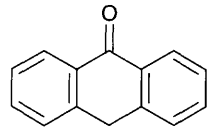
The conductance behaviour of selected sulfur–nitrogen compounds, namely thiotrithiazyl chloride, bromide and their adducts $(S_4N_3)[TeBr_5]$, $(S_4N_3)_2[TeBr_6]$, $(S_4N_3)[SbCl_4]$ and $(S_4N_3)[SbBr_4]$ were studied in pyrosulfuric ($H_2S_2O_7$), chlorosulfonic and fluorosulfonic acids.[31]

2.1 Oxidation–Reduction Reactions

Some oxidation–reduction reactions have been carried out in chlorosulfonic acid using Cl_2, Br_2, ICl and NOCl as oxidants and PCl_3, PBr_3, $AsCl_3$, $AsBr_3$, PPh_3, $AsPh_3$ and $SbPh_3$ as the reducing agents. The reactions afforded the compounds $PCl_4^+SO_3Cl^-$, $PCl_3Br^+SO_3Cl^-$, $Ph_3PCl \cdot SO_3Cl$ and $Ph_3PBr \cdot SO_3Cl$.[32] The behaviour of the inorganic halides PCl_3, PBr_3, PCl_5, PBr_5 and PCl_6I was examined conductometrically in chlorosulfonic acid.[33] The pentahalides and the hexachloroiodide ionized to give the stable PX_4^+ cationic species (X = Cl, Br); while the trihalides were oxidized to yield the conjugate acid $[HO^+PX_3]$. Conductometric titrations of phosphorus trihalides (PX_3) with halogens and interhalogen com-

pounds (ICl) indicate the formation of the cationic species PCl_3Br^+ and PBr_3Cl^+ as stable entities in solution. Solutes like $AsCl_3$, $SbF_3$and $SbCl_3$ were only partially ionized in chlorosulfonic acid and $SbCl_5$, $BiCl_3$ and VCl_3 were insoluble.[33]

The reactions of fluoro and chlorosulfonic acid, sulfuric, pyrosulfuric, hydrochloric and hydrobromic acids, together with tri-, di- and monochloroacetic acids with anthrone **3** were studied by conductometric and potentiometric techniques.[34]



3

The results indicated that the anthrone–acid adducts are ionic and the heats of reaction of anthrone with the acids vary with concentration and the acid strength decreases in the order shown in Scheme 1.

$$H_2S_2O_7 > FSO_3H > ClSO_3H > H_2SO_4 > HBr > HCl > Cl_3CCO_2H > Cl_2CHCO_2H, ClCH_2CO_2H > CH_3CO_2H$$

Scheme 1

Similar reactions of the protic acids with benzanthrone and dibenzanthrone were carried out;[35] in all cases titrations with acetic, monochloro and dichloroacetic acids were unsuccessful indicating relatively weak interactions of the acids with the ketones.

Chlorosulfonic acid has also been used for the titrimetric titration of some anilines and pyridines in the presence of diethylamine in dioxan and a mixture of acetic acid–chloroform (1:10) as solvents for the acid and bases respectively.[36]

3 Sodium Azide

Chlorosulfonic acid reacts with sodium azide (one equivalent) in dichloromethane at 30 °C to give the azidosulfonate **4** which precipitates out from solution (Equation 11, see also Chapter 6, ref. 12).[37]

An analogous reaction between sodium azide and excess chlorosulfonic acid (two equivalents) yielded the very reactive addition compound **5** (Equation 12).[37]

$$Na^+N_3^- + \underset{(1\ eq.)}{ClSO_3H} \xrightarrow[30\,^\circ C]{CH_2Cl_2} \underset{\mathbf{4}}{NaO_3S{-}N{=}\overset{+}{N}{=}\overset{-}{N}} + HCl \qquad (11)$$

$$Na^+N_3^- + 2ClSO_3H \xrightarrow{CH_2Cl_2} \underset{\mathbf{5}}{NaO_3SN_3{\cdot}ClSO_3H} + HCl \qquad (12)$$

The adduct **5** may be used for the introduction of nitrogen as N_3, NH or NCO groups into organic compounds (Chapter 6, ref. 12).

4 Nitric Acid

Chlorosulfonic acid reacts with 100% nitric acid (prepared by distillation of concentrated nitric acid and 30% oleum) to give nitryl chloride **6** (Equation 13).[38] Chlorosulfonic acid (one equivalent) is added dropwise to stirred 100% nitric acid at 0 °C, and after half an hour at RT, nitryl chloride distils as a pale yellow liquid (bp −17 to −18 °C). Pure nitryl chloride is a colourless gas and this reaction provides the best synthetic route to the compound.[38]

$$HNO_3 + ClSO_3H \longrightarrow H_2SO_4 + \underset{\mathbf{6}}{NO_2Cl} \qquad (13)$$

5 Sulfanes

The reaction of chlorosulfonic acid with sulfanes in ethereal solution at −80 °C yields sulfanemonosulfonates, which are intermediates in polythionate reactions. Thus, the reagent reacts with hydrogen sulfide at −80 °C to give thiosulfuric acid **7** and then the trithionate **8** as shown (Equations 14 and 15).[39]

$$HO{-}SO_2{-}Cl + H_2\ddot{\underset{\cdot\cdot}{S}} \xrightarrow[-78\,^\circ C]{Et_2O} \underset{\mathbf{7}}{HO{-}SO_2{-}SH} + HCl \qquad (14)$$

$$HO{-}SO_2{-}SH + ClSO_3H \longrightarrow \underset{\mathbf{8}}{H_2S_3O_6} + HCl \qquad (15)$$

The sulfanesulfonic acid **7** is very unstable and readily decomposes into hydrogen sulfide and sulfur trioxide.

6 Hydrofluoric Acid

Chlorosulfonic acid reacts with hydrofluoric acid to yield fluorosulfonic acid **9** (Equation 16).[40] The process may be used in the manufacture of fluorosulfonic acid **9** by injecting gaseous hydrogen fluoride into the bottom of a layer of chlorosulfonic acid in a steel reactor at 10–20 °C at a rate of $6 \pm 0.5\ kg\,h^{-1}$. The pressure in the hydrogen fluoride evaporator is $1.2\ kg\,cm^{-2}$ and the liberated hydrogen chloride is absorbed by water in a graphite heat absorber–heat exchanger.[40]

$$ClSO_3H + HF \xrightarrow[10\text{–}30\,^\circ C]{} \underset{\mathbf{9}}{FSO_3H} + HCl \qquad (16)$$

7 Hydrogen Peroxide

Chlorosulfonic acid reacts with hydrogen peroxide in isoamyl alcohol to yield peroxymonosulfuric acid **10** (Equation 17).[41] The reaction involves nucleophilic attack by hydrogen peroxide on the electrophilic sulfur atom of chlorosulfonic acid. A peroxydisulfuric acid **11** can also be prepared by this route using excess chlorosulfonic acid (Equation 18).[41]

$$ClSO_3H + H\ddot{O}\ddot{O}H \longrightarrow \underset{\mathbf{10}}{HO-O-SO_2(OH)} + HCl \quad (17)$$

$$2ClSO_3H + HOOH \longrightarrow \underset{\mathbf{11}}{HO_3S-O-O-SO_3H} + 2HCl \quad (18)$$

The reaction of chlorosulfonic acid with *N*-methylhydroxylamine to yield the corresponding *O*-sulfonic acid is described in Chapter 4, p 129.

Hydroxylamine hydrochloride also reacts with chlorosulfonic acid (1.03 equivalents) in chloroform or 1,2-dichloroethane to give hydroxylamine *O*-sulfate.[42]

8 References

1 K.E. Jackson, *Chem. Rev.*, 1939, **25**, 67.

2 Z.A. Siddiqi, N.A. Ansari and S.A.A. Zaidi, *Bull. Soc. Chim. Fr.*, 1979, **11–12**,(1), 482; *Chem. Abs.*, **92**, 83442.

3 E.S. Rudakov, M.V. Savoškin, R.I. Rudakov and V.A. Sapunov, *Ukr. Khim. Zh.*, 1984, **50**, 38; *Chem. Abs.*, **100**, 198390.

4 A. Yaddaden, B. Iskander and P. Vast, *Ann. Chim. (Paris)*, 1981, **6**, 351; *Chem. Abs.*, **95**, 90402.

5 T.L. Myslin, V.I. Rogovik and P.P. Karpukhin, *Zh. Prikl. Khim.(Leningrad)*, 1973, **46**, 2716; *Chem. Abs.*, **80**, 74611.

6 I. Khalil, M. Herlem and A. Thiebault, *Rev. Chim. Miner.*, 1974, **11**, 460; *Chem. Abs.*, **82**, 104867.

7 S.A.A. Zaidi, Z.A. Siddiqi and N.A. Ansari, *Acta. Chim. Acad. Sci. Hung.*, 1978, **97**, 207; *Chem. Abs.*, **89**, 186761.

8 R.C. Paul, D. Konwer, D.S. Dhillon and J.K. Puri, *Indian J. Chem.*, 1978, **16A**, 253; *Chem. Abs.*, **89**, 31707.

9 R.C. Paul, D. Konwer and J.K. Puri, *Indian J. Chem.*, 1982, **21A**, 81; *Chem. Abs.*, **96**, 209783.

10 S.A.A. Zaidi, Z.A. Siddiqi and N.A. Ansari, *Acta. Chim. Acad. Sci. Hung.*, 1977, **93**, 395; *Chem. Abs.*, **88**, 42295.

11 R.C. Paul, D. Konwer, D.S. Dhillon and J.K. Puri, *Inorg. Nucl. Chem. Lett.*, 1977, **13**, 389; *Chem. Abs.*, **87**, 91582.

12 S.A.A. Zaidi, Z.A. Siddiqi and N.A. Ansari, *Proc. Symp. Chem. React. Non-Aqueous Media Molten Salts*, Bombay, India, 1980; *Chem. Abs.*, **96**, 92689.

13 S.A.A. Zaidi, M. Yamin, M. Shakir and Z.A. Siddiqi, *Bull. Soc. Chim. Fr.*, 1987, **3**, 441; *Chem. Abs.*, **107**, 189581.

14 Z.A. Siddiqi, Lutfallah and S.A.A. Zaidi, *Bull. Soc. Chim. Fr.*, 1980, **11–12**,(1), 466; *Chem. Abs.*, **94**, 113568.

15 W.R. Hardstaff and R.F. Langler, 'The Sulfur–Chlorine Bond' in *Sulfur in Organic and Inorganic Chemistry*, A. Senning (ed), M. Dekker Inc., New York, 1982, Vol. 4, 263.

16 R.C. Paul, D.S. Dhillon, D. Konwer and J.K. Puri, *Chem. Ind. (London)*, 1975, 615; *Chem. Abs.*, **83**, 153443.

17 R.C. Paul, D.S. Dhillon, D. Konwer and J.K. Puri, *Indian J. Chem.*, 1977, **15A**, 23; *Chem. Abs.*, **87**, 44937.

18 J.K. Puri and J.M. Miller, *Inorg. Chim. Acta.*, 1983, **75**, 215; *Chem. Abs.*, **100**, 16763.

19 S.A.A. Zaidi, S.R. Zaidi, S.A. Shaheer, Z.A. Siddiqi and M. Shakir, *Synth. React. Inorg. Metal-Org. Chem.*, 1985, **15**(4), 449; *Chem. Abs.*, **103**, 97907
20 S.A.A. Zaidi and Z.A. Siddiqi, *Acta. Chim. Acad. Sci. Hung.*, 1977, **92**, 57; *Chem. Abs.*, **87**, 44936.
21 J.K. Puri, P. Singh and J.M. Miller, *Inorg. Chim. Acta.*, 1983, **74**, 139; *Chem. Abs.*, **99**, 201362.
22 R.C. Paul, D.S. Dhillon, D. Konwer and J.K. Puri, *Indian J. Chem.*, 1980, **19A**, 473; *Chem. Abs.*, **93**, 102177.
23 K.B. Dillon, M.P. Nisbet and T.C. Waddington, *J. Chem. Soc., Dalton Trans.*, 1978, 1455; *Chem. Abs.*, **90**, 80204.
24 K.B. Dillon, M.P. Nisbet and T.C. Waddington, *J. Chem. Soc., Dalton Trans.*, 1981, 212; *Chem. Abs.*, **94**, 192412.
25 K.B. Dillon, M.P. Nisbet and T.C. Waddington, *J. Chem. Soc., Dalton Trans.*, 1979, 883; *Chem. Abs.*, **91**, 101297.
26 R.C. Paul, J. Kaur, D. Konwer and J.K. Puri, *Indian J. Chem.*, 1981, **20A**, 1212; *Chem. Abs.*, **96**, 209834.
27 R.C. Paul, D. Konwer, D.S. Dhillon and J.K. Puri, *J. Inorg. Nucl. Chem.*, 1981, **43**, 1071; *Chem. Abs.*, **95**, 79565.
28 R.C. Paul, D. Konwer, D.S. Dhillon, V. Sharma and J.K. Puri, *J. Inorg. Nucl. Chem.*, 1979, **41**, 825; *Chem. Abs.*, **92**, 48128.
29 R.C. Paul, D.S. Dhillon, D. Konwer and J.K. Puri, *J. Inorg. Nucl. Chem.*, 1977, **39**, 1011; *Chem. Abs.*, **87**, 190114.
30 R.C. Paul, D. Konwer, D.S. Dhillon and J.K. Puri, *J. Inorg. Nucl. Chem.*, 1979, **41**, 55; *Chem. Abs.*, **90**, 210977.
31 R.C. Paul, R.P. Sharma, R.D. Verma and J.K. Puri, *Indian J. Chem.*, 1979, **18A**, 516; *Chem. Abs.*, **92**, 120994.
32 J.K. Puri, P. Singh and V. Sharma, *Indian J. Chem.*, 1983, **22A**, 795; *Chem. Abs.*, **100**, 44431.
33 Z. Siddiqi, M. Aslam, N.A. Ansari, M. Shakir and S.A.A. Zaidi, *Indian J. Chem.*, 1981, **20A**, 773; *Chem. Abs.*, **95**, 231152.
34 R.C. Paul, S.C. Ahluwalia and R. Parkash, *Indian J. Chem.*, 1969, **7**, 815; *Chem. Abs.*, **71**, 101146.
35 R.C. Paul, R. Parkash, S.C. Ahluwalia, *Indian Chem. Soc.*, 1971, **48**, 49; *Chem. Abs.*, **75**, 11032.
36 S.V. Sreeram and P.R. Naidu, *Acta. Cienc. Indica, [Ser.] Chem.*, 1982, **8**, 181; *Chem. Abs.*, **98**, 154732.
37 H. Elsner and H. Ratz, *Ger.*, DE 886298 (1953); *Chem. Abs.*, **52**, 13774.
38 R. Kaplan and H. Shechter, 'Nitryl Chloride' in *Inorganic Syntheses*, J. C. Bailar (ed), McGraw-Hill Inc, New York, 1953, Vol. IV, 52.
39 T.L. Pickering and A.V. Tobolsky, 'Inorganic and Organic Polysulfides' in *Sulfur in Inorganic and Organic Chemistry*, A. Senning (ed), M. Dekker Inc, New York, 1972, Vol. 3, 24.
40 G.A. Eremina, E. V. Osipov and V.A. Buslaev, *Khim. Promst. (Moscow)*, 1977, **4**, 315; *Chem. Abs.*, **88**, 24978.
41 S.M. Afzal, *Pak. J. Sci.*, 1980, **32**(3–4), 201; *Chem. Abs.*, **95**, 196448.
42 S.A. Mamaev and L.I. Osadchaya, *USSR*, SU 154893 (1990); *Chem. Abs.*, **112**, 237765.

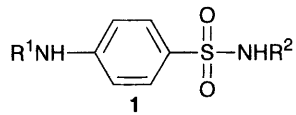
CHAPTER 8

Commercial Uses of Chlorosulfonic Acid

Many important industrial chemicals are manufactured by procedures involving chlorosulfonic acid. Examples include: medicinal agents such as sulfonamide antibacterials and diuretics; disinfectants (chloramine and dichloramine T); pesticides like sulfonylurea; carbamate herbicides and aryl sulfone acaricides; synthetic sweeteners, *e.g.* saccharin and cyclamate; long chain alkyl and alkylarylsulfonates as detergents; sulfonyl polymers, sulfonyl azides and hydrazides as blowing agents used in the preparation of foam plastics; sulfonyl dyes and pigments (see Chapter 1, p 5). Chlorosulfonic acid mixed with sulfur trioxide is also used as a chemical smoke in warfare (see Chapter 7, ref. 1).

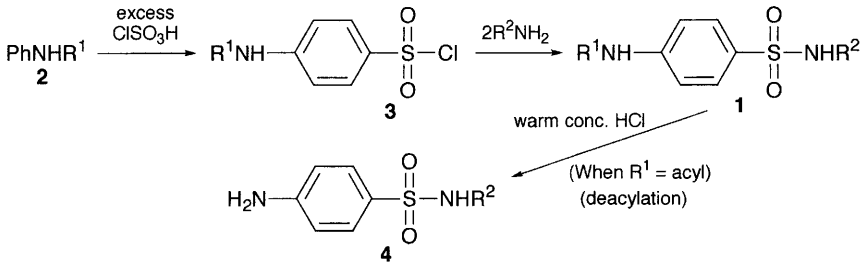
1 Medicinal Agents

Since the discovery of the antibacterial activity of sulfonamides in 1935, some 15 000 derivatives of sulfanilamide (**1**; $R^1 = R^2 = H$) have been synthezised[1] (see also Chapter 6, ref. 33). They were the first synthetic antibacterial agents to be widely effective in humans. The antibacterial action was found to be generally confined to derivatives of sulfanilamide (*p*-aminobenzenesulfonamide) of the type depicted by structure **1** with variations in R^1 and R^2; in the majority of the sulfa drugs the substituent $R^1 = H$, but there is considerable variation in the other substituent, R^2.



1

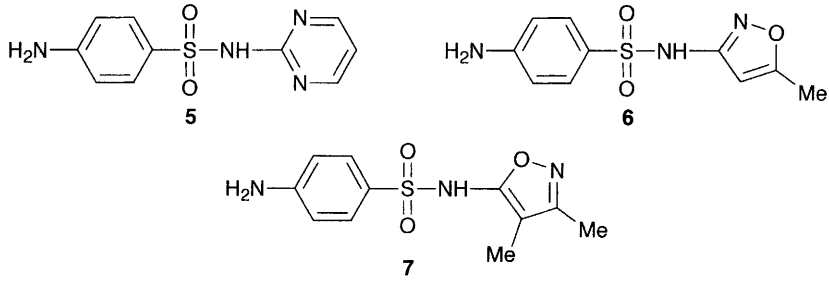
Sulfanilamides are synthezised by reaction of the appropriate substituted aniline **2** with excess chlorosulfonic acid to yield the sulfonyl chloride **3** and subsequent condensation with the amine gives the corresponding sulfanilamide **1**. If R^1 is an acyl group then treatment of the acylsulfonamide **1** with hot concentrated hydrochloric acid results in selective hydrolysis of the acyl moiety yielding the desired sulfanilamide **4** (Scheme 1).



Scheme 1

For instance, sulfanilamide (**4**, $R^2 = H$) is obtained by heating acetanilide (**2**; $R^1 = COMe$) with chlorosulfonic acid (five equivalents) at 60 °C (2 hours) to give N^4-acetylsulfanilyl chloride (**3**; $R^1 = COMe$). Treatment with ammonia and selective hydrolysis of the resultant acetylsulfanilamide afforded the product **4**, ($R^2 = H$). The chlorosulfonation of acetanilide is of considerable industrial importance in the manufacture of sulfa drugs, consequently various modifications have been investigated to improve the yield of N^4-acetylsulfanilyl chloride (see Chapter 4, p 102).

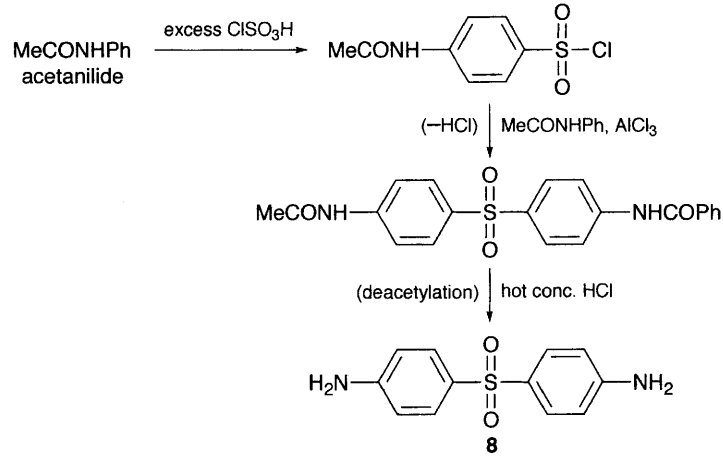
Sulfanilamide and other sulfa drugs owe their antibacterial properties to their ability to mimic *p*-aminobenzoic acid (PABA) which is an essential metabolite for many bacteria (Chapter 6, ref. 33) since it is an intermediate in the biosynthesis of folic acid. Many strains of bacteria have now become resistant to the antibacterial action of sulfonamides and consequently their use has declined and they have been often superseded by antibiotics in the treatment of many infectious diseases. However, sulfonamides are still important antimicrobial agents; some of the most useful chemicals contain a heterocyclic nucleus, for instance sulfadiazine **5**, sulfamethoxazole **6** and sulfaisoxazole **7**.[1]



The compounds (**5–7**) are made from N^4-acetylsulfanilyl chloride (**3**, $R^1 = MeCO$) by condensation with the appropriate heterocyclic amine and deacetylation as indicated in Scheme 1. The introduction of a combination of sulfamethoxazole **6** and trimethoprim in the 1970s led to an increased use of sulfonamides. The mixture, known as co-trimoxazole is useful in the treatment of bladder and gastrointestinal infections and bronchitis.

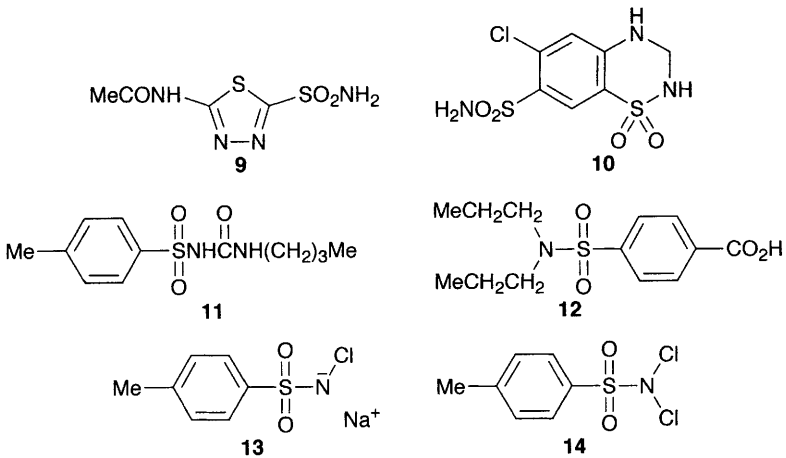
The antibacterial sulfone, dapson **8** is effective in the treatment of leprosy and malaria. It acts by a similar biochemical mechanism to the other sulfa drugs and

may be prepared by Friedel–Crafts reaction of N^4-acetylsulfanilyl chloride with acetanilide (Scheme 2).



Scheme 2

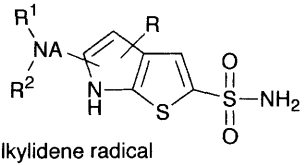
The widespread use of sulfonamide antibacterials and chemical elaboration led to the discovery of other members of this group with different pharmacological properties. Some sulfonamides are widely used diuretics and act as carbonic anhydrase inhibitors; examples include acetazolamide **9** and hydrochlorothiazide **10**. These are used in the treatment of hypertension and the eye disease glaucoma. Sulfonylureas, *e.g.* tolbutamide **11** are oral hypoglycaemic drugs used in the treatment of diabetes; they act as antidiabetics by stimulating the pancreas to secrete increased amounts of insulin. Probenecid **12** is a uricosuric agent used in the treatment of gout and functions by increasing the amount of uric acid excreted in urine.



N-chloro- and *N,N*-dichlorosulfonamides are widely used as antiseptics; they are prepared by chlorination of the appropriate sulfonamide. For instance,

chloramine T **13** and dichloramine T **14** are obtained from *p*-toluenesulfonamide by reaction with sodium hypochlorite.

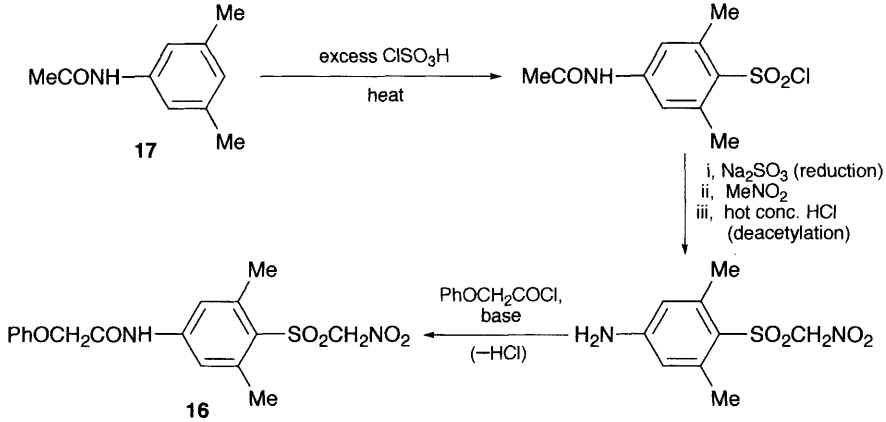
Substituted thieno [2,3-*b*]pyrrole-5-sulfonamides **15** have been developed specifically for treatment of glaucoma.[2] They reduce elevated intraocular pressure by functioning as carbonic anhydrase inhibitors.



15 A = C_1–C_8 alkylidene radical
R = H, C_1–C_8 alkyl radical
R^1,R^2 = H or alkyl or NR^1R^2 = 5 or 7-membered heterocycle

In the synthesis of **15**, the chlorosulfonation step was achieved by the use of chlorosulfonic acid containing phosphorus pentachloride. Sulfadiazine **5** also has antimalarial properties and other sulfonamides are used as anticonvulsant and antipsycotic drugs.[1]

[2,6-Dimethyl-4-(2-phenoxyacetamido)phenylsulfonyl]nitromethane **16** and related compounds are aldose reductase inhibitors, useful in the treatment of diabetes.[3] The active compound **16** was prepared from *N*-acetyl-3,5-dimethylaniline **17**; the first step in the synthesis involved chlorosulfonation of **17** by chlorosulfonic acid (Scheme 3).



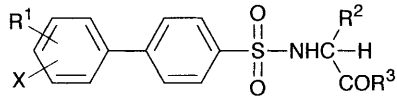
Scheme 3

Heparin, a sulfated polysaccharide and a natural blood anticoagulant (Chapter 6, ref. 33) may be converted into the polysulfate, used in the treatment of retroviral diseases, by reaction of heparin pyridinum salt with chlorosulfonic acid in pyridine at 50 °C.[4]

A novel heparin-like material may be obtained by conversion of chitosan flake into the hydroxypropylchitosan, followed by reaction with chlorosulfonic acid and formamide to give the sulfonated derivative, which has good aqueous solubility.[5]

Biphenylsulfonamides **18**, made by sulfonation of the appropriate substituted biphenyl with chlorosulfonic acid, are useful for inhibiting matrix metalloprotei-

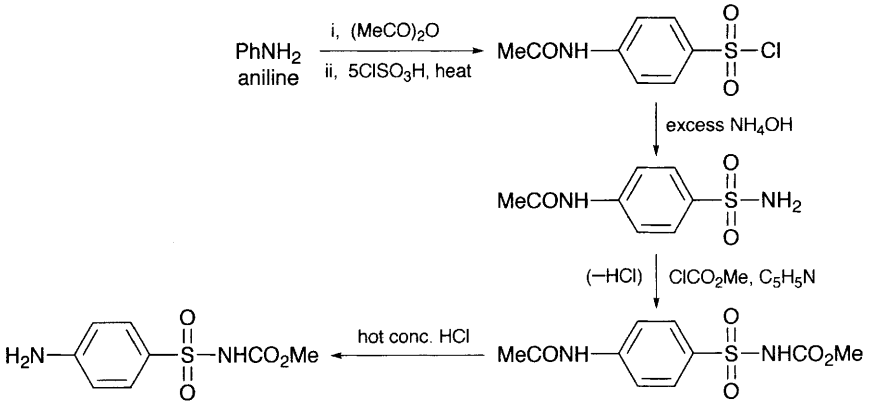
nase enzymes in animals and hence prevent and treat diseases resulting from breakdown of connective tissues.[6]



18 X = H, halo; R^1 = alkyl, halo, NO_2, NH, CN; R^2 = alkyl; R^3 = OH, NHOH

2 Agrochemicals

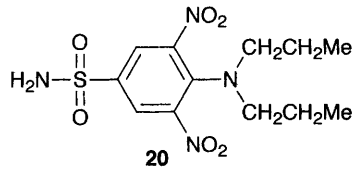
Several sulfonamides are useful in agriculture and are manufactured by procedures using chlorosulfonic acid[7] (see also Chapter 6, ref. 33) The sulfonylcarbamate, asulam **19**, used to kill docks and bracken in grassland, is synthesized from aniline *via* chlorosulfonation by reaction with chlorosulfonic acid (Scheme 4). The sulfonamide oryzalin **20** provides pre-emergence weed control in a wide range of agricultural crops.



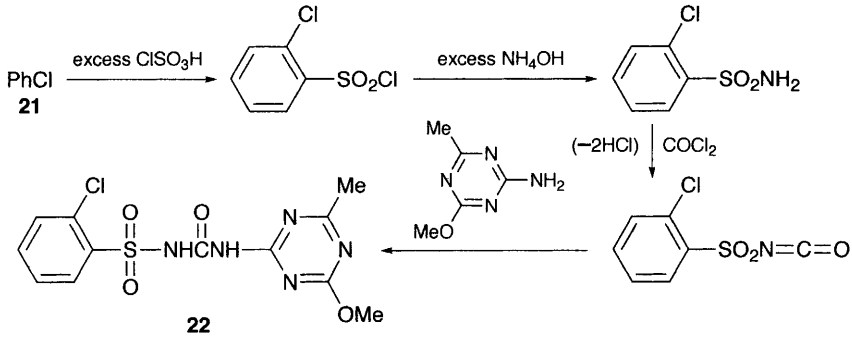
19

Scheme 4

In 1982, DuPont introduced the sulfonylurea herbicides which are effective at remarkably low dose rates; an important example is chlorsulfuron **22** used for selective control of broad-leaved weeds in cereals at rates of 10–40 g ha^{-1}; this herbicide can be prepared from chlorobenzene **21** (Scheme 5)[7] (see also Chapter 6, ref. 33). The first stage of the synthesis, namely the reaction of chlorobenzene with chlorosulfonic acid yields a mixture of the *o*- and *p*-sulfonyl chlorides, which may be separated by fractional distillation, since the *o*-isomer has the lower bp (Chapter 6, ref. 33).



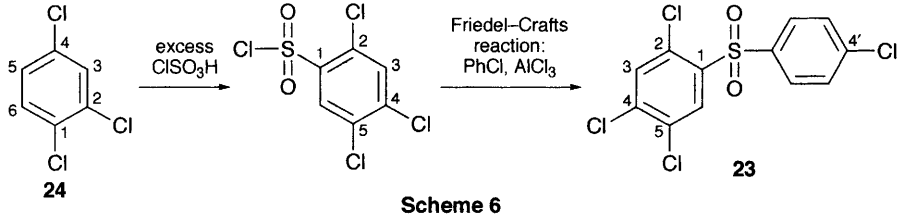
20



Scheme 5

Several arylsulfones are effective acaricides; thus diphenyl sulfone is especially toxic to the eggs of the fruit tree spider mite and the 2,4,5-trichloro- and the 2,4,5,4′-tetrachloro derivative (tetradifon **23**) are valuable acaricides.[7]

Tetradifon **23** is synthesized from 1,2,4-trichlorobenzene **24** as indicated in Scheme 6. In the reaction of the trichlorobenzene **24** with chlorosulfonic acid, sulfonation occurs preferentially in the 5-position which is *o/p* to the electron-donating chlorine atoms (see Chapter 4, p 49).

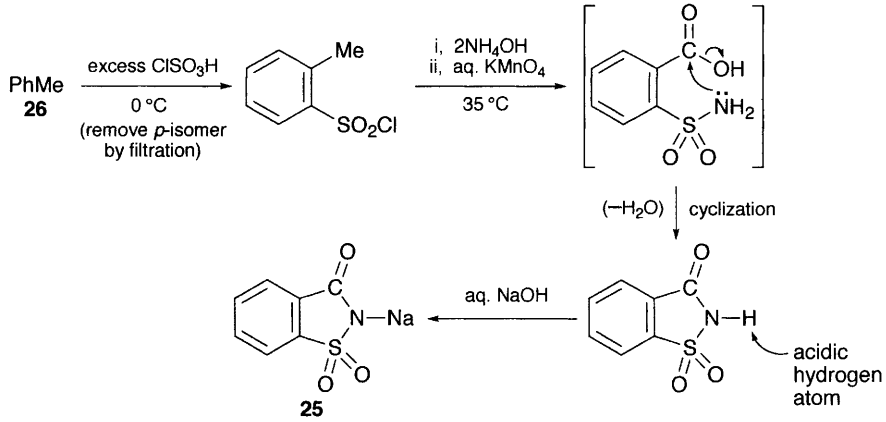


Scheme 6

Sulfonamides also display antifungal action against rust diseases on cereals, but the action is rather limited.[7] N^4-Acetylsulfanilyl hydrazide and derivatives had systemic antifungal action against wheat rust and were prepared by condensation of N^4-acetylsulfanilyl chloride with hydrazide hydrate.[8,9]

3 Synthetic Sweeteners

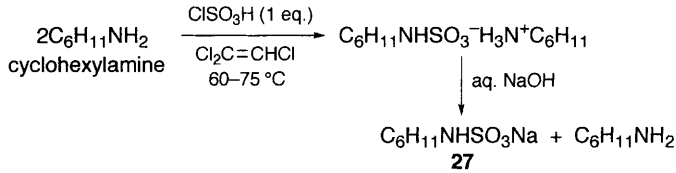
Several organosulfur compounds have been developed as commercial sweeteners and some of these may be prepared using chlorosulfonic acid (Chapter 6, ref. 33). Saccharin **25**, discovered in 1878, is the most economical sweetener and can be manufactured from toluene **26** (Scheme 7).



Scheme 7

The chlorosulfonation of toluene by treatment with excess chlorosulfonic acid yields a mixture of the *ortho* and *para* sulfonyl chlorides, but the mixture may be separated by freezing out the solid *p*-isomer (see Chapter 4, p 37). Saccharin **25** contains an acidic hydrogen atom and is generally formulated as the sodium salt to increase water solubility. It is some 300 times sweeter than sucrose and is non-calorific so can be used by diabetics as a sugar substitute. A number of saccharin derivatives have been synthesized as potential sweetening agents (Chapter 6, ref. 33).

The sulfamic acid derivative cyclamate **27**, discovered in 1937, is some 30 times sweeter than sucrose and may be obtained by the action of chlorosulfonic acid on cyclohexylamine (two equivalents) in hot trichloroethene as solvent (see Chapter 5, p 175) as shown in Scheme 8 (Chapter 6, ref. 33).



Scheme 8

Cyclamate was withdrawn from use in the USA and Canada in 1970 and later in the UK, because American tests showed that rats fed with large doses of cyclamate developed bladder cancer. However, later tests failed to confirm this result and the sweetener is currently permitted in some 50 other countries.

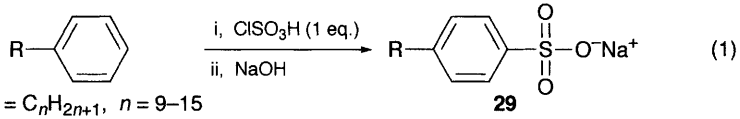
Many other sulfamates are sweet and considerable studies have been made on structure–taste relationships in this group of chemicals (Chapter 6, ref. 33).

4 Detergents

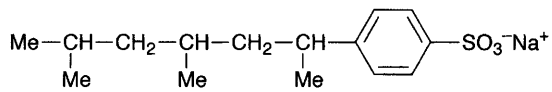
Synthetic detergents (surfactants) may be obtained by sulfonation of suitable lipophilic compounds using oleum, chlorosulfonic acid or sulfur trioxide as the sulfonating agents.

Some of the most widely used detergents are manufactured by sulfonation of long chain alkylaryl hydrocarbons **28** and the resultant sodium alkylbenzenesulfonates **29** are important anionic surfactants. The alkyl group (R) must be highly lipophilic to dissolve oils and fats; the formation of the detergents **29** is shown (Equation 1), (Chapter 6, ref. 33).

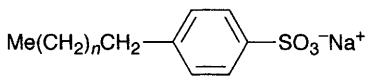
In these alkylbenzenesulfonates, the alkyl radicals were originally branched chains based on tetrapropene as depicted in structure **30**, but were later replaced by linear alkyl groups to give compounds of structure **31**. The linear alkylbenzenesulfonates **31** can be effectively degraded by microorganisms unlike the branched chain analogues **30**, consequently their use does not damage the environment. They are used in liquid detergents for dishwashing and laundering. Another very important group of synthetic anionic detergents are long chain alkyl sulfates **32** manufactured by sulfation of the appropriate alkanols **33** with chlorosulfonic acid followed by treatment with sodium hydroxide (Equation 2), (Chapter 6, ref. 33).



28 R = C_nH_{2n+1}, n = 9–15 **29** (1)



30



31 n = 7–13

A specific example is sodium lauryl sulfate (**32**, $n = 11$) obtained by sulfation of lauryl alcohol (**33**, $n = 11$) and extensively used in handwashing of fabrics, shampoos and dentrifices. The sulfation of alcohols has been described in detail in Chapter 5. In this reaction, chlorosulfonic acid is often the preferred reagent and the use of chlorosulfonic acid in ether is the standard procedure for sulfation of higher primary and secondary alkanols (see Chapter 5, p 155). However, in the modern large scale manufacture of detergents by sulfation of alcohols, sulfur trioxide is often the reagent of choice.

The continuous sulfation of higher alcohols has been achieved by the use of chlorosulfonic acid or sulfur trioxide gas in which the flow of the alcohol and the sulfonating agent is automatically controlled.[10]

Sulfonation of suitable alkenes **34**, by treatment with chlorosulfonic acid or sulfur trioxide, yields α-alkenesulfonates **35** (Equation 3), see also Chapter 5, p 148.

The alkenesulfonates are extensively used in liquid soap formations. Sulfonated ethoxyalcohols of type **36** are of increasing significance as detergents; they are manufactured by sulfonation of the appropriate ethoxyalcohol using chlorosulfonic acid or gaseous sulfur trioxide as the sulfonating agent.

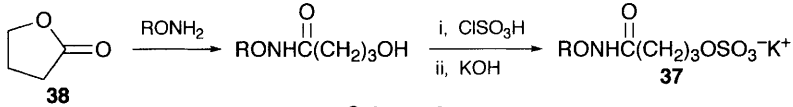
$$\underset{\textbf{33}\ n = 11\text{–}17}{Me(CH_2)_nCH_2OH} \xrightarrow[\text{ii, NaOH}]{\text{i, } ClSO_3H} \underset{\textbf{32}}{Me(CH_2)_nCH_2SO_3^-Na^+} \quad (2)$$

$$\underset{\textbf{34}\ R = C_{10}\text{–}C_{16}}{RCH{=}CH_2} \xrightarrow[\text{ii, NaOH}]{\text{i, } ClSO_3H \text{ or } SO_3/air} \underset{\textbf{35}}{RCH{=}CHSO_3^-Na^+} \quad (3)$$

$$\underset{\textbf{36}}{R\{OCH_2CH_2\}_nOSO_3^-Na^+}$$

The sulfonation of higher fatty acid monoethanolamides with 96% sulfuric acid, 20% oleum or chlorosulfonic acid has been examined under various conditions: the optimum sulfonation was found to occur at the exothermal reaction temperature.[11]

Several novel alkoxyamidosulfates **37** form valuable surfactants. They may be prepared by reaction of butyrolactone **38** with a long chain alkoxyamine and subsequent treatment of the adduct with chlorosulfonic acid, followed by neutralization with potassium hydroxide (Scheme 9).[12]



38 **37**

Scheme 9

Synthetic detergents are also produced by sulfating C_7–C_{18} alkanols, C_7–C_{16} fatty acid monoethanolamides and C_{10}–C_{16} ethoxyalcohols or their mixtures with chlorosulfonic acid using a molar reactant–substrate ratio of 1–1.2:1 and a reaction temperature of 20–60 °C, followed by cooling and neutralization (sodium hydroxide) to pH 7.5–7.9.[13] Mixtures of sulfated pseudoceramides as emulsifiers have been manufactured using chlorosulfonic acid,[14] and alkylsulfoxyalkanoates are used as surfactants in cosmetics.[15] Surfactants with powerful wetting and emulsifying properties have been obtained by sulfonation of waste lipids from the manufacture of insulin with chlorosulfonic acid, followed by neutralization at 25–30 °C to pH 8–9 with sodium hydroxide or triethanolamine. The type of neutralizing agent used affected the surface-active properties of the resultant products.[16]

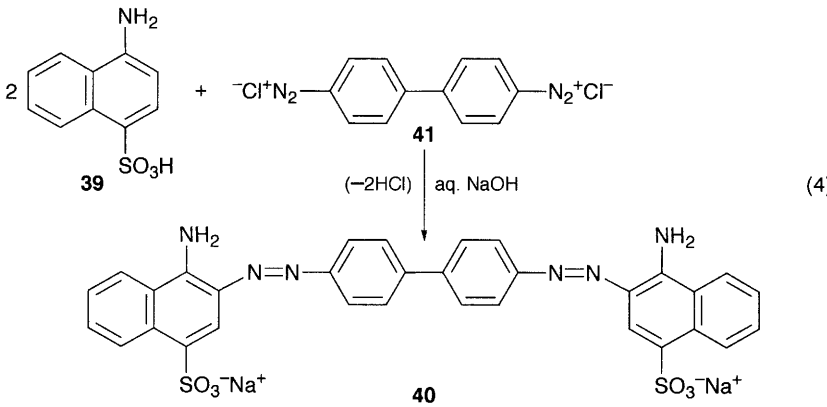
Synthetic detergents may also be obtained by sulfonation of polyoxypropylene glycols and alkyldiphenyl ethers (see Chapter 1, p 5). In addition, oxo-alcohol ether sulfate detergents may be prepared by sulfonation of mixtures of ethylene oxide and a long chain alkanol (see Chapter 6, p 182).

5 Dyes

Many of the dyes used in the clothing industry contain sulfonic acid groups which induce water-solubility and can function as leaving groups in nucleophilic substitutions. They assist the dye to become fast in the fabric by becoming attached to polar sites in the fibres of, for instance, cotton, silk or wool.

The sulfonation step may be achieved by treatment of the starting material with sulfuric acid, oleum or chlorosulfonic acid, when the use of a large excess of acid is undesirable, chlorosulfonic acid is the preferred sulfonating reagent, (Chapter 6, ref. 33).

For example α-naphthylamine, by reaction with chlorosulfonic acid (one equivalent) in an organic solvent at 0 °C, yields the corresponding chlorosulfate (see Chapter 4, p 100). The chlorosulfate, by heating at 190 °C, is converted into naphthionic acid **39**, which is an intermediate in the synthesis of the azo dye Congo Red **40** (Equation 4), (Chapter 6, ref. 33).



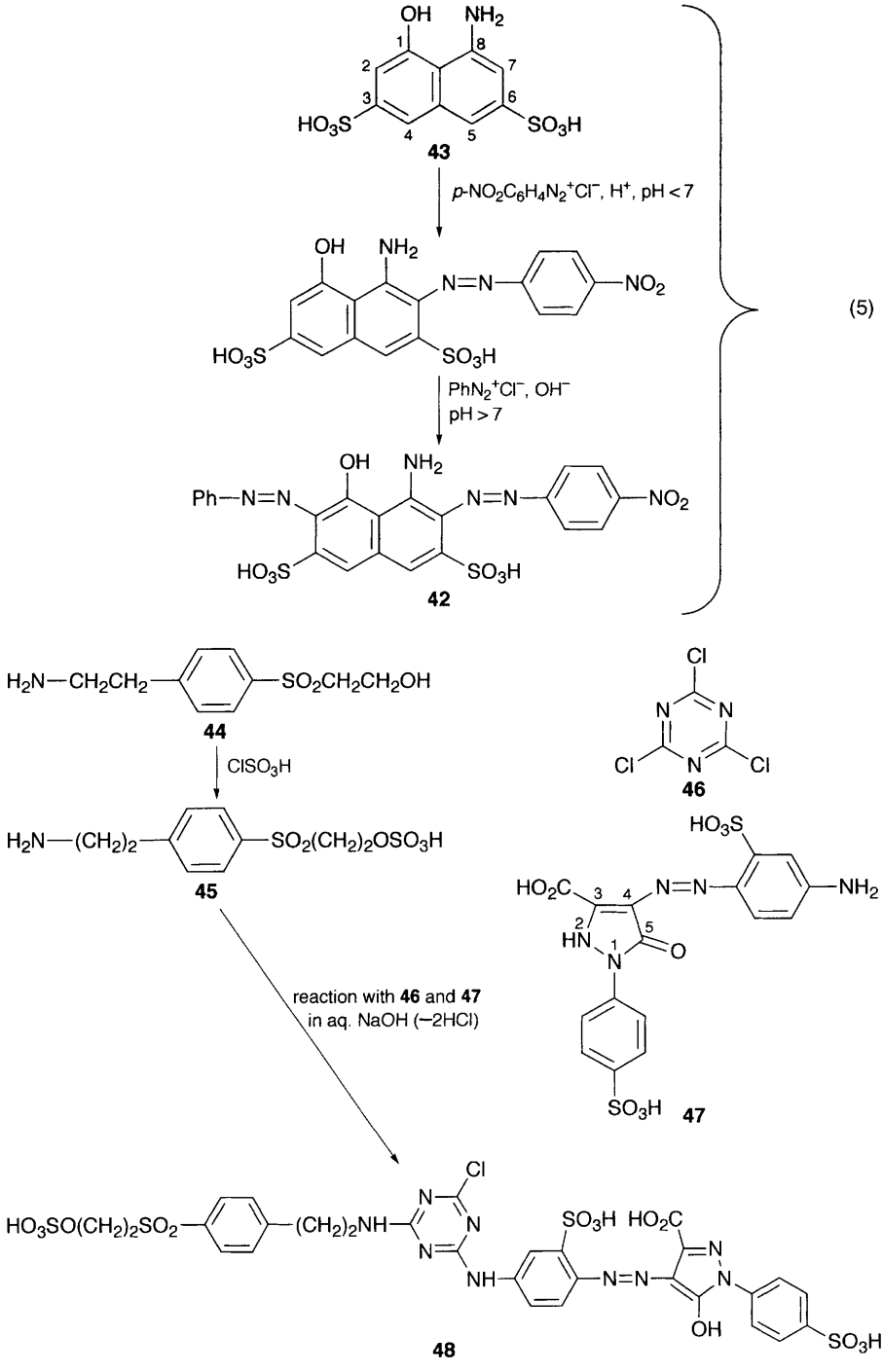
(4)

The reaction involves coupling naphthionic acid **39** with diazotised 4,4′-diaminobiphenyl (benzidine, **41**) in alkaline solution. The darkness of the shade of the dye may sometimes be increased by the presence of several sulfonic acid groups in the molecule which function as auxochromes. An example is the formation of CI Acid Black **42**, by coupling H-acid (8-amino-1-hydroxynaphthalene-3,6-disulfonic acid, **43**) with firstly diazotized *p*-nitroaniline in acid solution, and secondly with diazotized aniline in alkaline solution as shown in Equation 5.

The synthesis demonstrates the versatility of H-acid **43** which may couple with diazonium salts either next to the amino group in acidic media or adjacent to the hydroxyl group in alkaline conditions.

Condensation azo pigments are obtained by reaction of CI Pigment Red 242 (50 parts) with chlorosulfonic acid (125 parts) and *N,N*-di-n-butyl-1,3-propanediamine (660 parts). The product provides a useful, good-flowing pigment, which may be mixed with other suitable compounds, such as amino-alkyl resins to give gloss paints.[17]

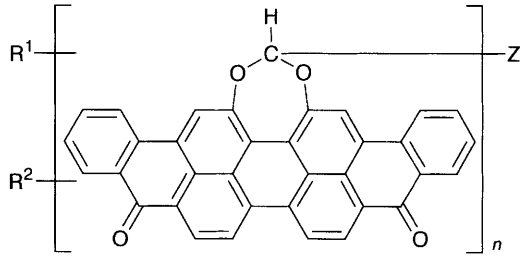
Chlorosulfonic acid may also be used in the manufacture of (amino-alkyl)-phenyl reactive dyes; thus the hydroxyethyl sulfone **44** was reacted with chlorosulfonic acid to yield the sulfate **45**. The latter was subsequently condensed with cyanuric chloride **46** and the azo-5-pyrazolone **47** to yield the golden-yellow dye **48** (Scheme 10).[18]


OH
NH2
HO3S
SO3H
43
p-NO2C6H4N2+Cl−, H+, pH < 7
N=N
NO2
PhN2+Cl−, OH−
pH > 7
Ph—N=N
42
(5)
H2N—CH2CH2—SO2CH2CH2OH
44
ClSO3H
H2N—(CH2)2—SO2(CH2)2OSO3H
45
Cl
N
46
HO3S
HO2C
NH2
HN
O
SO3H
47
reaction with 46 and 47
in aq. NaOH (−2HCl)
HO3SO(CH2)2SO2—(CH2)2NH—
NH
SO3H HO2C
OH
48

Scheme 10

The first step in the synthesis involves sulfation of the hydroxyl group of the sulfone **44** followed by base-catalysed condensation of the amino groups of **45** and **47** with two of the reactive chlorine atoms of cyanuric chloride **46** to yield the dye **48**, which is useful for dyeing cotton fabrics.[18]

Vat dyes can be manufactured by treatment of dihydroxydibenzanthrone in chlorosulfonic acid with mono- or dicarboxaldehydes $Z(CHO)_n$, which may be subsequently chlorinated or sulfamoylated using chlorosulfonic acid and an amine. The process yields vat dyes of general structure **49**.[19] A vat dye has also been obtained in high yields by chlorination of isodibenzanthrone with chlorosulfonic acid in the presence of iodine catalyst at 30–45 °C. The resultant dye is valuable for dyeing cellulosic fibres.[20] Vat dyes for similar uses are prepared from dibenzanthrone by halogenation using bromine and chlorosulfonic acid in the presence of a suitable catalyst yielding a product containing bromine and chlorine (26–32% and 1–5% respectively), which was subsequently condensed with 1-aminoanthraquinone to yield the dye.[21]



49 R^1 = H, Cl; R^2 = H, Cl, alkyl or arylsulfamoyl group; n = 1 or 2; Z = alkyl, aryl or heterocyclic radical

Copper phthalocyanine is an important blue-green organic pigment which can be rendered water soluble by sulfonation, often by treatment with chlorosulfonic acid. This is the basis of the synthesis of a range of useful sulfonyl and sulfamoyl phthalocyanine pigments (see Chapter 6, p 194). A highly chlorinated copper phthalocyanine pigment is manufactured by chlorination of copper phthalocyanine by heating it with a mixture of chlorosulfonic acid, chlorine gas and suitable catalysts, *e.g.* sulfur chloride and sulfur iodide at 140 °C.[22] Octaphenyltetraazaporphine was chloromethylated in chlorosulfonic acid by treatment with paraformaldehyde–sodium chloride (ratio 1:5:1) at 0–6 °C during 10 hours. The resultant octa (*p*-chloromethyl) derivative reacted with pyridine by substitution of the chlorine atoms yielding a water-soluble pyridinium salt, useful as a pure green dye for acrylic fibres or cotton textiles.[23]

6 Polymers

Polymers containing sulfonic acid and related groups are commercially important because the groups may increase the degree of cross-linking of the polymer chains and the strongly acidic sulfonic acid group (SO_3H) allows water to be absorbed by the polymer causing swelling or gel formation. The hydrogen atom of the sulfonic acid group can be exchanged for other cations so sulfonated

polymers are valuable as ion-exchange resins for many industrial uses, *e.g.* demineralization, and as membranes for electrodialysis.[24] The sulfonic acid group may be converted into other sulfonyl derivatives such as the chloride, amides, *etc.* which will modify the properties of the resultant polymer.

Chlorosulfonic acid can be used to sulfonate certain polymers, such as polyethylene, to improve the physical properties of the resultant polymer. Alkanes can be polymerized by treatment with a mixture of chlorosulfonic acid and a Lewis acid (see Chapter 5, p 147). The physico-chemical properties of the sulfonated polymer depend on the precise experimental conditions of sulfonation because these affect both the degree of sulfonation and the extent of cross-linking in the polymer molecules.

Chlorosulfonic acid is generally an effective catalyst for the cationic polymerization of alkenes like isobutene (see Chapter 5, p 152).

Treatment of polyethylene with chlorosulfonic acid before the application of adhesive enhanced the adhesion of the polymer to itself and to aluminium and natural sponge rubber.[25]

The sulfonation of polyethylene membranes was examined under various experimental conditions and the results showed that sulfonation greatly enhanced the water permeability of the resultant membranes. A lower concentration of chlorosulfonic acid at low temperature was preferable, so that only the surface and inner walls of the polymer were sulfonated and the mechanical properties of the membrane were not damaged.[26] The electromicroscopy of polythene is facilitated by staining the polymer by immersing pieces of the polymer in chlorosulfonic acid at 60 °C for several hours.[27] Chlorosulfonated polyethylene rubbers are useful for specific purposes, *e.g.* as ozone-resistant hoses.[28]

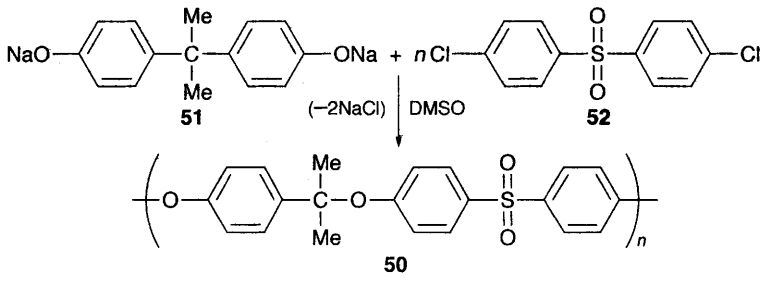
Sulfonated 1,2-polybutadienes are strong acid ion-exchange resins and may be conveniently prepared by sulfonation of the polymer in carbon tetrachloride at < 30 °C with a solution of chlorosulfonic acid in carbon tetrachloride for 2 hours; the resultant product had a total ion exchange capacity of 4.6 m equiv. g^{-1}.[29]

Poly-*p*-phenylene (PPP), after doping with a mixture of antimony pentachloride and chlorosulfonic acid, had a greatly increased electrical conductivity due to the formation of a charge-transfer complex.[30] The term doping refers to the addition of an impurity to a material to enhance its physical properties.

Poly(phenylene oxide) is stablized by a reaction with chlorosulfonic acid[31] and poly(aryl ether) resins are sulfonated by a mixture of chlorosulfonic acid and a silyl halide followed by base-catalysed cleavage of the silyl group.[32] Antistatic polyoxyphenylenes were obtained by surface sulfonation with a saturated solution of chlorosulfonic acid in n-hexane for 25–30 minutes.[33]

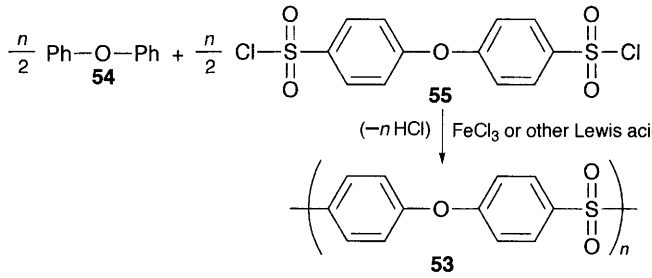
Poly-3,5-dimethylphenyl ether is sulfonated by chlorosulfonic acid, the sulfonated polymer was cast from a 2–10% methanolic solution to give negatively charged membranes with an ion-exchange capacity of up to 5 m equiv. g^{-1} which can be used in desalination.[1]

Polyarylether sulfones are an important group of high performance polymers; the first member, Bakelite polysulfone (Udel **50**), may be made by condensation of a bisphenol (as the disodium salt, **51**) with 4,4′-dichlorodiphenyl sulfone **52** (Equation 6).



(6)

These sulfone polymers (*e.g.* **53**) may also be prepared by polysulfonation of diphenyl ether **54** with the corresponding 4,4′-disulfonyl chloride **55** (Equation 7).



(7)

Both the sulfone **52** and the disulfonyl chloride **55** may be made by reactions involving the use of chlorosulfonic acid (see Chapter 3, p 29 and Chapter 4, p 74 respectively). A polyarylether sulfone **53** can be efficiently sulfonated by treatment with sulfuric acid followed by chlorosulfonic acid. The reaction mixture was left at 25 °C for 12 hours to yield a sulfonated resin of ion-exchange capacity 0.2 m equiv. g^{-1}.[34] Sulfonated polysulfones, useful in reverse osmosis desalination membranes, may be prepared by sulfonation of a commercial polysulfone with chlorosulfonic acid.[35] The polysulfone Udel P1700 can be sulfonated by chlorosulfonic acid or trimethylsilylchlorosulfonate to form proton-conducting membranes for fuel cells and supercapacitors.[36]

The sulfonation of polyethersulfone with sulfuric and chlorosulfonic acid has been investigated: experiments demonstrated that the degree of sulfonation increased with time and temperature.[37] The resultant sulfonated material functions as a polymer electrolyte with an ion-exchange equivalent of 800–5000 g mol^{-1}.[38]

Formaldehyde can be cationically polymerized at low temperatures by strong acids, *e.g.* chlorosulfonic acid in n-hexane,[39] while trioxan is polymerized to poly(oxymethylene) by heating at 65 °C in the presence of a catalytic amount of chlorosulfonic acid.[40]

Polyketones are sulfonated by reaction with chlorosulfonic acid (see Chapter 5, p 162) and sulfonated aromatic polyether–polyketones have been obtained by treatment with mixtures of sulfur trioxide and chlorosulfonic acid. The sulfonated polymers are compression mouldable at high temperatures.[41] Poly(arylether ketone) fibres of good dyeability were produced by treating the fibres with chlorosulfonic acid, sulfuric acid or sulfur trioxide.[42]

Chlorosulfonic acid is an effective catalyst for the copolymerization of carbon

monoxide with formaldehyde (using trioxan or paraformaldehyde as the formaldehyde source); the maximum yield of the copolymer was achieved at 180 °C.[43]

Poly(aryl sulfoxides) may be conveniently obtained by suspending poly(thiophenylenes) in sulfuric or chlorosulfonic acid and subsequent oxidation with 30–85% hydrogen peroxide.[44] Sulfonated poly(arylene sulfides), useful as cation-exchange resins, can be prepared by sulfonation with chlorosulfonic acid either alone or with sulfuric acid or acetic anhydride. The polymers are soluble in polar aprotic solvents and function as polymer electrolytes.[45] Sulfonation of polyvinyl chloride (PVC) beads with concentrated sulfuric or chlorosulfonic acid afforded cation-exchange resins with large porous structure and ion-exchange capacities of 1.6–2.0 or 2.5–3.5 m equiv. g^{-1}. The mechanism of sulfonation depended on the reagent used.[46] PVC also reacted with chlorosulfonic acid to yield a polymer catalyst, PVC–SO_3H, which effectively catalysed the esterification of carboxylic acids to the corresponding esters (82–92% yields).[47]

Poly(vinyl fluoride) films have also been sulfonated with chlorosulfonic acid and the state of water in the sulfonated polymer membranes was examined by FTIR spectroscopy. The results showed that the water contained hydrogen and non-hydrogen bonded molecules containing a large number of proton complexes, *e.g.* H_3O^+ or $H_5O_2^+$.[48]

Polyacrylonitrile is cyclized by sulfonation with excess chlorosulfonic acid under mild conditions; the sulfonated polymer was a thermally stable, water-soluble polyelectrolyte. Heating was discovered to increase the degree of cyclization and reduce the water solubility of the product.[49]

An adipic acid–diethylene glycol copolymer, by treatment with a THF polymer or polypropylene glycol in the presence of chlorosulfonic acid, afforded polyether polyesters useful for the preparation of thermoplastic block copolyester rubbers and polyurethans.[50] Strongly acid sulfonate derivatives of hydrophilic polymers may be prepared by reacting glycidyl methacrylate–ethylene dimethacrylate copolymer or ethylene dimethacrylate–glycidyl methacrylate–styrene copolymer with chlorosulfonic acid or oleum at 0–60 °C.[51]

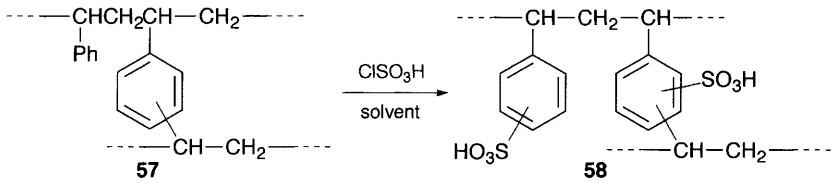
Block or graft copolymerization of cyclophosphazene oligomers with cyclosiloxane oligomers using chlorosulfonic acid as catalyst yields heat-resistant elastomers.[52]

Chlorine-resistant aromatic polyamide-based reverse-osmosis films are manufactured by treatment of polysulfone film supports with a solution of chlorosulfonic acid in acetic anhydride for 2–10 hours, followed by soaking the film in polyamide and poly(acid chloride) solutions, and finally baking at 100 °C.[53]

Sulfated fluoropolyethers are prepared by polymerization of trifluoropolypropylene oxide, initiated by potassium tert-butoxide, followed by reaction with chlorosulfonic acid.[54]

The copolymerization of trifluoropropylene oxide with ethylene oxide and/or propylene oxide in the presence of alkali metal alkoxides or hydroxides, initiated by reaction with chlorosulfonic acid, yields fluoropolyethers $HO(AO)_nR$ (**56**; A = ethylene, propylene, $CH_2{=}C(CF_3)H$; R = H, C_1–C_{30} alkyl, acyl or alkylsilyl group; n = 5–2000).[55] The copolymers are useful for colouring thermoplastics as they are light-absorbing materials.

Many valuable commercial cation-exchange resins may be manufactured by sulfonation of a suitable polymer containing aryl groups. For instance, polystyrene resins **57**, by treatment with chlorosulfonic acid in an appropriate solvent, afforded the sulfonated resin **58** (Equation 8).[1] The latter functions as a cation-exchange material as indicated in Equation 9.



(8)

$$R{-}SO_3H + M^+OH^- \rightleftharpoons R{-}SO_3^-M^+ + H_2O \qquad (9)$$

R = resin and M = the metal cation

A divinylbenzene–ethylene–styrene copolymer is sulfonated by 3.5–10% solutions of chlorosulfonic acid in organic solvents, *e.g.* chloroform or 1,2-dichloroethane at RT to yield cation-exchange resins.[56] Porous styrene–divinylbenzene–ethylvinylbenzene copolymers have also been treated with the reagent and hydrazine hydrate to form ion-exchange resins containing sulfonyl hydrazide groups.[57]

The chemical characteristics of the polymer were affected by the composition of the sulfonating mixture of chlorosulfonic acid, n-heptane and 2-ethyl-1-hexanol used. The chlorosulfonation was shown, by chemical analysis, to be a two-stage reaction leading to the formation of both sulfonyl and chlorosulfonyl derivatives.[58]

Chlorosulfonyl styrene–divinylbenzene copolymer is a highly reactive intermediate used in organic synthesis. The aromatic styrene groups of the copolymer are sulfonated with chlorosulfonic acid in dichloroethane, followed by chlorination of the sulfonate groups with phosphorus pentachloride–phosphorus oxychloride mixture.[59]

Strongly acid catalyst resins have been prepared by using polystyrene foam as the matrix material; the foam was simultaneously cross-linked and functionalized by reactions with chlorosulfonic acid or its mixtures with chloral. The products were effective in the inversion of raw sugar.[60]

Synthetic fibres with ion-exchange properties were obtained from tapes extruded from polystyrene or its mixtures with polyethylene or polypropylene, by chlorosulfonation by chlorosulfonic acid for cross-linking, followed by treatment with aniline.[61] Ion-exchange composite spun fibres have also been synthesized from a thermoplastic polymer and an aromatic vinyl polymer by immersion of the drawn fibres in chlorosulfonic acid at 20 °C, followed by treatment with dichloromethane, methanol and 10% sodium hydroxide, and drying to yield fibres with an ion-exchange capacity of 2.1 m equiv. g^{-1}.[62]

Cross-linked polystyrene film was sulfonated by treatment with a mixture of chlorosulfonic acid and anhydrous sulfuric acid (8:92) at 0 °C. The kinetics of the sulfonation reactions were determined: the initial rate was slow, reached a

maximum and then declined. At relatively high sulfonate group concentration, the groups were uniformly distributed in the film.[63]

A polymer matrix of 75% polyethylene and 25% styrene divinyl benzene copolymer was chlorosulfonated by reaction with chlorosulfonic acid in dichloromethane–dioxan–ethyl acetate mixture and subsequently treated with amines, *e.g.* aniline, butylamine, *etc.* The resultant sulfonamidopolymer membranes were useful cation-exchange materials having modified properties.[64]

A new *N*-chlorosulfonamide derivative of cross-linked polystyrene has been prepared by amidation of chlorosulfonated polystyrene, followed by treatment with sodium hypochlorite; the product was useful in decreasing the COD of water.[65]

Water-insoluble polystyrene fibrous sheets with chelating properties were obtained by cross-linking a polystyrene fibrous sheet by treatment with chlorosulfonic acid, followed by reaction with amines[66] or a chelate-forming aromatic compound.[67]

Macronet ion-exchangers were prepared by treatment of styrene–acrylonitrile copolymer and polystyrene foam with chlorosulfonic acid. The reaction involved simultaneous sulfonation and the formation of sulfone cross-links.[68,69]

Porous silica-supported polymeric catalysts were prepared by sulfonation of divinylbenzene (DVB) or styrene–DVB copolymers with chlorosulfonic acid. The resultant acidic polymers had an ion-exchange capacity of up to 0.41 m equiv. g^{-1}.[70] Treatment of the styrene–divinylbenzene copolymer (one part) with chlorosulfonic acid (three to four parts) in 1,2-dichloroethane at 10–25 °C afforded the cation-exchange resin.[71]

Styrene, dissolved in 1,2-dichloroethane, was treated with chlorosulfonic acid (0.001 mol) in 1,2-dichloroethane at 30–35 °C (1 hour) and the mixture was steam distilled to yield oligomeric polystyrene (MW 3700, 72%).[72]

Chlorosulfonation of a styrene–divinylbenzene (8%) copolymer was achieved by reaction with chlorosulfonic acid in 1,2-dichloroethane 0–20 °C for 12 hours. The optimum conditions involved the use of a large excess of the reagent (10 equivalents) at 20 °C for 7 hours, which afforded the chlorosulfonyl polymer (40% yield).[73]

Polystyrene foam has been extensively sulfonated by treatment with one or more of the following reagents; oleum, chlorosulfonic acid, fluorosulfonic acid or sulfur trioxide.[74] The polysulfonated polystyrenes were useful as shock absorbers in packaging[74] and formed conductive, antistatic, condensation-inhibiting, fire-resistant coatings.[75,76]

Radiation-induced graft copolymerization of styrene onto polyethylene hollow fibre membrane and its subsequent sulfonation by reaction with chlorosulfonic acid produced cation-exchange hollow fibre membranes.[77] Sulfonation by the reagent in dichloromethane gave a membrane with a sulfonic acid group content in the range 2 to 5 m mol g^{-1}, whereas the use of chlorosulfonic acid in sulfuric acid gave a sulfonic acid group content of 0.5 to 6 m mol g^{-1}. Experiments indicated that the absorption of the cobalt (Co^{2+}) ion by the cation-exchange membranes increased with the sulfonic acid content.[77]

Sulfonation of a mixture of styrene and tri(alkoxy)silylmethacrylate with

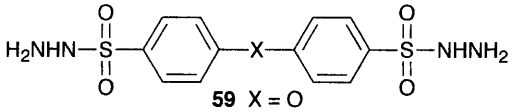
chlorosulfonic acid in chloroform at RT (12 hours) yields a novel resin-type catalyst. The catalyst is an organic–inorganic hybrid containing the O–Si–O unit and benzene rings and the degree of sulfonation is controlled by the amount of the reagent used.[78]

Sulfonated polyether ketones are obtained by reaction with chlorosulfonic acid and have potential as asymmetric membranes. Under suitable conditions, the polymer chain was not degraded, although chlorosulfonated derivatives were not isolated.[79]

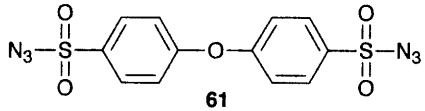
A water-soluble externally (HCl)-doped conducting polyaniline was obtained by sulfonation of the emeraldine salts using chlorosulfonic acid in dichloroethane at 80 °C.[80]

7 Blowing Agents

The chemistry of sulfonyl hydrazides and azides has been discussed[81] and both derivatives are used as 'blowing' and cross-linking agents in the manufacture of foam rubbers and plastics. Some of the best hydrazides for this purpose are diphenyl ether-4,4′-disulfonyl hydrazide **59** together with the corresponding thio analogue **60**. These hydrazides are respectively prepared by reaction of diphenyl ether or diphenyl sulfide with excess chlorosulfonic acid as previously described (Chapter 4, p 74, 76), followed by condensation of the appropriate disulfonyl chloride with excess hydrazine hydrate.[81]



59 X = O
60 X = S



61

The corresponding disulfonyl azide **61** and other sulfonyl azides are also valuable 'blowing' agents. In addition, the ability of sulfonyl azides to insert into carbon–hydrogen bonds enables them to function as effective agents for cross-linking hydrocarbon polymers. The sulfonyl azides are generally obtained from the corresponding disulfonyl chlorides by condensation with sodium azide (two equivalents) in aqueous acetone.[81]

8 References

1 A. Kalir and H.H. Kalir, 'Biological Activity of Sulfonic Acid Derivatives' in *The Chemistry of Sulfonic Acids, Esters and their Derivatives*, S. Patai and Z. Rappoport (eds), Wiley, Chichester, 1991, 767.

2 W. Halczenko and G.D. Hartman, US 4751231 (1988), *Chem. Abs.*, **110**, 44954.

3 D.R. Brittain, S.P. Brown, A.L. Cooper, J.L. Longridge, J.J. Morris, J. Preston and L. Slater, *Eur.*, EP 469888 (1992); *Chem. Abs.*, **116**, 193931.

4 H. Dieter, T. Doerper, L. Daum, H. Geiss and A. Moeller, *Ger. Offen.* DE 3744119 (1989); *Chem. Abs.*, **112**, 191923.
5 B. Fang and T. Jiang, *Huadong Ligong Daxue Xuebao*, 1988, **24**(3), 286; *Chem. Abs.*, **129**, 204376.
6 P.M. O'Brien and D.R. Sliskovic, US 5756545 (1998); *Chem. Abs.*, **129** 32284.
7 R.J. Cremlyn, *Agrochemicals: Preparation and Mode of Action*, Wiley, Chichester, 1991.
8 R.J. Cremlyn, *J. Chem. Soc.*, 1962, 2133.
9 R.J. Cremlyn, *J. Chem. Soc.*, 1965, 1132.
10 K. Kunikawa, M. Hatsutori and M. Yuzaki, *Jpn. Kokai*, JP 01135761 (1989); *Chem. Abs.*, **11**, 156500.
11 L. Petrova and Z.B. Zhurovska, *Khim. Ind. (Sofia)*, 1972, **44**, 154; *Chem. Abs.*, **77**, 125912.
12 A.J. O'Lenick, US 5034555 (1991); *Chem. Abs.*, **116**, 66895.
13 D.I. Zemenkov, M.A. Podustov, V.A. Malinovskii, A.A. Pashchenko, V.G. Pravdin, I.I. Bozhko, Yu.D. Panaev, I.F. Sukhomlinov and A.Z. Xainullin, *USSR* SU 1544769 (1990); *Chem. Abs.*, **113**, 80985.
14 H. Moeller, T. Foerster and M. Claas, *Ger. Offen.*, DE 19748399 (1999); *Chem. Abs.*, **130**, 339721.
15 S.H. Cho, *Eur.*, 202054 (1992); *Chem. Abs.*, **118**, 219448.
16 N. Zhukov, Yu.V. Remizov, V.N. Yurchenko, Z.V. Ushakova, Yu.A. Kravtsov and E.I. Bogdanova, *Khim. Prom-st. (Moscow)*, 1992, **1**, 11; *Chem. Abs.*, **116**, 196617.
17 K. Ito, T. Furubayashi and K. Yamamoto, *Jpn. Kokai*, JP 11228858 (1999); *Chem. Abs.*, **131**, 171594.
18 R. Iden. *Ger. Offen.*, DE 3628090 (1988); *Chem. Abs.*, **109**, 8023.
19 A. Tazikas, *Eur.*, EP 76235 (1983); *Chem. Abs.*, **99**, 89625.
20 P.V. Gheorghe, A.G. Savulescu, C. Teodorescu and M.V. Sandulescu, *Rom.*, RO 82776 (1983); *Chem. Abs.*, **103**, 55428.
21 M. Niedenbrueck, M. Patsch and M. Schmitt, *Ger. Offen.*, DE 4436386 (1995); *Chem. Abs.*, **123**, 146697.
22 T. Segawa and S. Kuramoto, *Fr.*, FR 2475055 (1981); *Chem. Abs.*, **95**, 205425.
23 R.A. Petrova, O.G. Khelevina, B.O. Berezin and F.L. Saidelova, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.*, 1993, **36**(2), 102: *Chem. Abs.*, **119**, 141168.
24 D.M. Vofsi, 'Polymers containing SO_3H and Related Groups' in *The Chemistry of Sulfonic Acids, Esters and their Derivatives*, Wiley, Chichester, 1991, 879.
25 M.G.D. Hocknay and J.H. Sewell, *Brit.* GB 1350577 (1974); *Chem. Abs.*, **81**, 106568.
26 A. Dimov and M.A. Islam, *J. Appl. Polym. Sci.*, 1991, **42**, 1285; *Chem. Abs.*, **114**, 123608.
27 A.M. Hodge and D.C. Bassett, *J. Mater. Sci.*, 1977, **12**, 2065; *Chem. Abs.*, **88**, 7537.
28 T. Noda and Y. Kato, *Jpn. Kokai*, JP 107872 (1998); *Chem. Abs.*, **128**, 271592.
29 T. Ono, I. Iwama and E. Okuya, *Jpn. Kokai*, JP 62034906 (1987); *Chem. Abs.*, **107**, 155780.
30 T.A. Ezquevva, M.E. Cagiao, D.R. Rueda, C.F.J. Balta and L. Alonso, *J. Mater. Sci. Lett.*, 1985, **4**, 1119; *Chem Abs.*, **103**, 187432.
31 T. Takamura, I. Nakagawa and S. Nakashio, *Jpn. Kokai*, JP 4600899 (1971); *Chem. Abs.*, **75**, 21885.
32 H.S. Chao and D.R. Kelsey, US 4625000 (1986); *Chem. Abs.*, **106**, 85292.
33 S.Y. Lee, S. Corbino and G.B. Wood, *Polym. Eng. Sci.*, 1976, **16**, 389; *Chem. Abs.*, **85**, 78760.
34 S. Miwa and M. Furuichi, *Jpn. Kokai*, JP 02208322 (1990); *Chem. Abs.*, **114**, 123345.

35 Y-J. Kim, J-Y. Jeon, S-H. Koo and T-M. Tak, *Memburein*, 1996, **6**(1), 10; *Chem. Abs.*, **125**, 12661.
36 C.J.L. Poinsignon, J.V. Sanchez, Y. Piffard, G. Vitter, B. Baradie and A. Denoyelle, *Fr.*, FR 2751119 (1998); *Chem. Abs.*, **128**, 259510.
37 H.-J. Lu, L.-C. Shen, C.-X. Wang and D.-Z. Jiang. *Gaodeng Xuexiao Huaxue Xuebao*, 1988, **19**(5), 833; *Chem Abs.*, **129**, 149326.
38 K. Iwasaka, T. Yamamoto, A. Terahara and M. Isobe, *Jpn. Kokai*, JP 10045913 (1998); *Chem. Abs.*, **128**, 155201.
39 T. Yamaguchi, T. Kawasakia and H. Matsuda, *Makromol. Chem.* 1968, **112**, 40; *Chem. Abs.*, **68**, 87642.
40 K. Nakatsuka, F. Ide, M. Takamura and S. Kawakami, *Jpn. Kokai*, JP 4400869 (1969); *Chem. Abs.*, **70**, 115739.
41 H. Sugimoto, *Jpn. Kokai*, JP 63291920 (1988); *Chem. Abs.*, **110**, 155086.
42 M. Umezewa and S. Miura, *Jpn. Kokai*, JP 03124880 (1991); *Chem. Abs.*, **115**, 185339.
43 T. Masuda, K. Kagami, K. Murata, A. Matsuda and Y. Takami, *Nippon Kagaku Kaishi*, 1982, **2**, 257; *Chem. Abs.*, **96**, 143397.
44 D. Zierer and H. Scheckenbach, *Ger. Offen.*, DE 19751239 (1999); *Chem. Abs.*, **130**, 352811.
45 F. Helmer-Metzmann, A. Schleicher, A. Schneller and H. Witteler, *Ger. Offen.*, DE 19527435 (1995); *Chem. Abs.*, **126**, 199963.
46 C. Zhou and Y. Li, *Lanzhou Daxue Xuebao Ziran Kexueban*, 1986, **22**, 76; *Chem. Abs.*, **105**, 192387.
47 S. Yu, Z. Zhao and J. Yang, *Chin. J. React. Polym.*, 1993, **2**(2), 182; *Chem. Abs.*, **123**, 32646.
48 D. Ostrov, M. Paronen, F. Sundholm and L.M. Torell, *Solid State Ionics*, 1999, **116**(3,4), 301; *Chem. Abs.*, **130**, 183398.
49 S.N. Gupta and U.S. Nandi, *Indian J. Technol.*, 1972, **10**, 233; *Chem. Abs.*, **78**, 85002.
50 J. Blahak, R. Gipp, K. Wagner, J. Mazanek and E. Meuller, *Ger. Offen.*, DE 2544195 (1977); *Chem. Abs.*, **86**, 190865.
51 F. Svec. J. Hradil, V.V. Azanova and J.E.F. Panarin, *Czech.*, CS 269299 (1991); *Chem. Abs.*, **116**, 152658.
52 T. Horichi, *Jpn. Kokai*, JP 60255823 (1985); *Chem. Abs.*, **105**, 44500.
53 S. Wu, C. Zhang and G. Zheng, *Faming Xuanli Shenqing Gonghai Shuomingshu, Chin.*, CN 1145918 (1991); *Chem. Abs.*, **128**, 155132.
54 M. Tsuji and H. Nanbu, *Jpn. Kokai*, JP 10036501 (1998); *Chem. Abs.*, **128**, 193062.
55 M.A. Weaver, J.J. Krutak, B.E. Maxwell, G.F. Rhodes, S.D. Hilbert, J.C. Fleischer and W.W. Parnham, *PCT. Int.*, WO 9823690 (1998); *Chem. Abs.*, **129**, 55411.
56 P.K. Narayanan, S.K. Adhikary, W.P. Harkare and K.P. Govindan, *Ind.*, IN 160830 (1987); *Chem. Abs.*, **109**, 74522.
57 T. Misumi and T. Miwa, *Jpn. Kokai*, JP 47035083 (1972); *Chem. Abs.*, **78**, 148711.
58 I. Rabia, J. Zerouk, Z. Bencheikh, F. Layadene, H. Guettaf and A. Saygou, *Polym. Adv. Technol.*, 1996, **7**, 543; *Chem. Abs.*, **125** ,115945.
59 I. Rabia, J.E. Zerouk and S. Mekhalif, *Polym. Adv. Technol.*, 1998, **9**(2), 107; *Chem. Abs.*, **128**, 193174.
60 G. Hille, G. Schwachula and R. Hauptmann, *Plaste Kautsch.*, 1981, **28**, 453; *Chem. Abs.*, **95**, 170159.
61 H. Suzuki, N. Yamamoto and K. Sumitani, *Jpn. Kokai*, JP 50102586 (1975); *Chem. Abs.*, **84**, 6367.
62 H. Suzuki, A. Shimomai, H. Togawa and N. Yamamoto, *Jpn. Kokai*, JP 50094233 (1975); *Chem. Abs.*, **84**, 6367.

63 G. Zundel and H. Metzger, *Z. Phys. Chem. (Leipzig)*, 1969, **240**(1–2), 90; *Chem. Abs.*, **71**, 3882.
64 M.T. Bryk, V.G. Simyavskii and A.P. Melnik, *Synth. Polym. Membr. Proc. Microsymp. Macromol.*, 29th Meeting, 1986, 43; *Chem. Abs.*, **107**, 121780.
65 S.C. Gupta, S.K. Jain, A. Mehra, N.K. Mathur and C.K. Narang, *J. Polym. Mater.*, 1989, **6**(1), 57; *Chem. Abs.*, **111**, 40393.
66 H. Susuki and N. Yamamoto, *Jpn. Kokai*, JP 4903692 (1974); *Chem. Abs.*, **81**, 106646.
67 H. Susuki and N. Yamamoto, *Jpn. Kokai*, JP 49036591 (1974); *Chem. Abs.*, **81**, 106615.
68 N.P. Valkanas, V.D. Vrekou, A.G. Theodoropoulos, G.W. Valkanus and I.C. Konstantakopoulos, *J. Mater. Sci.*, 1996, **31**(18), 4831; *Chem. Abs.*, **125**, 277778.
69 G.N. Valkanus, *PCT. Int.*, WO 9921897 (1999); *Chem. Abs.*, **130**, 325527.
70 E.S. Sujatha, A.K. Kolah, V.C. Malashe and M.M. Sharma, *React. Funct. Polym.*, 1996, **31**(1), 39; *Chem. Abs.*, **125**, 196627.
71 I. Poinescu and C.D. Vlad, *Rom.*, RO 111371 (1996); *Chem. Abs.*, **132**, 335055.
72 S. Matsuzawa and M. Yauagisawa, *Jpn. Kokai*, JP 48054189 (1973); *Chem. Abs.*, **80**, 71375.
73 I.N. Azerbaev and D.M. Romanov, *Izv. Akad. Nauk. Kaz. SSR, Ser. Khim.*, 1969, **19**, 65; *Chem. Abs.*, **72**, 67640.
74 N. Sakota, *Jpn. Kokai*, JP 02055744 (1990); *Chem. Abs.*, **113**, 25314.
75 N. Sakota and A. Sakai, *Jpn. Kokai*, JP 0129051 (1989); *Chem. Abs.*, **112**, 160730.
76 N. Sakota and A. Sakai, *Jpn. Kokai*, JP 02008231 (1990); *Chem. Abs.*, **113**, 61011.
77 S.-H. Choi and C.Y. Nho, *J. Appl. Polym. Sci.*, 1999, **71**, 2227; *Chem. Abs.*, **130**, 238397.
78 Y. Zhang and J. Ma, *Lizi Jiaohuan Yu Xifu*, 1998, **14**(2), 160; *Chem. Abs.*, **130**, 53297.
79 F. Trotta, E. Drioli, G. Moraglio and E. Baima Poma, *J. Appl. Polymer Sci.*, 1998, **70**, 477; *Chem. Abs.*, **129**, 302940.
80 S. Ito, K. Murata, S. Teshima, R. Aizawa, Y. Asako, K. Takahashi and B.M. Hoffman, *Synth. Met.*, 1998, **96**(2), 161; *Chem. Abs.*, **129**, 331096.
81 R.J. Cremlyn, *Int. J. Sulfur Chem.*, 1973, **8**(1), 113.

CHAPTER 9

Miscellaneous Reactions of Chlorosulfonic Acid

Chlorosulfonic acid, although primarily used in the sulfonation/chlorosulfonation of organic compounds, also participates in several other important reactions as briefly mentioned in the introduction (Chapter 1, p 5). Examples of these miscellaneous reactions include: (1) halogenation; (2) cyclization; (3) alkylation; (4) polymerization; (5) condensation (in which the reagent acts as an acidic dehydrating agent, including its use in esterification); (6) isomerization and rearrangements; (7) other reactions.

In this discussion, reference is made to other chapters in the book, which mention many of the reactions and give literature references which are therefore not reported here.

1 Halogenation

Chlorosulfonic acid may function as a chlorinating agent for aromatic substrates at high temperatures, thus *p*-dichlorobenzene, by heating with excess of the reagent at 140 °C, yields 1,2,4,5-tetrachlorobenzene while at higher temperatures (210–220 °C), the reaction gives hexachlorobenzene (Chapter 6, ref. 13). These high temperature chlorinations are probably homolytic reactions.

The presence of iodine is known to catalyse the chlorination of organic compounds by chlorosulfonic acid, enabling the reaction to proceed under comparatively mild conditions. So chlorination is a feature of the attempted sulfonation of aromatic iodo compounds with chlorosulfonic acid (see Chapter 2, p 19); for instance, reaction of *p*-diiodobenzene with excess reagent (five equivalents) at 50 °C yields tetrachlorodiiodobenzene (82%), (Chapter 6, ref. 13). The chlorination is catalysed by traces of iodine and the reaction under these conditions probably involves both homolytic and heterolytic steps (see Chapter 4, p 49). Hexachloro-*p*-xylene, by treatment with a mixture of chlorosulfonic acid, iodine and chlorine afforded either the 2,5-dichloro derivative or tetrachloroterephthaloyl chloride depending on the experimental conditions (see Chapter 4, p 51).

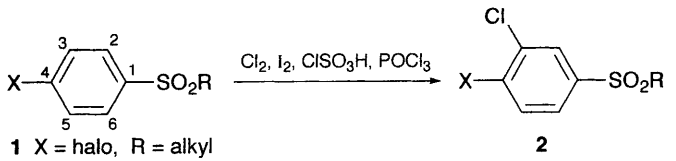
Nitrobenzene, by prolonged heating with excess chlorosulfonic acid at 150 °C, gave tetrachloro-*p*-benzoquinone (chloranil); in this reaction, the reagent functions as both a chlorinating and an oxidizing agent (see Chapter 4, p 56). On the other hand, when nitrobenzene was warmed (30 °C) with a mixture of chlorosulfonic acid, sulfuric acid and iodine, the product was pentachloronitrobenzene (87% yield). The rate of chlorination increased with the iodine concentration and it was also discovered that nitrobenzene with hot chlorosulfonic acid (85 °C) afforded a mixture of *o*, *m* and *p*-chloronitrobenzenes (see Chapter 4, p 57). Vat dyes are manufactured by halogenation of dibenzanthrone and isodibenzanthrone with chlorosulfonic acid–iodine or bromine (see Chapter 8, p 246). Aromatic compounds can be brominated by treatment with bromine in chlorosulfonic acid as solvent; bromination only occurred in the absence of oxidation. Thus, compounds containing CHO, CO_2H, NO_2 and CN groups suffered bromolysis yielding bromobenzene derivatives, whereas those with OH, NH_2 and OMe groups were oxidized to bromanil.[1] The procedure may also be applied to synthesize highly brominated biphenyl derivatives. For instance, when biphenyl was dissolved in warm chlorosulfonic acid containing bromine (eight equivalents), iron filings and iodine and the mixture was heated at 110–150 °C (7 hours), the reaction gave octabromobiphenyl (90.4%).[2]

A solution of hexachlorocyclopentadiene in chlorosulfonic acid is chlorinated, by passing chlorine gas into the solution at 20 °C, to yield octachlorocyclopentadiene; this procedure provides a useful synthetic route to perchlorocyclopentenes (see Chapter 5, p 151). The hydrocarbon adamantane, by reaction with chlorosulfonic acid, is converted into a mixture of polychloroadamantanes, the composition of which depended on the reaction conditions (see Chapter 5, p 147). For instance, 1,3,5,7-tetrachloroadamantane was prepared by heating the 1,3,5-trichloro derivative with chlorosulfonic acid at 40–70 °C for 150 hours.[3]

C_{60} Fullerene is chlorinated by treatment with chlorosulfonic acid, whereas in oleum, the substrate is converted into the sultone. Both of these reactions involved initial oxidation of the substrate, followed by *in situ* trapping of the electrophilic C_{60} cation.[4] With maleic anhydride, chlorosulfonic acid can function both as a chlorinating and a sulfonating agent depending on the reaction conditions (see Chapter 4, p 128).

Ethyl phenyl sulfide, by prolonged heating with excess chlorosulfonic acid, was chlorinated to give ethyl pentachlorophenyl sulfide (see Chapter 4, p 76).

Dihalophenyl sulfones may be obtained by chlorination of 4-haloaryl sulfones **1** by treatment with chlorine in the presence of iodine using a mixture of chlorosulfonic acid and phosphorus oxychloride as solvent. The reaction afforded the corresponding 3-chloro derivative **2** (Equation 1).[5]



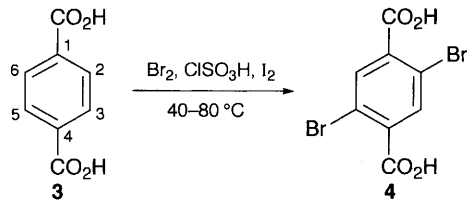
1 X = halo, R = alkyl **2** (1)

Chlorosulfonic acid is an effective catalyst for the selective α-halogenation of

aliphatic carboxylic acids. The reagent functions as an acidic enolization catalyst and is used in conjunction with the appropriate halogen and a suitable radical trapper, *e.g.* oxygen or chloranil, to inhibit radical halogenation of the acid at other positions of the alkyl chain.

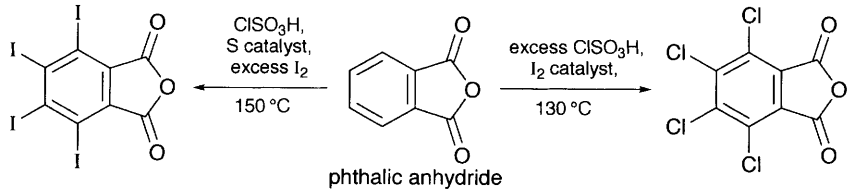
The procedure can be extended to achieve selective α-bromination and iodination of carboxylic acids and the general mechanism of the α-halogenation is outlined in Chapter 5, p 170. The autocatalytic effects in the selective α-chlorination of propionic acid to the 2-chloro and 2,2-dichloro acids have been studied in a semibatch reaction at 90–130 °C.[6] The reaction was performed in the presence of chlorosulfonic acid and dichloroacetic acid as catalysts and oxygen as the radical scavenger. Kinetic experiments indicated autocatalytic formation of both products and that the selectivity was independent of the chlorine concentration in the liquid phase. The results confirmed the validity of the proposed reaction scheme which involved formation of the reaction intermediate, propanoyl chloride from propionic acid and chlorosulfonic acid, the acid-catalysed enolization of the acid, and a hydroxyl–chlorine exchange reaction. The acid-catalysed enolization was the rate-determining step in the reaction sequence.[6]

Aliphatic acid chlorides may be similarly α-chlorinated by heating them with a mixture of chlorosulfonic acid, chlorine, an antioxidant, oxygen and TCNQ at 100–120 °C (see Chapter 5, p 171). Terephthalic acid **3** can be converted into 2,5-dibromoterephthalic acid **4** by heating with bromine in chlorosulfonic acid in the presence of iodine catalyst at 40–80 °C (Equation 2).[7] The 2,5-dibromo compound **4** is used as an intermediate in the production of flame-retardant polymers.



3 **4** (2)

The halogenation of certain aromatic substrates in the presence of chlorosulfonic acid may be controlled by the experimental conditions; thus phthalic anhydride may be either chlorinated or iodinated as shown in Scheme 1.



Scheme 1

Phthalic anhydride, by heating with excess chlorosulfonic acid in the presence of iodine as catalyst, gave tetrachlorophthalic anhydride, whereas heating it with the reagent using excess iodine and sulfur catalyst afforded the corresponding

tetraiodo derivative. Highly chlorinated copper phthalocyanine (see Chapter 6, p 194 and Chapter 8, p 246) may be manufactured by heating copper phthalocyanine with chlorosulfonic acid under pressure in the presence of sulfur or sulfur monochloride as catalyst. The product was a bright yellow-green pigment (98% yield and 14.5 chlorine mol^{-1}); different experimental conditions afforded differently coloured products.[8]

More recently,[9] polychlorophthalocyanine (average chlorine content 10.3) was obtained by heating crude copper phthalocyanine with chlorosulfonic acid, sulfur and iodine in a stream of chlorine gas at 90 °C. As mentioned in the Introduction (Chapter 1, p 3), chlorosulfonic acid acts as a chlorinating agent in its reaction with sulfur, which is converted into sulfur dichloride and other products. Similarly warm chlorosulfonic acid converted arsenic, antimony and tin into the corresponding tetrachlorides (see Chapter 7, p 226).

2 Cyclization

Chlorosulfonic acid can mediate a large number of cyclizations which are collected together in this section. Research has demonstrated that when suitable diaryl substrates are heated with a very large excess of chlorosulfonic acid, under forcing conditions, cyclization often occurs, probably *via* the initially formed sulfonyl chlorides. Thus, biphenyl with the reagent (20 equivalents) at 150 °C (4 hours) afforded the dibenzothiophene dioxide disulfonyl chloride **5**. Similar cyclizations, achieved by treatment with a large excess of the reagent under forcing conditions, were observed with diphenylmethane and 1,2-diphenylethane (Chapter 4, p 39), diphenyl ether (Chapter 4, p 74) and diphenylamine (Chapter 4, p 100). Benzilic acid cyclizes with chlorosulfonic acid in boiling chloroform to yield 9-chlorofluorene-2,7-disulfonyl chloride **6** (see Chapter 4, p 94).

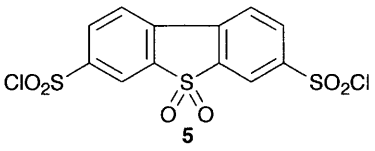
Alkyl phenols, *e.g.* cresols and xylenols, by heating with a large excess of chlorosulfonic acid (10 equivalents), are sulfonated and cyclized to the corresponding sulfonylide disulfonyl chlorides. Thus *o*-cresol yields the cyclized product **7** and a similar reaction was also observed with 8-acetyl-7-hydroxy-4-methylcoumarin (see Chapter 6, p 202).

Acetophenone is claimed to cyclize on heating with chlorosulfonic acid at 120 °C to yield 3-chlorobenzothiophene-1,1-dioxide-2-sulfonyl chloride and propiophenone undergoes a similar cyclization to give 3-chloro-2-methylbenzothiophene-1,1-dioxide (see Chapter 4, p 79).

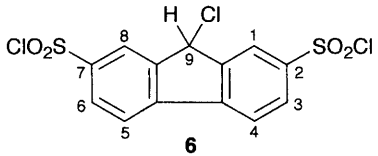
Chlorosulfonic acid also causes smooth cyclization of Mannich bases to the cyclic sulfones **8**. The last three cyclizations occur *via* the enolic sulfonic acid intermediates (see Chapter 4, p 79).

Benzil undergoes a novel cyclization reaction on warming with chlorosulfonic acid (six equivalents) at 40 °C yielding 3-chloro-2-phenylbenzofuran-6,4′-disulfonyl chloride **9**; the cyclization to the benzofuran nucleus probably occurs *after* sulfonation (see Chapter 4, p 86). The cyclization reaction with chlorosulfonic

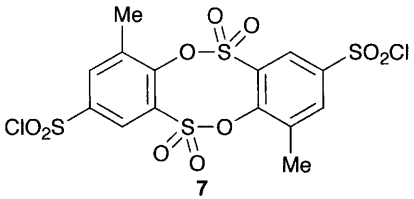
acid has been successfully extended to other benzils to synthesize the corresponding benzofuran derivatives.



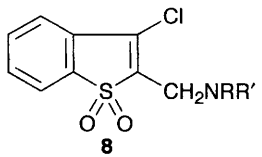
5



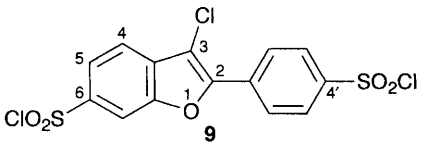
6



7



8

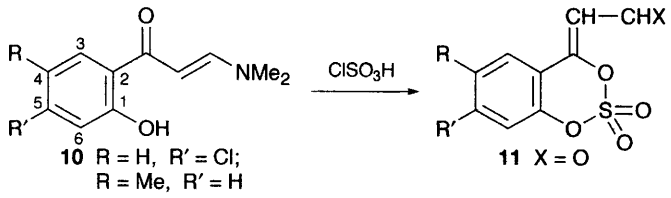


9

Some aryl enaminoketones **10** cyclize on treatment with hot chlorosulfonic acid to form novel 1,3,2-benzodioxathiins **11** (Equation 3).[10]

In contrast, when the reaction was performed at RT, chlorosulfonation of the aryl enaminoketones (**10**; $R = R^1 = H$) occurred at the 4-position (*para* to the hydroxyl group), but cyclization to the benzodioxathiin ring was not observed (see Chapter 4, p 88).

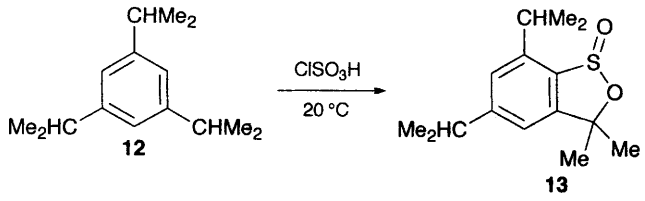
1,3,5-Triisopropylbenzene **12**, by reaction with chlorosulfonic acid at 20 °C, cyclized to the sulfonic acid ester **13** (Equation 4).[11]



10 R = H, R' = Cl; R = Me, R' = H

11 X = O

(3)



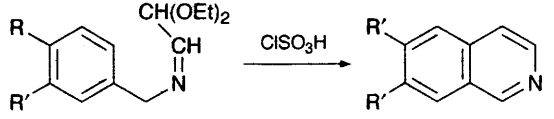
12

13

(4)

Several other heterocyclic compounds can be prepared by cyclizations involving the use of chlorosulfonic acid. For instance, benzylaminoacetals **14**, on treatment with the reagent, cyclize to the corresponding isoquinolines **15** (Equation 5).[12,13]

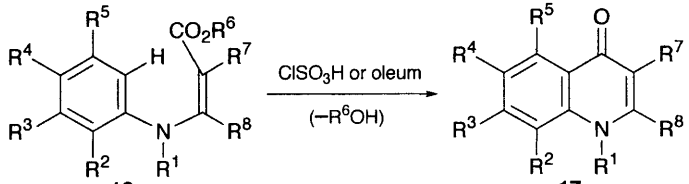
Anilinomethylenemalonates, anilinofumarates and anilinomaleates **16** are similarly cyclized in the presence of chlorosulfonic acid or oleum to yield quinolinecarboxylic acids and their derivatives **17** (Equation 6).[14] The procedure can be applied to synthesize a wide range of substituted and unsubstituted 1,4-dihydro-4-oxo-2- and 3-quinolinecarboxylic acids. As a specific example, diethyl 2,3,4-trifluoroanilinomethylenemalonate cyclized in excess chlorosulfonic acid (10 equivalents) to give 1-*H*-1,4-dihydro-4-oxo-6,7,8-trifluoro-3-quinolinic acid (89% yield).[14] Chlorosulfonic acid acts as an acidic dehydrating agent in the cyclization of phenoxypropionic acids to the corresponding 4-chromanones; the reaction generally proceeds under mild conditions and gives high yields.



(5)

14 R = R′ = H or MeO;
R = H, R′ = MeO;
R = H, R′ = Me

15



(6)

16 **17**

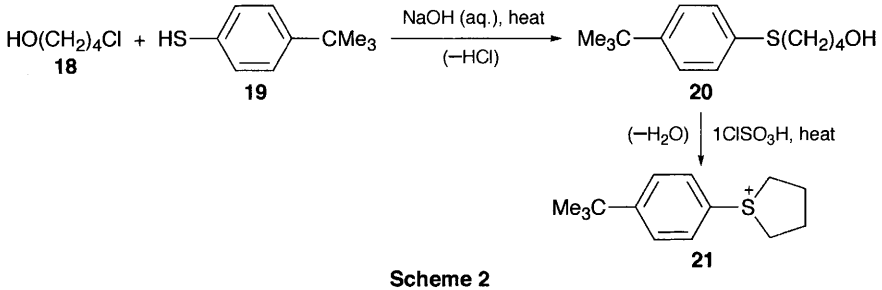
R^1 = *e.g.* H, C_1—C_5 alkyl or haloalkyl, C_3—C_6 cycloalkyl. R^1 with R^2 can be joined with an alkylidene group to form a heterocyclic ring; R^2 = *e.g.* H, halo, C_1—C_5 alkyl, cycloalkyl or haloalkyl, NO_2. R^2 can be joined with an alkylidene group to form a heterocyclic ring; R^3 = R^5 = *e.g.* H, halo, alkyl; R^7 = *e.g.* H, C_1—C_5 alkyl, alkoxycarbonyl; R^6 = H, C_1—C_5 alkyl, C_3—C_6 cycloalkyl or phenyl; R^8 = alkoxycarbonyl.

Arylthioglycolic acids undergo a rather similar cyclization on treatment with a mixture of chlorosulfonic acid and an inorganic halide, *e.g.* phosphorus trichloride (see Chapter 4, p 92).

Chloral (trichloroacetaldehyde) cyclizes to metachloral in the presence of chlorosulfonic acid (0.5–5%) as catalyst at −20 to 50 °C. The cyclization was performed in an airtight polyethylene reactor; the mixture solidified after 3 hours and the reaction was complete after 80 hours giving a yield of 97.9%, which was much better than that obtained by the conventional method using sulfuric acid.[15]

Hydroxyalkylaryl sulfides cyclize with the reagent to yield cyclic arylsulfonium salts, which are useful for increasing the water resistance of carboxylated polymers.[16]

As a specific example, 4-chlorobutanol **18** and the *p*-tert-butylthiol **19**, by refluxing with sodium hydroxide (2 hours), gave the thioalcohol (**20**, 85%), which by treatment with chlorosulfonic acid (one equivalent) in dichloromethane, followed by vacuum distillation at 70 °C, afforded the sulfonium salt (**21**, 80%) (Scheme 2).[16]



Scheme 2

(*Z*)-γ-Azido α,β-ethylenenitriles cyclized with chlorosulfonic acid in chloroform under mild conditions to give the corresponding pyrrolotetrazoles. The cyclization involves a double ring closure and was stereospecific: only the *Z*-azidonitriles reacted (see Chapter 4, p 120).

3 Alkylation

Studies by Kiersznicki and co-workers[17–22] demonstrated that chlorosulfonic acid is an effective catalyst in the alkylation of arenes by reaction with alkenes. Benzene, toluene and ethylbenzene were alkylated by propene, ethene and 2-butene in the presence of chlorosulfonic acid which strongly catalysed the alkylations and inhibited polyalkylation. Increasing the concentration of the catalyst enhanced the proportion of *p*-isomers in the products.[17] Fluoro-, chloro- and bromobenzenes were similarly alkylated by reaction with C_2–C_4 alkenes using chlorosulfonic acid as catalyst. The optimum alkylation conditions were with a halobenzene:alkene ratio of 1:0.25, a catalyst concentration of 0.33 mol mol^{-1} of fluorobenzene and 0.5 mol mol^{-1} of the other halobenzenes, a temperature of 70 °C and a reaction time of 2 hours.[18] Alkylation with propene gave haloisopropylbenzenes; the monoalkyl products were obtained as *o*-, *m*- and *p*- mixtures, the relative amounts depended on the quantity of catalyst used and the by-products were dialkyl derivatives, sulfonic acids and sulfones.[18] In the reaction of benzene with propene, fluorosulfonic acid was a more potent alkylation catalyst than chlorosulfonic acid.[19]

The kinetics of the alkylation of benzene by propene in the presence of chlorosulfonic acid was studied using different rates of addition of propene to the reaction mixture.[20] The degree of alkylation was increased by addition of water or higher temperatures and the ratio of the rates of formation of the mono-, di- and trialkylchlorobenzenes was temperature dependent.[20] The alkylation of benzene with propene was catalysed by chlorosulfonic acid at 20 °C and 80 °C, and the loss of catalytic activity during reaction was due to the formation of alkyl esters.[21] The reaction yield was increased by raising the temperature, the catalyst concentration and reducing the rate of propene addition. The alkylation of benzene by *n*-pentenes in the presence of the reagent was studied under various conditions at 20–70 °C. The maximum yield of the monoalkylated benzene was achieved using a benzene:catalyst:n-pentene ratio of 1:0.3:0.20–0.25 at 70 °C.[22]

Toluene and ethylbenzene have also been alkylated by reaction with propyl and butyl alcohols in the presence of chlorosulfonic acid catalyst. In these experiments, the optimum conditions were an arene:alcohol:catalyst ratio of 3–5:1:1–1.1 and a reaction temperature of 70 °C for 4 hours.[23] The alkylating activity of the monohydric alcohol was low and the products were mainly the monoalkylarenes but arenesulfonic acids were also formed.

Benzene, toluene and chlorobenzene were also alkylated by C_1–C_3 alkyl sulfates in the presence of chlorosulfonic acid catalyst, which proved the intermediacy of alkyl sulfates in alkylation of benzenes by alkenes–chlorosulfonic acid mixture.[24] Diisopropyl sulfate showed strong alkylating properties only in the presence of chlorosulfonic acid.

4 Polymerization

The commercial applications of chlorosulfonic acid in the synthesis and doping of polymers are discussed in Chapter 8, p 246.

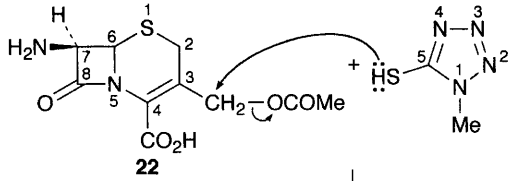
Alkenes are polymerized in the presence of strongly acid reagents, such as sulfuric or chlorosulfonic acid (cationic polymerization). Polymerization catalysts containing titanium chloride and chlorosulfonic acid in n-hexane are effective in the polymerization of propene to isotactic polypropene and in the copolymerization of propene and α-alkenes. (See Chapter 5, p 152) In general, highly active, stereospecific catalysts for polymerizing α-alkenes were prepared from aliphatic halides, titanium(IV) halides, electron donors, magnesium alkoxides, Group II or IIIA metal alkyls and chlorosulfonic acid.[25] Chlorosulfonic acid also catalyses ring-opening polymerization of saturated oxygen heterocycles, *e.g.* THF and oxepine to yield polymethylene glycols (see Chapter 6, p 182).

5 Condensation

Here chlorosulfonic acid functions as an acidic dehydrating agent and, as was mentioned in the introduction (Chapter 1, p 6), it can be employed as a catalyst in the esterification of carboxylic acids. The reagent was thus effective in the conversion of acetonedicarboxylic acid into the diethyl ester (72% yield) (see Chapter 5, p 174).

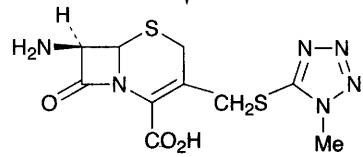
7-Aminocephalosporanic acid **22** condenses with 1-methyl-1,2,3,4-tetrazol-5-thiol in the presence of chloro- or fluorosulfonic acid in acetonitrile at RT to give 7-amino-3-(1-methyltetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid (**23**, 90% yield) (Equation 7).[26]

Imidazole **24** condenses with triphenylmethanol **25** in presence of chloro- or fluorosulfonic acid catalyst in dichloromethane at RT yielding 1-(triphenylmethyl) imidazole (**26**, 75%) (Equation 8).[27]

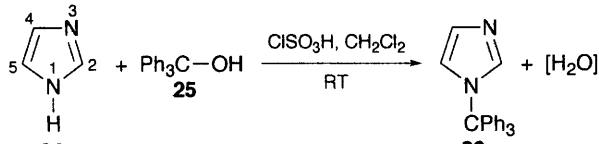


22

$ClSO_3H$ | MeCN (−$MeCO_2H$) (7)



23



24 **25** **26** (8)

The procedure was also successfully applied to the synthesis of 1-[(2-chlorophenyl)diphenylmethyl] imidazole.[27]

Dehydrations using chlorosulfonic acid–pyridine (pyridinium sulfamates) provide a convenient synthetic route to amides without the intermediacy of acyl halides. The carboxylic acid was condensed with the amine in pyridine solution containing chlorosulfonic acid at 0–10 °C to give the amides (Equations 9 and 10).[28]

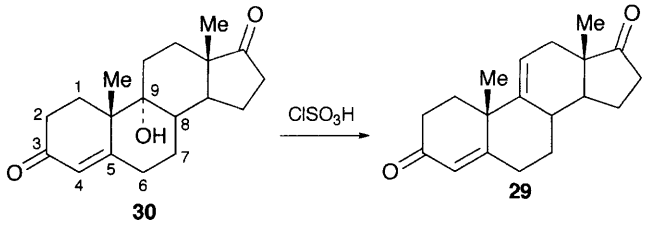
$$RNH_2 + ClSO_3H \xrightarrow{C_5H_5N} \underset{\mathbf{27}}{RNHSO_3^-\overset{+}{N}HC_5H_5} + [HCl] \quad (9)$$

$$RNHSO_3^-\overset{+}{N}HC_5H_5 + R'CO_2H \longrightarrow \underset{\mathbf{28}}{R'CONHR} + (C_5H_5\overset{+}{N}H)_2SO_4^{2-} \quad (10)$$

In the first stage (Equation 9), the amine condenses with chlorosulfonic acid to give the pyridinium sulfamate **27**, which subsequently reacts with the carboxylic acid to yield the corresponding acid amide **28** (Equation 10). In this reaction, the yields of the amides are generally high, but the best yields were obtained with aliphatic acids.[28]

Riboflavin (vitamin B2) was esterified to the tetraesters using chlorosulfonic acid as catalyst, thus riboflavin, by warming with acetic anhydride in the presence of the reagent, afforded riboflavin tetraacetate (95% yield).[29]

Androstenediones **29** have been prepared in quantitative yield by chlorosulfonic acid-catalysed dehydration of 9-α-hydroxyandrostenediones **30** (Equation 11).[30]



(11)

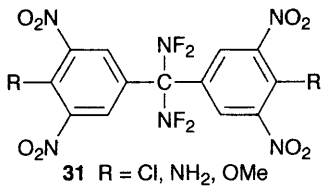
6-Demethyl-6-deoxy-6-methylene-5-oxytetracycline was obtained in 90% yield by dehydration of 11*a*-chloro-5-oxytetracycline-6,12-hemiketal or its salts by treatment with a mixture of chlorosulfonic and formic acid in dichloromethane at −10 °C and then at RT.[31]

Heating diammonium 4,6-disulfoisophthalate with excess chlorosulfonic acid afforded 4,6-disulfoisophthalic anhydride.[32]

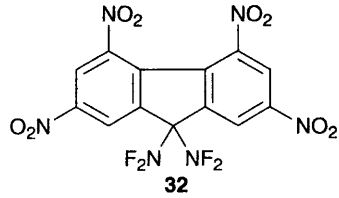
Methyl formate couples with formaldehyde to give methyl glycolate and methylmethoxyacetate in the presence of acidic catalysts. The performance of different catalysts for the reaction have been evaluated under various conditions: chlorosulfonic and methanesulfonic acids were the most active catalysts.[33,34] The acid strength had a great influence on the reaction, the stronger acids had greater activities; the reaction temperature and time were also critical factors and the optimum conditions varied with the catalyst used.[33,34]

Iodosobenzene suffers self condensation in the presence of excess chlorosul fonic acid and the initial product reacts with suitable aromatic substrates to form the corresponding *p*-phenylene bisiodonium salts (see Chapter 4, p 119).

3,3′,5,5′-Tetranitrobenzophenones and 2,4,5,7-tetranitrofluorene condense with difluoramine (two equivalents) in the presence of oleum or chlorosulfonic acid with loss of water yielding the products **31** and **32** respectively, which had explosive properties.[35]



31 R = Cl, NH_2, OMe



32

6 Rearrangement

Certain alicyclic diketones, on treatment with chlorosulfonic acid, rearrange to yield chlorosulfites (see Chapter 4, p 88). Iodoazoxybenzenes, with a mixture of chlorosulfonic and 90% sulfuric acid, undergo the Wallach rearrangement forming the corresponding iodoazobenzenes. *p*-Nitroazoxybenzenes, by treatment with the same mixture, afforded the *o*- and *p*-hydroxynitroazobenzenes; however, use of chlorosulfonic acid alone gave relatively more of the *o*-hydroxy isomer (see Chapter 4, p 117). *p*-Methylazoxybenzene rearranged on treatment with chlor-osulfonic acid to yield a mixture of *p*-methylazobenzene and the *o*- and *p*-

hydroxy derivatives, also octafluoroazoxybenzene gave octafluoroazobenzene-4-chlorosulfonate (see Chapter 4, p 118).

Chlorosulfonic acid catalyses several interesting rearrangements of ozonides, which probably involve heterolytic fusion of the carbon–oxygen bond of the peroxide bridge. For instance, methylcyclopentene ozonide, on treatment with chlorosulfonic acid (0.3 equivalents) in dichloromethane at RT, rearranged to form a *trans* tetraoxan (see Chapter 4, p 125). Stilbene ozonide with chlorosulfonic acid under similar conditions, also afforded the corresponding tetraoxan and this appears a fairly general reaction.

1,6-Diphenyl-2,4-dioxohexahydro-s-triazine reacted with excess chlorosulfonic acid (six equivalents) in thionyl chloride at RT to give *N*-(*p*-chlorosulfonylphenyl)-*N'*-carbamoylurea by a novel ring-opening reaction. 3,7-Dihydro-2,6-diphenyl-1,3,5,7-tetraazobicyclo[3.3.0]octane-4,8-dione with chlorosulfonic acid–thionyl chloride rearranged to give hydrazinodicarbonamide and benzaldehyde. Both these ring-opening reactions occurred by a similar type of mechanism involving the formation of a stabilized benzylic cationic intermediate (see Chapter 6, p 95).

Chlorosulfonic acid–aluminium oxide was active as a heterogeneous catalyst in promoting the isomerization of tricyclic naphthenes to adamantanes. This mixture was one of six catalysts examined to determine their activity in facilitating the gas-phase isomerization of perhydroacenaphthene to alkyladamantanes, the most active catalyst was a mixture of thionyl chloride-activated platinum–aluminium oxide.[36]

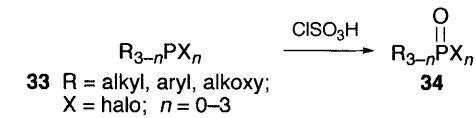
7 Other Reactions

7.1 Oxidation

Chlorosulfonic acid is a strong oxidizing agent, thus alkanes are readily oxidized by sulfur trioxide, oleum and chlorosulfonic acid, so attempted sulfonation of an n-alkane generally yields a complex mixture of oxidation and sulfonation products (see Chapter 5, p 146).

Anthracite is oxidized to mellitic acid by heating at 130 °C with a mixture of chlorosulfonic and nitric acid in a stream of air. Charcoal, on warming with chlorosulfonic acid, is converted into a mixture of sulfur dioxide, carbon dioxide and hydrogen chloride (see Chapter 7, p 226).

Organophosphorus compounds **33** are oxidized, on treatment with chlorosulfonic acid in a homogeneous liquid phase, to give the corresponding phosphoryl analogues **34** (Equation 12).[37]



(12)

As a specific example, methylphosphonous dichloride reacted with an equimolar quantity of chlorosulfonic acid at 25–30 °C to give methylphosphonic

dichloride (99% yield). Oxidation was also observed in the reaction of chlorosulfonic acid with nitrobenzene under forcing conditions and in the initial reaction of C_{60} fullerene with the reagent (see p 257).

7.2 Reactions with Acids and their Derivatives

7.2.1 Carboxylic acids

Aliphatic carboxylic acids ($R^1R^2CHCO_2H$), by warming with a mixture of chlorosulfonic acid and phosphorus oxychloride gave the mixed chloride [$R^1R^2C(COCl)SO_2Cl$]. However, when the carboxylic acid was strongly heated with the same reagent mixture (2.2 equivalents) at 105–110 °C, the reaction afforded the corresponding disulfonyl chloride [$R^1R^2C(SO_2Cl)_2$] (see Chapter 5, p 165). As mentioned in the Introduction (Chapter 1, p 5), chlorosulfonic acid reacts with acid anhydrides at low temperature to give excellent yields of the corresponding acid chlorides. For instance, butanoic anhydride with the reagent at −5 °C afforded butanoyl chloride (95% yield) (see Chapter 5, p 173).

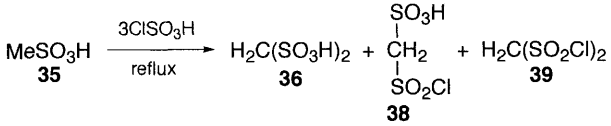
Carboxylic acid esters by heating with an equimolar mixture of phthaloyl chloride and chlorosulfonic acid at 70–250 °C gave good yields of the corresponding acid chlorides. Thus, ethyl chlorofluoroacetate, by heating with the mixture at 180 °C, afforded chlorofluoroacetyl chloride (88% yield), but when the ester was heated with chlorosulfonic acid alone the yield of the acid chloride was reduced to 50%. The procedure provides a valuable synthetic route for the direct conversion of carboxylic acid esters into the corresponding acid chlorides (see Chapter 5, p 167).[38]

7.2.2 Sulfonic Acids

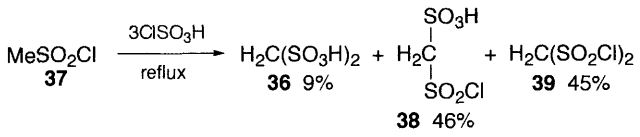
Methanesulfonic acid **35** reacts with chlorosulfonic acid at 100 °C to give a mixture containing some methanedisulfonic acid (**36**, 34%) (see Chapter 5, p 148). More recently[39] methanesulfonic acid **35** and the sulfonyl chloride **37** were each separately refluxed with chlorosulfonic acid for 18 hours. ^{13}C NMR spectroscopic analysis of the reaction products indicated that refluxing the acid **35** with the reagent (three equivalents) for 18 hours afforded a mixture of methanedisulfonic acid (**36**, 36%), the monosulfonyl chloride (**38**, 46%) and the disulfonyl chloride (**39**, 18%) (Equation 13). Methanesulfonyl chloride **37**, by refluxing with chlorosulfonic acid (18 hours), gave the same three products **36**, **38** and **39** (Equation 14), but the mixture contained more of the disulfonyl chloride (**39**, 45%). In contrast, when the reaction was carried out using a larger excess of the reagent (four equivalents) under the same conditions, only the mono- and disulfonyl chlorides **38** and **39** were formed (Equation 15).[39]

The latter reaction gave a substantially increased yield of methanedisulfonyl chloride (**39**, 61%), although chlorosulfonic acid under these conditions did not yield pure methanedisulfonyl chloride **39**, which was instead obtained by warming methanedisulfonic acid **36** with phosphorus pentachloride. However, it is possible that the disulfonyl chloride **39** could have been prepared as the sole product by

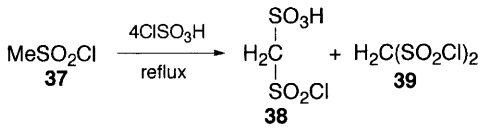
heating methanesulfonyl chloride **37** with a large excess of chlorosulfonic acid in thionyl chloride.



(13)

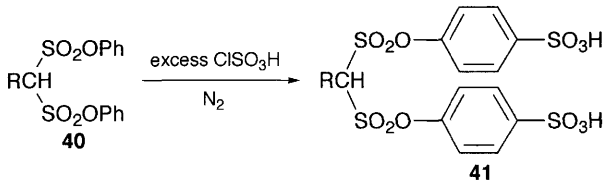


(14)



(15)

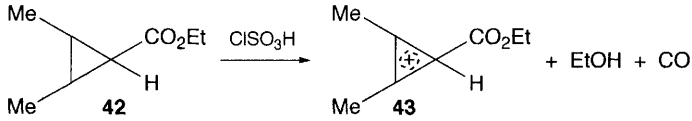
Alkanedisulfonic acid diphenyl esters **40** react with chlorosulfonic acid under nitrogen to give the corresponding diphenyl ester disulfonic acid **41** (Equation 16).[40] The sulfonation of **40** to **41** was improved by using chlorosulfonic acid instead of oleum or other sulfonating agents.



(16)

7.2.3 Decarbonylation of Esters

Chlorosulfonic acid can be used for the decarbonylation of esters. For instance, when ethyl 1,2-dimethylcyclopropene-3-carboxylate **42** is dissolved in chlorosulfonic acid at RT, carbon monoxide is evolved and the corresponding dimethylcyclopropenium ion **43** is formed in almost quantitative yield. (Equation 17).[41]



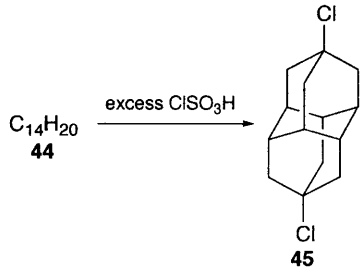
(17)

The procedure using chlorosulfonic acid is preferable to that originally proposed for the preparation of the diphenylcyclopropenium ion, which employed perchloric acid as the strongly acidic reagent.

7.3 Reaction of Chlorosulfonic Acid with Tetrahydrobinor S

Norbornadiene dimer (binor S) by hydrogenation (Pt/H_2) gave the tetrahydro derivative **44**, which reacts with chlorosulfonic acid (5.7 equivalents) at −15 °C

(9 hours) to give an excellent yield of 4,9- dichlorodiamantane (**45**, 82%) (Equation 18).[42]

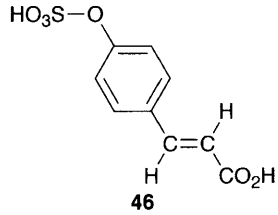


(18)

Chlorosulfonic acid is an effective reagent for bridgehead chlorination of adamantane and diamantane; however in the rearrangement of **44** to **45**, the reagent acts as a Lewis acid catalyst. The dichloride **45** was successfully converted into the corresponding diamine, dicarboxylic acid and dihydroxy derivatives. The chlorosulfonic acid-catalysed rearrangement thus provides a valuable, highly regioselective synthetic route to apically disubstituted diamantanes.[42]

7.4 Reaction of Chlorosulfonic Acid with *p*-Coumaric Acid

Zosteric acid [3-(4-sulfooxyphenyl)-2(*E*)-propenoic acid] **46**, useful as a marine antifouling agent, can be prepared by reaction of a solution of *p*-coumaric acid (*p*-hydroxycinnamic acid) with chlorosulfonic acid. Addition of water, ether extraction and evaporation of the aqueous phase afforded solid zosteric acid, which was purified using basic anion exchangers and acidic cation exchangers.[43]



8 References

1 A.L. Hashem, *J. Appl. Chem. Biotechnol.*, 1973, **23**(8), 621; *Chem. Abs.*, **80**, 26872.
2 H. Fujii and I. Ohno, *Jpn.*, JP 7411689 (1974); *Chem. Abs.*, **82**, 3939.
3 B.M. Lerman, Z.Ya. Aref'eva, A.R. Kuzyev and G.A. Tolstikov, *USSR*, SU 362803 (1972); *Chem. Abs.*, **79**, 31589.
4 G.P. Miller, M.A. Buretea, J.W. Swirczewski and J.M. McConnachie, *Mater. Res. Soc. Symp. Proc.*, 1994, 349 (Novel Forms of Carbon II), 115; *Chem. Abs.*, **122**, 81165.
5 M.V. Kolotilo, G.V. Esipov, E.E. Nizhnikova and N.A. Onishchenko, *USSR*, SU 1735279 (1992); *Chem. Abs.*, **119**, 180525.
6 T. Salmi, P. Maki-Arvela, E. Paatero and R. Byggningbacka, *J. Chem. Technol. Biotechnol.*, 2000, **75**, 89; *Chem. Abs.*, **132**, 236667.

7 J.O. Knobloch, US 3894079 (1975); *Chem. Abs.*, **83**, 113992.
8 R. Matsuura, T. Seguwa, Y. Nomiyama, Y. Kumada and H. Sawada, *Jpn. Kokai*, JP 54081334 (1979); *Chem. Abs.*, **91**, 176660.
9 A. Yoshida, T. Tanaka and T. Takei, *Jpn. Kokai*, JP 08291260 (1996); *Chem. Abs.*, **126**, 76139.
10 W. Lowe and T. Braden, *Arch. Pharm. (Weinheim, Ger.)*, 1991, **324**(12), 949; *Chem. Abs.*, **116**, 106243.
11 J. Pedain, O. Bayer and G. Oertel, *Ger.*, DE 1643341 (1975); *Chem. Abs.*, **83**, 131333.
12 K. Kido and Y. Watanabe, *Heterocycles*, 1980, **14**(8), 1151; *Chem. Abs.*, **94**, 30531.
13 K. Kido and Y. Watanabe, *Daiichi Yakka Daigaku Kenkyu Nenpo*, 1983, **14**, 1; *Chem. Abs.*, **101**, 38326.
14 J.C. Saukaitis and F.B. Gupton, US 5430152 (1995); *Chem. Abs.*, **123**, 143661.
15 J. Swietoslawski, Z. Zerkowski, J. Zamarlik and I. Draczynska, *Pol.*, PL 130239 (1985); *Chem. Abs.*, **107**, 136,309.
16 D.L. Schmidt, H.B. Smith, M.J. Hatch and W.E. Broxterman, *Ger. Offen.*, 2434594 (1975); *Chem. Abs.*, **84**, 5824.
17 T. Kiersznicki, *Zesz. Nauk. Politech. Slask. Chem.*, 1976, **76**, 57; *Chem. Abs.*, **86**, 170969.
18 T. Kiersznicki, *Zesz. Nauk. Politech. Slask. Chem.*, 1976, **76**, 93; *Chem. Abs.*, **86**, 170974.
19 T. Kiersznicki, *Zesz. Nauk. Politech. Slask. Chem.*, 1976, **76**, 125; *Chem. Abs.*, **86**, 170968.
20 T. Keirsznicki, *Zesz. Nauk. Politech. Slask. Chem.*, 1976, **76**, 139; *Chem. Abs.*, **86**, 170630.
21 T. Kiersznicki and J. Majewski, *Zesz. Nauk. Politech. Slask. Chem.*, 1978, **87**, 123; *Chem. Abs.*, **91**, 210535.
22 T. Kiersznicki and J. Majewski, *Zesz. Nauk. Politech. Slask. Chem.*, 1979, **87**, 43; *Chem. Abs.*, **91**, 192921.
23 T. Kiersznicki, *Zesz. Nauk. Politech. Slask. Chem.*, 1976, **76**, 37; *Chem. Abs.*, **86**, 189344.
24 T. Kiersznicki, J. Mzyk and W. Pawlus, *Zesz. Nauk. Politech. Slask. Chem.*, 1978, **87**, 135; *Chem. Abs.* **91**, 210534.
25 N.M. Karayannis and J.S. Skryantz, US 4353813 (1982); *Chem. Abs.*, **98**, 4901.
26 Yamanouchi Pharmaceutical Co. Ltd, Japan, *Jpn. Kokai*, JP 55153790 (1980); *Chem. Abs.*, **94**, 208887.
27 Kyowa Hakko Kogyo Co. Ltd, Japan, *Jpn. Kokai*, JP 58170766 (1983); *Chem. Abs.*, **100**, 121070.
28 C.I. Chiriac, *Rev. Roum. Chim.*, 1980, **25**(3), 403; *Chem. Abs.*, **93**, 238996.
29 N. Iribe and K. Kondo, *Jpn. Kokai*, JP 47016499 (1972); *Chem. Abs.*, **77**, 130589.
30 J.M. Beaton, G.A. Padilla, J.E. Huber and M.E. Breuer, *Ger. Offen.*, DE 2814747 (1978); *Chem. Abs.*, **91**, 74781.
31 L. Gyorgy, M. Hima, M. Bakonyi and S. Szoke, *Ger. Offen.*, DE 3431009 (1985); *Chem. Abs.*, **103**, 178114.
32 B.A. Tagief, R.I. Mustafaev and M.N. Dzhumaeva, *USSR*, SU 1659415 (1991); *Chem. Abs.*, **116**, 128901
33 D. He, W. Huang, J. Liu, M. Zhou and Q. Zhu, *Tianranqi Huagong*, 1997, **22**(4), 1; *Chem. Abs.*, **129**, 202667.
34 D. He, W. Huang, J. Liu, M. Zhou and Q. Zhu, *Korean J. Chem.*, 1998, **15**(5), 556; *Chem. Abs.*, **130**, 155242.
35 J. Lambert and A. Becuwe, *Fr.*, FR 2213268 (1974); *Chem. Abs.*, **82**, 155736.

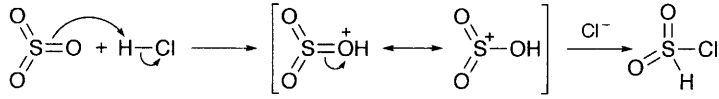
36 Z. Weidenhoffer and S. Hala, *Collect. Czech. Chem. Commun.*, 1975, **40**(2), 560; *Chem. Abs.*, **83**, 78699.
37 J. Grosse, *Ger. Offen.*, DE 3033957 (1982); *Chem. Abs.*, **97**, 110191.
38 W.J. Middleton, US 4122115 (1978); *Chem. Abs.*, **90**, 103433.
39 J.F. Lewis, PhD Thesis, University of Staffordshire, 2000.
40 J. Hinz and H. Welz, *Ger. Offen.*, DE 2603589 (1977); *Chem. Abs.*, **87**, 201091.
41 D.G. Farnum, G. Mehta and R.G. Silberman, *J. Amer. Chem. Soc.*, 1967, **89**, 5048.
42 F. Blaney, D.E. Johnston, M.A. McKervey and J.J. Rooney, *Tetrahedron Lett.*, 1975, 99.
43 S.D. Alexandratos, US 5990336 (1999); *Chem. Abs.*, **131**, 336884.

CHAPTER 10

Preparation, Manufacture and Properties of Chlorosulfonic Acid

1 Preparation

The formation of chlorosulfonic acid has been described in outline in the Introduction (Chapter 1); the various preparative routes to the reagent are given in several sources, such as Mellor's classic work on inorganic chemistry[1] and Jackson's review (Chapter 7, ref. 1). The most important synthesis of chlorosulfonic acid involves the direct action of hydrogen chloride on oleum or sulfur trioxide and this procedure is widely employed in the manufacture of the reagent (see Chapter 1, p 1). For example, a vigorous stream of hydrogen chloride gas is passed into 80% oleum (200 g) in a large flask at RT; the reaction is highly exothermic and the flask is cooled by ice. When no more hydrogen chloride is absorbed, the product is distilled using an air condenser, collecting the distillate of bp 150–165 °C. The liquid is then redistilled and the fraction boiling at 153 °C is collected.[1] The reagent may also be obtained by distillation of oleum with phosphorus pentoxide in a stream of hydrogen chloride gas. The reaction is essentially an acid-catalysed chlorination of sulfur trioxide by hydrogen chloride (Scheme 1).



Scheme 1

Generally, in agreement with this scheme, the reagent may be prepared by the action of various chlorinating agents, *e.g.* phosphorus tri-, penta- and oxychlorides or thionyl chloride on concentrated or fuming sulfuric acid (Equations 1–4) (Chapter 7, ref. 1).

For instance, phosphorus pentachloride (226 g) is gradually added to oleum (d 1.84) at 15 °C, the reaction mixture becomes warm and a considerable amount of hydrogen chloride gas is evolved. The mixture is then heated until no more

hydrogen chloride is given off and finally the liquid product is purified by distillation. Chlorosulfonic acid may also be prepared by the action of moisture on sulfuryl chloride (Equation 5), or by chlorine or sulfur monochloride on sulfuric acid (Chapter 7, ref. 1).

$$PCl_3 + 2H_2SO_4 \longrightarrow HPO_3 + ClSO_3H + 2HCl + SO_2 \quad (1)$$

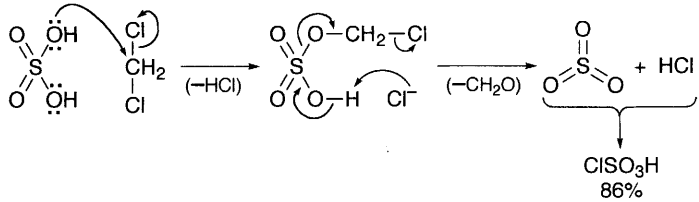
$$PCl_5 + H_2SO_4 \longrightarrow POCl_3 + ClSO_3H + HCl \quad (2)$$

$$POCl_3 + 2H_2SO_4 \longrightarrow HPO_3 + 2ClSO_3H + HCl \quad (3)$$

$$SOCl_2 + H_2SO_4 \longrightarrow ClSO_3H + HCl + SO_2 \quad (4)$$

$$SO_2Cl_2 + H_2O \longrightarrow ClSO_3H + HCl \quad (5)$$

Another preparative method involves the treatment of oleum with either carbon tetrachloride or dichloromethane as the chlorinating agent. The reaction of dichloromethane on 70% oleum initially yields a mixture of formaldehyde, sulfur trioxide and hydrogen chloride; the latter two products subsequently combine to form chlorosulfonic acid (Scheme 2).[2] This reaction provides a convenient laboratory preparation of chlorosulfonic acid which is obtained in excellent yield (86%). The analogous reaction between carbon tetrachloride and oleum presumably follows a similar mechanistic pathway.



Scheme 2

A method and switching system for the simultaneous manufacture of chlorosulfonic acid and sodium sulfate involves heating sodium chloride and sulfuric acid at 550–600 °C, cooling and grinding.[3] Chlorosulfonic acid may also be obtained by the action of sulfur trioxide on sodium chloride yielding the corresponding chlorosulfonate, which is subsequently heated with 40% oleum at 146–153°C to yield the reagent.[4] Gaseous hydrogen chloride and chlorosulfonic acid are simultaneously produced by feeding chlorine gas into a liquid mixture of sulfur, sulfur monochloride and water under conditions which keep the reaction medium in the liquid state.[5]

2 Manufacture

As mentioned in the Introduction (Chapter 1, p 1), modern chemical plants produce chlorosulfonic acid by the direct union of sulfur trioxide and gaseous hydrogen chloride using a continuous flow operation involving two or more vessels in series for gas–liquid contact, heat exchangers for controlling the reaction temperature and the use of excess chlorosulfonic acid as a solvent during

part of the reaction.[6,7] Recently, pure sulfur trioxide has been generally favoured for the manufacture of chlorosulfonic acid as it reduces problems arising from waste gases and permits the use of a more compact design of the chemical plant.[8]

The manufacture of chlorosulfonic acid is the subject of many patents, some of which are described in the reviews,[6–8] while details of early patents have been given by Jackson (Chapter 7, ref. 1). Several patents describe the recycling of recovered hydrogen chloride and sulfur trioxide to enhance the yield of chlorosulfonic acid.[7,8] Manufacturing procedures vary both in the manner of bringing the two reactants into contact and in the methods by which the heat of reaction is removed.

The reactor can be a packed column with chlorosulfonic acid spray at the top and a mixture of hydrogen chloride and sulfur trioxide entering at the bottom. In this case, the reaction and heat removal take place in one piece of equipment; alternatively these steps can be separated by first vigorously mixing the components together in a mixing nozzle. The hot reaction product is then rapidly cooled with cold chlorosulfonic acid in a packed column or by a water-cooled condenser. As an example of this procedure, spraying sulfur trioxide (118 kg) and anhydrous hydrogen chloride (54 kg) through a two-component nozzle into the cooled reactor produced chlorosulfonic acid (172 kg $hour^{-1}$).[9]

In one modification of the process the initial crude chlorosulfonic acid containing a slight excess of sulfur trioxide is cooled and saturated with hydrogen chloride gas in a bubble column. The off-gas is scrubbed with 98% sulfuric acid and then with water.[9]

The sulfonation of an organic substrate yields a mixture of hydrogen chloride gas and an organic solvent which can be utilized in the manufacture of chlorosulfonic acid by mixing it with sulfur trioxide at 0–40 °C. For example, a solution of hydrogen chloride in dichloromethane, derived from the sulfonation of naphthalene, was continuously converted into chlorosulfonic acid by reaction with sulfur trioxide at 15–20 °C.[10] Pure chlorosulfonic acid can be prepared from gaseous sulfur trioxide and hydrogen chloride in a continuous process in the presence of boiling chlorosulfonic acid. The reaction mixture was afterwards rapidly cooled to < 50 °C and the evaporated chlorosulfonic acid returned *via* a reflux condenser. Thus, in a packed column chlorosulfonic acid (129 kg $hour^{-1}$) was prepared from sulfur trioxide (88.6 kg $hour^{-1}$) and hydrogen chloride (40.5 kg $hour^{-1}$).[11] Various modifications to the reaction of sulfur trioxide and hydrogen chloride for the manufacture of chlorosulfonic acid have been described.[12,13]

In the first patent,[12] gaseous sulfur trioxide and hydrogen chloride are reacted together in the first reaction tower at the boiling point of chlorosulfonic acid. The crude product is passed through a condenser at ~ 60 °C to remove hydrogen chloride and yield chlorosulfonic acid of $> 99.5\%$ purity. The separated hydrogen chloride is then reacted with excess sulfur trioxide in a second reaction tower to give crude chlorosulfonic acid, which is heated at 150 °C to remove some of the dissolved sulfur trioxide and recycled to the first reaction tower. By this procedure, the reaction of sulfur trioxide (228 kg $hour^{-1}$) with hydrogen chloride (93.8 kg $hour^{-1}$) produced 99.6% pure chlorosulfonic acid (300 kg $hour^{-1}$).[12]

In the second patent,[13] high grade chlorosulfonic acid is manufactured by reacting hydrogen chloride gas with sulfur trioxide at $> 150\,^{\circ}C$. The crude product, containing pyrosulfuryl chloride, was treated with a mixture of hydrogen chloride gas and sulfuric acid (1–3 wt%) at 80–110 °C and the unreacted hydrogen chloride recirculated to the reaction process. Improved devices for the production of chlorosulfonic acid are described in two Russian patents.[14,15]

The first apparatus consists of a vertical vessel containing two reaction chambers separated by a dead-end plate with an overflow nipple. The upper chamber contains the mixer, inlets for hydrogen chloride and sulfur trioxide, and outlets for the inert gases and the condenser.[14] The second method and device involves the reaction of 100% sulfur trioxide and hydrogen chloride at elevated temperature, followed by condensation of the resultant product and heating it with hydrogen chloride at 155–175 °C. The apparatus for this process contains a reactor divided by a partition into a settling and a reaction chamber, a mixer and a modified heat exchanger.[15]

In another method, chlorosulfonic acid is manufactured by addition of hydrogen chloride to chlorosulfonic acid containing sulfur trioxide (7 wt%) in a steel reaction tower to react with 93% of the sulfur trioxide. Part of the resultant crude chlorosulfonic acid was recycled to the SO_3-absorption tower. The remainder of the crude product was treated with hydrogen chloride in a teflon-lined steel reactor tower to produce chlorosulfonic acid [1500 kg hour^{-1}, containing iron (0.3 ppm)].[16]

Chlorosulfonic acid can be prepared by the gas-phase reaction of hydrogen chloride and sulfur trioxide at 400–500 mbar pressure using 25–35% oleum as the sulfur trioxide source.[17] The heat of reaction is utilized for the evolution of sulfur trioxide from oleum; the resultant chlorosulfonic acid is cooled down to 95 °C with oleum and then with water to 40 °C. By this procedure, the reaction of 30% oleum (600 ml) with hydrogen chloride (300 ml) at 260 mbar pressure afforded 98.5% chlorosulfonic acid (353 g).[17] In another process, chlorosulfonic acid is circulated through a first reaction vessel (A), a cooler, a gas cooling tower (B) above a second reaction vessel (C) and a cooler. Stabilized liquid sulfur trioxide (1007 kg hour^{-1}) was fed into A to contain sulfur trioxide ($5.3 \pm 0.5\%$) in A and hydrogen chloride gas at 15 °C 225 kg hour^{-1} each into A and C (hydrogen chloride from B is recycled into A) to be at 90–95 °C in A and C and at 35–38 °C in B. This operation produces 99.2% chlorosulfonic acid in 98.6 and 100% yield relative to stabilized sulfur trioxide and hydrogen chloride respectively.[18] A process for the production of high purity chlorosulfonic acid suitable for use in the manufacture of shampoos and detergents involves contacting the hydrogen chloride and sulfur trioxide at the point of reaction with sulfuric acid (0.75–1.5 wt%) based on the stoichiometric rate of chlorosulfonic acid produced from the reaction of the sulfur trioxide with excess hydrogen chloride. The chlorosulfonic acid obtained contains < 1 wt% H_2SO_4, < 0.47 wt% SO_3, < 5 ppm Fe and $< 0.5\%$ pyrosulfuryl chloride.[19]

A Chinese paper[20] discusses the problems involved in the manufacture of chlorosulfonic acid from sulfur trioxide and hydrogen chloride in sulfuric acid plants. These include the optimum raw gas composition (SO_3:HCl molar ratio

1.15–1.20:1), initial mixed gas reaction temperature (120–125 °C) and the selection of suitable corrosion-resistant materials and equipment.

In a recent process,[21] the manufacture of chlorosulfonic acid from high concentration sulfur trioxide involves absorbing sulfur trioxide-containing tail gas in an absorbing tower to yield 20–30% oleum, followed by desorption to give > 99% sulfur trioxide. This is then reacted with dry hydrogen chloride at 140–160 °C using a SO_3:HCl molar ratio of 1:1–1.05 forming gaseous chlorosulfonic acid and cooling the gas to give the liquid product. The tail gas, after adsorption of sulfur trioxide, is recycled back to the sulfuric acid process stage.[21]

The direct preparation of high concentration chlorosulfonic acid from low concentration hydrogen chloride is achieved by cooling gaseous hydrogen chloride (from a Mannheim furnace used in production of potassium sulfate) followed by reaction of the dry gaseous hydrogen chloride with sulfur trioxide gas in a secondary reactor. The product, after condensation, was then reacted with dry hydrogen chloride gas in the first reactor.[22]

3 Properties

Chlorosulfonic acid is a highly corrosive, fuming liquid, which attacks brass, bronze, lead and the majority of non-ferrous metals. As far as corrosion is concerned, cast iron and carbon steel are acceptable materials for containing chlorosulfonic acid at temperatures < 35 °C, provided that iron content and colour are not critical. Stainless steels (300-series), certain aluminium alloys and Hastlelloy are suitable materials for the construction of chemical plants used in the manufacture of the reagent. However, enamel, glass or PTFE-lined steel or teflon-lined piping are the preferred materials for use with chlorosulfonic acid at elevated temperatures or when trace contamination by iron must be avoided as when the reagent is to be used in the synthetic detergent industry.[6]

In the construction of tank wagons for the transport of chlorosulfonic acid, stainless steel was discovered to be the most suitable material. Studies were made of the effect of the reagent on mild steel, stainless steel and aluminium specimens, fully and half-immersed in the acid and when exposed to the acid vapour. When the samples were immersed, the stainless steel suffered almost no attack, whereas the other materials were appreciably corroded. Under the half-immersed conditions, the stainless steel was attacked above the liquid level, while in the vapour phase all the specimens were slightly attacked.[23]

A mixture of chlorosulfonic acid and sulfur trioxide in the ratio 45:55, known as FS, is widely employed as a chemical smoke in warfare (Chapter 7, ref. 1). The addition of red lead oxide (0.04–0.1%) to the mixture has been shown to inhibit corrosion of the steel and aluminium tanks used to store the FS smoke mixture.[24] Other studies demonstrated that stainless steels can be protected from corrosion by chlorosulfonic acid by the introduction of nitrate and/or nitrite ions.[25] Commercial chlorosulfonic acid should contain almost no iron; a typical analysis would be as follows: 98–99.5% purity with H_2SO_4 (0.2–2%); free SO_3 (0–2%); free HCl (0–0.5%) and Fe (5–30 ppm).[8]

4 World Production

It has been reported[6,7] that there are some twenty manufacturers of chlorosulfonic acid in Europe, Asia and Australia, together with other companies in Brazil and Mexico. In the USA, the two major producers are DuPont and the Gabriel Chemical Co. with an annual capacity of > 30 000 tons and 13 600 tons, respectively. More recently,[8] the following companies have also been listed as producers of the reagent. In Europe: BASF and Bayer (Germany); UCB (Belgium); Eni Chem (Italy); Säurefabrik (Switzerland); ICI (Britain); and Tiszamenti (Holland). In Asia: Mitsubishi, Nippon Soda, Nissan Chemicals, and Takuyama (Japan); Choheung (Korea); also Chen Yeh and Kuo Kai (Taiwan).

A recent article[26] claimed that the average annual production of chlorosulfonic acid in Western Europe is 120 000 tons, while the comparable figures for the USA and Japan are 67 000 and 50 000 tons respectively. Indian annual capacity for chlorosulfonic acid production totals 88 800 tons by seven companies. The largest producer is DMC, followed by Grasim Industries with 16 500 tons; Indian production in 1993–94 was estimated to be 73 000 tons. On a global scale, the uses of chlorosulfonic acid are as already reported (see Introduction, p 5).[7,26]

5 Toxicity

Chlorosulfonic acid is a powerful acid and dehydrating agent producing severe burns on contact with skin or by inhalation of the vapour. Care must therefore be taken when using this toxic, corrosive reagent (see Introduction p 5). Adequate protective clothing, gloves, safety glasses and boots should be worn. In addition, a face-mask equipped with a filter element to absorb acid fumes should be available if needed. The materials used for protection must be acid-resistant, *e.g.* polychloroprene coated with a copolymer of vinylidene fluoride and hexafluoropropylene, while the boots may be made of PVC.[8]

The acute toxicity of chlorosulfonic acid has been evaluated.[27] In rats, after a 4 hour inhalation period, the average lethal concentration (LC_{50}) of the compound was 38.5 mg m^{-3}. For mice, the LC_{50} figure, after a 2 hour inhalation period, was 52.5 mg m^{-3}. Examination of the internal organs of the acutely poisoned animals indicated respiratory and ocular irritation as well as histopathological changes. It was suggested from the results, that the maximum permissible concentration of chlorosulfonic acid should be 0.1 mg m^{-3}.[27]

6 References

1 J.W. Mellor, *A Comprehensive Treatise on Inorganic and Theoretical Chemistry*, Vol. X, Longmans, London, 1930, 686.
2 M. Saljoughian, E. Alipour and M.J. Sadeghi, *Synth. Commun.*, 1985, **15**(13), 1213, *Chem Abs.*, **103**, 204722.
3 G. Jeney, T. Marosi, F. Onodi and S. Szanti, *Hung. Teljes*, HU 35213 (1985); *Chem Abs.*, **104**, 112217.
4 N.A. Laury, US 2354464 (1944); *Chem. Abs.*, **38**, 6504.

5 A. Redniss, S. Goodman and T. Cantor, US 2871098 (1959); *Chem. Abs.*, **58**, 11777.
6 C.E. McDonald, 'Chlorosulfonic Acid' in *Kirk-Othmer's Encyclopaedia of Chemical Technology*, 4th Edn., Vol. 6, Wiley, New York, 1993, 168.
7 F. Baunick, 'Chlorosulfonic Acid' in *Ullmann's Encyclopaedia of Industrial Chemistry*, 5th Edn., Vol. A7, VCH, Weinheim, 1986, 17.
8 J. Maas and F. Baunack, 'Chlorosulfonic Acid' in *Ullmann's Encyclopaedia of Industrial Inorganic Chemicals and Products*, Vol. 2, Wiley – VCH, Weinheim, 1999, 1329. (Also *Ullmann's Encyclopaedia of Industrial Chemistry*, online version Wiley – VCH, Weinheim, 2000).
9 H. Wolf, W. Göesele and S. Schreiner, *Ger. Offen.*, DE 2059293 (1972); *Chem. Abs.*, **77**, 64116.
10 M. Buerli and A. Henz, *Swiss*, CH 597094 (1978); *Chem. Abs.*, **89**, 45817.
11 Badische Anilin- and Soda - Fabrik A-G., *Neth.*, NL 6514410 (1966); *Chem. Abs.*, **65**, 8401.
12 M. Kawamoto and H. Ejiri, *Jpn*, JP 2664 (1957); *Chem. Abs.*, **53**, 14435.
13 Y. Yasui, *Jpn*, JP 45024648 (1970); *Chem. Abs.*, **73**, 100561.
14 G.A. Zagulygaev, V.F. Golovanov and A.T. Khaidas, *USSR*, SU 652958 (1979); *Chem. Abs.*, **92**, 96242.
15 L.P. Ryadneva, V. Taratorkin, E.M. Popov, M.K. Chistyakov, G.V. Belousov, V.P. Budnik, R.A. Iskakov, V.A. Najdenova and L.L. Rybakova, *USSR*, SU 865780 (1981); *Chem. Abs.*, **96**, 54710.
16 Tokuyama Soda Co. Ltd., Japan, *Jpn. Kokai*, JP 57203055 (1982); *Chem. Abs.*, **98**, 218082
17 K.H. Schultz and F. Baunack, *Ger. Offen.*, DE 3129976 (1983); *Chem. Abs.*, **98**, 218076.
18 Nippon Soda Co. Ltd., Japan, *Jpn. Kokai*, JP 58055313 (1983); *Chem. Abs.*, **99**, 40578.
19 N.A. Carlson and G.R. Evers, US 4891196 (1990); *Chem. Abs.*, **112**, 185566.
20 Y. Hu and R. Bao, *Liusuan Gongye*, 1992, **5**, 47; *Chem. Abs.*, **121**, 13065.
21 S. Chen, J. Zhang and Z. Yu, *Faming Zhuanli Shenqing Gongkai Shuomingshu, Chin.*, CN 1203188 (1998); *Chem. Abs.*, **132**, 209860.
22 S. Chen, J. Zhang and Z Yu, *Faming Zhuanli Shenqing Gongkai Shuomingshu, Chin.*, CN 1165779 (1997); *Chem. Abs.*, **132**, 51924.
23 B.C. Srivastava, *LABDEV*, Pt. A, 1969, **7**(1), 43; *Chem. Abs.*, **71**, 52914.
24 J.N. Mallis, US 3446748 (1969); *Chem. Abs.*, **71**, 4153.
25 Tokuyama Soda Co. Ltd, Japan, *Jpn. Kokai*, JP 57185989 (1982); *Chem. Abs.*, **98**, 147773.
26 'Chlorosulfuric Acid' in *Chemical Business (India)*, 1995, Vol. 8 (Issue 11), 52.
27 N.K. Mamleeva and G.Z. Bakhtizina, *Gig. Tr. Okhr. Zdorov'ya Rab. Neft. Neftekhim. Prom-sti.*, 1976, **9**, 110; *Chem. Abs.*, **90**, 17214.

APPENDIX

Recent References to Chlorosulfonic Acid

The appendix contains a selection of the most recent references to chlorosulfonic acid together with details of the relevant chapters in the main text for cross-reference. The literature has been covered up to December 2001.

Contents of Appendix

Acid Catalytic Effects in the Chlorination of Propanoic Acid

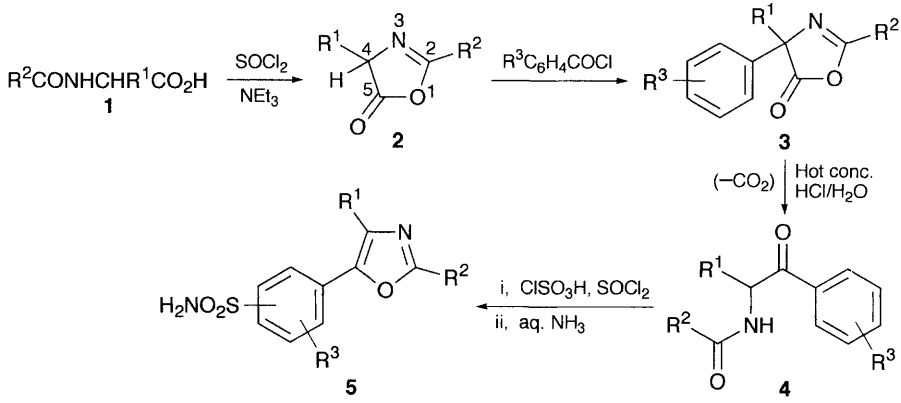
T. Salmi, P. Maki-Arvela, E. Paatero and R. Bygginskacka, *J. Chem. Technol. Biotechnol.*, 2000, **75**(1), 89; *Chem. Abs.*, **132**, 23667.

The selective α-chlorination of propanoic acid to 2-chloro- and 2,2-dichloropropanoic acid at 80–130 °C in the presence of chlorosulfonic and dichloroethanoic acid as catalysts and oxygen as the radical scavenger was examined. The results confirmed previous studies (Chapter 5, Section 5.6), indicating that the intermediate was propanoyl chloride formed from propanoic acid and chlorosulfonic acid by acid-catalysed enolization and substitution of the hydroxyl group by chlorine.

Synthesis of 5-Phenyloxazole Derivatives

K. Matsuda, K. Hara and M. Akamatsu, *PCT Int. Appl.*, WO 001478 (2000); *Chem. Abs.*, **132**, 207843.

An *N*-acylamino acid (**1**) is reacted with thionyl chloride yielding the oxazolone (**2**), which by treatment with an aroyl chloride gave (**3**). The latter compound was hydrolysed and decarboxylated to yield (**4**), which reacted with chlorosulfonic acid–thionyl chloride to give the sulfonyl chloride, and subsequent reaction with ammonia afforded the sulfonamide (**5**) (Scheme 1).



Scheme 1

As an example of the procedure, DL-*N*-acetyl-2-cyclohexylglycine, by reaction with 3-fluorobenzoyl chloride in the second step, was converted into 5-(4-sulfamoyl-3-fluorophenyl)-4-cyclohexyl-2-methyloxazole (82% yield) (Chapter 6, Section 4.1.2).

Sulfation of High Alkanols

F. Zhang, W. Zhang, G. Wei and L. Bao, *Huagong Keji*, 1999, **7**(3), 44; *Chem. Abs.*, **132**, 266786.

Sodium octyl sulfate was synthesized by reaction of octyl alcohol with chlorosulfonic acid or concentrated sulfuric acid (yields > 70%) (Chapter 5, Section 3).

Synthesis of Sodium Lauryl Sulfate

Y. Pan and D. Kong, *Tianranqui Huangong*, 1999, **24**(3), 46; *Chem. Abs.* **132**, 182, 347

Studies were made of the reaction of lauryl alcohol with chlorosulfonic acid. It was found that, under the optimum conditions, the yield of sodium lauryl sulfate increased from 82 to 92.5% (see Chapter 5, Section 3).

Bromoisoquinolines and their Nitro Derivatives

A.H. Gouliaev and W. Hanson, *PTC Int. Appl.*, WO 9967218 (1999); *Chem. Abs.*, **132**, 51460.

Isoquinolines may be converted into the 5- or 8-bromo derivatives by reaction with a brominating reagent, *e.g.* NBS, and an acidic catalyst, like chlorosulfonic or sulfuric acid. The selectivity for producing the 5- rather than the 8-isomer increased with the acidity of the catalyst. Nitration may also be achieved by

addition of a nitrating agent, *e.g.* potassium nitrate, to the reaction mixture (Chapter 6, Section 1.1.6).

Phthalocyanine Dyes Useful for Ink Jet Printing

R. Bradbury, G. Wright and A.P. Shawcross, *PCT Int. Appl.*, WO 0008103 (2000); *Chem. Abs.*, **132**, 153266.

The phthalocyanine dyes are prepared from chlorosulfonated phthalocyanine by condensation with the appropriate amine. Thus, phthalocyanine was tetrachlorosulfonated by reaction with chlorosulfonic acid and the product condensed with 2-(2-methoxyethoxy) ethyl 4-aminobenzoate to yield the dye (λ max = 672 nm) (Chapter 6, Section 1.2.7).

Sulfonated Polymers

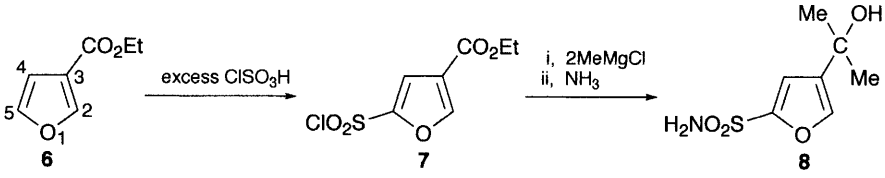
A. Denizli, N. Satiroglu, S. Pater, S. Bektas and O. Genc, *J. Macromol. Sci., Pure Appl. Chem.*, 2000, **A37**(12), 1647; *Chem. Abs.*, **134**, 163757.

Membranes composed of a sulfonated interpolymer of polyethylene and sytrene–DVB copolymer were prepared by reaction with mixtures of chlorosulfonic acid and dichloroethane of different compositions. It was discovered that the electrical properties of the resultant membranes were related to the degree of sulfonation. See also V.K. Shahi, S.K. Thampy and R. Rangarajan *React. Funct. Polym.*, 2000, **46**(1), 39: *Chem. Abs.*, **134**, 163756 (Chapter 8, Section 6).

Chlorosulfonation of Ethyl-3-furoate

F.J. Urban and V.J. Jasys, *Eur.*, EP 976742 (2000); *Chem. Abs.*, **132**, 122510.

Ethyl-3-furoate (**6**) reacted with excess chlorosulfonic acid at low temperature to give the 5-sulfonyl chloride (**7**), which reacted with methylmagnesium chloride (two equivalents) and ammonia to give the sulfonamide (**8**) (Scheme 2). The furansulfonamides are useful as drug intermediates (see Chapter 6, Section 2.1).



6 **7** **8**

Scheme 2

Synthesis of Chlorosulfonic Acid

Q. Wang, G. Chen, S. Zhang, H. Zhang and C. Lui, *Faming Zhuanli Shenqing Gongkai Shoumingshu, Chin.*, CN 1257039 (2000); *Chem. Abs.* **134**, 73611.

In the process, high temperature hydrogen chloride is cooled to 32–80 °C, dried,

and reacted with sulfur trioxide in the main reactor at 150–210 °C to yield a semi-product. This material is then reacted with dry hydrogen chloride at 20–50 °C and the gaseous products were cooled to yield highly pure chlorosulfonic acid (see Chapter 10, Section 2).

Physical Properties of some Superacids

R. Steudel and A.H. Otto, *Eur. J. Inorg. Chem.*, 2000, (**ii**), 2379; *Chem. Abs.*, **134**, 91737.

The gas-phase geometries, dipole moments, enthalpies and Gibbs' free energies of the superacids: thiosulfuric, peroxysulfuric, fluorosulfonic and chlorosulfonic acids were determined. The OH acidities of all the sulfur species were greater than that of sulfuric acid, so these acids may be termed superacids. In the gas phase, chlorosulfonic acid was a stronger proton donor than fluorosulfonic acid, whereas in the liquid phase the reverse was true (Chapter 1, Section 2).

Sulfonated Derivatives of Alkylbenzenes as Detergents

J. Li, *Riyong Huaxue Gougye*, 2000, **30**(3), 36; *Chem. Abs.*, **133**, 137082.

The article reviews the use of sulfonated derivatives of linear alkylbenzenes, obtained by sulfonation and chlorosulfonation, in the production of detergents and surfactants (see Chapter 8, Section 4).

Sulfated Asphalt

B. Wang and G. Zhao, *Faming Zhuanli Shenqing Gongkai Shuomingshu, Chin.*, CN 1239133 (1999); *Chem. Abs.*, **133**, 137716

Sulfated asphalt with improved mechanical properties is manufactured by dissolving coal tar and petroleum asphalt (containing 30–60% of fused ring compounds) in a solvent, *e.g.* octane, nonane, decane or 1,2-dichloroethane. The asphalt solution was then sulfonated by treatment with chlorosulfonic acid, sulfur trioxide or sulfuric acid, followed by neutralization with alkali (sodium or potassium hydroxide) and drying at 70–150 °C. Sulfonated asphalt is also employed as a water-plugging agent for oil wells, see R. Ding, *Faming Zhuanli Shenqing Gongkai Shuomingshu, Chin*, CN 1252426 (2000); *Chem. Abs.*, **133**, 364301 (Chapter 8).

Preparation of a Cement–Water Reducing Agent for Waste Polystyrene

Y. Huang, B. Liao, S. Zhoa, G. Lin, H. Pang, G. Cong and M. Chen, *Faming Zhuanli Shenqing Gongkai Shuomingshu, Chin.*, CN 1257848 (2000); *Chem. Abs.*, **134**, 90110.

A solution of waste polystyrene (30–80 wt%) in toluene, xylene or dichloro-

methane is sulfonated by heating the solution with chlorosuflonic acid or 50–90% sulfuric acid at 80–100 °C (3–5 hours), then at 110–140 °C and distilling the mixture for 1 hour (to recycle the solvent). Addition of water afforded sulfonated polystyrene solution (5–40 wt%), which was neutralized with lime forming calcium polystyrene sulfonate (Chapter 8, Section 6).

Manufacture and Use of Bifunctional Phenyl Monophosphonic–Sulfonic Acid Ion-exchange Resin

S. Alexandratos, C.A. Shelley, E.P. Horowitz and R. Chiarizia, US 6232353 (2001); *Chem. Abs.*, **134**, 341431.

As an example 2, 12 and 25% DVB cross-linked chloromethylstyrene–styrene copolymer beads were functionalized by treatment with triethyl phosphite and then with chlorosulfonic or sulfuric acid to give the ion-exchange resin with ion-exchange capacity of 10.89, 7.69 and 6.88 mmol g^{-1} respectively. The resin is useful for removing polyvalent metal cations from aqueous solutions (Chapter 8, Section 6).

A Composite Soap Containing Monoglyceride Sulfonate

J.K. Koo, Y.H. Choi, T.K. Huh, J.J. Choi, T.S. Kim, M.M. Nang and H.J. Ahn, *Jpn. Kokai*, JP 2000169879 (2000); *Chem. Abs.*, **133**, 45221.

The composite soap is a mixture of a fatty acid soap and a monoglyceride sulfonate (**9**, 2–35%).

$$RCO_2CH_2CH(OH)CH_2SO_3M$$

9 R = C_7–C_{17} alkyl; M = Na, K, NH_4^+

The composite is prepared by mixing a chlorohydroxylsulfonic acid, a fatty acid and an electrolyte, followed by neutralizing and drying. Thus, a solution for the preparation of the composite with a soap component involved reaction of chlorosulfonic acid, glycerol and potassium hydroxide (Chapter 8, Section 4).

Synthesis of Sildenafil (Viagra)

H. Fu, X. Wang, B. Pang, N. Wang and S. Ji, *Faming Zhuanli Shenqing Gongkai Shoumingshu, Chin.*, CN 1246478 (2000); *Chem. Abs.*, **133**, 281797.

In a stage of the synthesis, 4-(2-ethoxybenzamido)-1-methyl-3-propyl-pyrazole-5-carboxamide was chlorosulfonated by reaction with chlorosulfonic acid–thionyl chloride (18 hours) to yield 4-ethoxy-3-(5-aminocarbonyl-1-methyl-3-propylpyrazol-4-yl) carbamoylbenzenesulfonyl chloride. In this reaction, sulfonation occurs preferentially *para* with respect to the more powerful electron-donating ethoxy group as would be anticipated (Chapter 6, Section 1.2.4).

Chlorosulfonic Acid as a Cyclization Agent for the Preparation of Cyclic Ether Odourants

P. Linares, S. Salido, J. Altarejos, M. Nogueras and A. Sanchez, *Proc. Phytochem. Soc. Eur.*, 2000, **46** (Flavour and Fragrance Chemistry), Kluwer Academic Publishers, 101; *Chem. Abs.*, **134**, 266449.

Several benzopyran derivatives of potential use in the fragrance industry have been synthesized by superacid condensation of ionones, ionols and related compounds (Chapter 9, Section 2).

Manufacture of Sulfonated Aromatic Polymers and their Use in the Production of Membranes

W. Chu, T. Guth and G. Frank, *Ger. Offen.*, DE 19959289 (2001); *Chem. Abs.*, **135**, 46668.

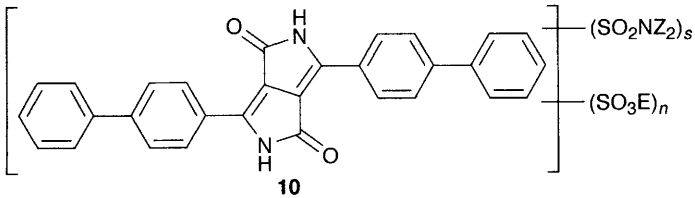
A useful mild method for sulfonation of aromatic polymers involves dissolving them in chlorosulfonic acid or oleum, adding an inert organic solvent, *e.g.* dichloromethane, followed by a carboxylic acid anhydride, *e.g.* acetic anhydride and allowing the sulfonation to proceed at a temperature of < 25 °C.

Polyether sulfone (PES) by this procedure, after 2 hours at 0–10 °C, afforded the sulfonated polymer (34.3% sulfonation). The degree of sulfonation was enhanced by the presence of acetic anyhdride (Chapter 8, Section 6).

Diketopyrrolopyrrole Compounds as Pigment Dispersants

J. Weber, F.W. Grimm and E. Dietz, *Eur.*, EP 1104789 (2001); *Chem. Abs.*, **135**, 20892.

The dispersants are pyrrolopyrroledione sulfo derivatives (**10**; E = H, metal or NH^+; Z = organic group; $n = 0$–2; $s = 0.1$–4.0).



10

The sulfo derivatives (**10**) are used as dispersants for diketopyrrolopyrrole pigments in coatings and plastics. They are manufactured by chlorosulfonation of the diketopyrrolopyrrole and subsequent condensation with the appropriate amine. For example, 1,4-diketo-3,6-bis(4-biphenylyl)pyrrolo[3,4-c]pyrrole was reacted with chlorosulfonic acid and thionyl chloride to give the sulfonyl chloride which was condensed with 3-(dimethylamino)-1-propylamine to yield the product. The dispersant was used with CI Pigment Red 264 in the production of a coating (Chapter 8, Section 5).

Phthalocyaninesulfonamide Inks with Good Storage Capacity and Resistance to Light and Water

Y. Matsuzaki and T. Oi, *Jpn.*, JP 200131453 (2001); *Chem. Abs.*, **134**, 368375.

The phthalocyanine compound was obtained by chlorosulfonation of a phthalocyanine with chlorosulfonic acid–thionyl chloride, followed by condensation of the sulfonyl chloride with an amine to yield the sulfonamide derivative used in the production of the inks (Chapter 6, Section 1.2.7).

Synthesis of Composites with Sulfonated Styrene–DVB copolymer

S. Rodriguez, A. Linares and J.L. Acosta, *Macromol. Mater.*, 2000, **283**, 68; *Chem. Abs.*, **134**, 132197.

A styrene copolymer cross-linked with DVB was lightly sulfonated and the product incorporated into poly(vinylidenefluoride) and ethylene–propylene–diene with addition of antimonic acid (HSb). The resultant composites were sulfonated using chlorosulfonic acid and the procedure afforded membranes showing good physical properties (Chapter 8, Section 6).

Manufacture of Hydrophilic Particles such as Pigments Free from Discolouration

T. Horiuchi, K. Morimoto, K. Wayaku and M. Yuhara, *Jpn. Kokai*, JP 2000256574 (2000); *Chem. Abs.*, **133**, 253954.

The method involves dissolving a hydrophobic substance, *e.g.* a pigment or dye, in a 20–1:1–20 (v/v) mixture of sulfuric and chlorosulfonic acid, then converting the solution into droplets and bringing these into contact with a saturated aqueous vapour which precipitates the substance into particles with a hydrophilic surface (Chapter 8, Section 5).

Sulfated Vitamin E Derivatives as Anion Surfactants

Y.-D Kim and B.-J. Ha, *Repub. Korea*, KR 9510683 (1995); *Chem. Abs.*, **133**, 238150.

The sulfate derivatives of, for instance, α-tocopherol, are prepared by reaction of the vitamin E derivative with sulfur trioxide or chlorosulfonic acid. The resultant sulfate was then neutralized by treatment with ammonia, sodium hydroxide or triethanolamine yielding an anion surfactant which is used in soaps, shampoos and cosmetics (Chapter 5, Section 3 and Chapter 8, Section 4).

The Effect of Chemical Treatment on Reinforcement/Matrix Interaction in Kevlar-fibre/Bismaleimide Composites

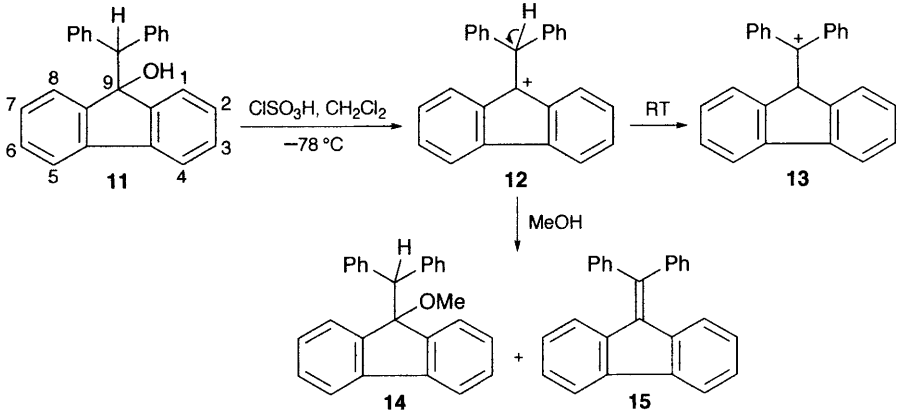
T.K. Lin, S.J. Wu, J.G. Loi and S.S. Shyu, *Compos. Sci. Technol.*, 2000, **60**(9), 1873; *Chem. Abs.*, **134**, 179145.

Surface modification of Kevlar fabrics with reactive functional groups can enhance the interlaminar shear strength (ILSS) of the Kevlar fibre/2,2-bis[4-(4-maleimidophenoxy)phenyl] propane (BMPP) composities. Chlorosulfonation of the fibres, by treatment with dilute chlorosufonic acid, improved the ILSS, but the use of higher concentrations of the reagent for a longer reaction times decreased ILSS. The optimum chlorosulfonation conditions involved the use of 0.2% chlorosulfonic acid for 150 seconds (Chapter 8, Section 6).

Intramolecular Hydride Ion Migration in a Substituted 9-Fluorenyl Carbocation

G. Mladenova, L. Chen, C.F. Rodriquez, K.W.M. Siu, L.J. Johnston, A.C. Hopkinson and E. Le-Ruff, *J. Org. Chem.*, 2001, **66**(4), 1109; *Chem. Abs.*, **134**, 265949.

9-(Diphenylmethyl) fluorenol (**11**), by reaction with a solution of chlorosulfonic acid in dichloromethane at low temperature (−78 °C), afforded the corresponding deep red fluoren-9-yl carbocation (**12**), which at room temperature was transformed into the yellow cation (**13**) by a reaction involving an apparent 1,2-hydride shift. The red carbocation (**12**) in methanol gave a mixture of the methoxy derivative (**14**, 15%) and the diphenylalkene (**15**, 60%) (Scheme 3).



Scheme 3

Synthesis of Chlorosulfonated Polyethylene by a Gas–Solid Method

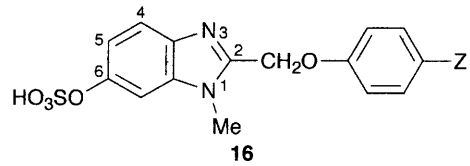
R. Zhao, Y. Sun, Y. Huang and S. Chen, *Huadong Lingong Daxue Xuebao*, 2001, **27**(1), 68, 72; *Chem. Abs.*, **135**, 61708, 61709. Also R. Zhao, S. Chen, S. Yan and Y. Huang, *J. Appl. Polym. Sci.*, 2001, **81**, 3582; *Chem. Abs.*, **135**, 274074.

Chlorosulfonated polyethylene was synthesized from chlorinated polyethylene by a gas–solid method involving reaction with a gaseous mixture of chlorine and sulfur dioxide. Elemental analysis showed that chlorination or dechlorination did not occur in the chlorosulfonation process. Increasing the temperature from 30 to 50 °C and the concentration of the gaseous mixture both increased the rate of chlorosulfonation and the optimum ratio of chlorine to sulfur dioxide was found to be 1:1. UV-light effectively initiates the reaction, but it also occurs in the dark at a slower rate. The presence of hydrogen chloride and oxygen both speed up the chlorosulfonation and yield a product with a higher sulfur content (Chapter 8, Section 6).

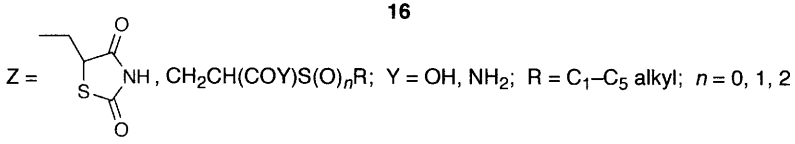
2-Phenoxymethyl-1-methyl-6-sulfoxybenzimidazoles

I. Iwabuchi, T. Fujiwara and T. Fujita, *Jpn Kokai*, JP 200197954 (2001); *Chem. Abs.*, **134**, 280842.

Compounds of general type (**16**) showed blood sugar lowering-activity and were useful against diabetes, hyperglycaema or cancer.



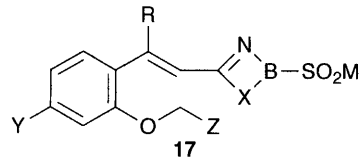
16



The active compounds (**16**) were prepared from the corresponding 6-hydroxy derivatives by treatment with a solution of chlorosulfonic acid in acetonitrile at RT (18 hours) (Chapter 6, Section 1.2.2).

Fluoresecent Coumarin Dyes

X. Luo and L. Cheng, *Faming Zhuanli Shenqing Gongkai Shuomingshu, Chin.*, CN 1258698 (2000), *Chem. Abs.*, **134**, 194554.



17

The fluoresecent dye (**17**; R = H, CN or CO_2H; X = O, S or NH; Y = NR^1R^2, OR^1, $NHCOR^1$ or $NHSO_2R^1$; R^1, R^2 = alkyl or aryl; Z = O, NR^6 (R^6 = H, alkyl or aryl); M = Cl, NR^1R^2 or OR^1; B = benzene, naphthalene or diazopyran ring) was prepared by chlorosulfonation of the coumarin derivative (similar to **17** but

without SO_2M), by reaction with chlorosulfonic acid at 10–180 °C (1–3 hours), followed by treatment with the appropriate amino or hydroxy-containing compound (Chapter 8, Section 5).

Sulfonated Sterols

N. Milstein and A. Behler, *PCT Int. Appl.*, WO 0075165 (2000); *Chem. Abs.*, **134**, 17622.

Treatment of sterols with chlorosulfonic acid provides a valuable synthetic route to high yields of pure sterol sulfates (Chapter 5, Section 3).

Synthesis of Disulfonyl Azides

D.A. Baker, G.E. East and S.K. Mukhopadhyag, *J. Appl. Polym. Sci.*, 2001, **79**(6), 1092; *Chem. Abs.*, **134**, 223942.

1,6-Hexane, 1,10-decane, 1,3-benzene, 1,5- and 2,6-naphthalene and biphenyl-4,4′-disulfonylazides were synthesized. The aliphatic derivatives were obtained from 1,6-dibromohexane and 1,10-dibromodecane by stirring them with aqueous sodium sulfate or hydrogen sulfate (Strecker reaction) to give the corresponding disodium sulfates (95%). The latter were stirred with chlorosulfonic acid (two equivalents) at RT for 24 hours to yield the disulfonyl chlorides which were condensed with sodium azide (two equivalents) in aqueous acetone (Forster–Fiertz reaction) to give the disulfonyl azides. The aromatic derivatives were obtained by chlorosulfonation of the relevant aromatic hydrocarbons by treatment with excess chlorosulfonic acid, followed by reaction with sodium azide. The disulfonyl azides were characterized by melting point and spectroscopic analysis and will be assessed as potential cross-linking agents for textile fibres (Chapter 3, Section 1 and Chapter 8, Section 7).

Sulfonated Polyether Sulfones

T. Pu and Z. Zhang, *Faming Zhuanli Shenqing Gongkai Shuomingshu, Chin.*, CN 1267676 (2000), *Chem. Abs.*, **134**, 266723.

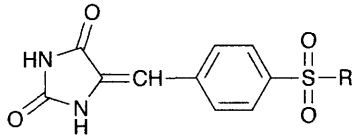
A polyether sulfone was conveniently sulfonated by reaction with a solution of chlorosulfonic acid in dichloromethane at 0–35 °C (30 minutes to 25 hours) under bubbling nitrogen gas. After reaction, the lower phase was separated, precipitated with water at 0–50 °C and purified. The molar ratio of chlorosulfonic acid to the polyether sulfone was 1:9 and the MW of the sulfone 20 000–80 000 (Chapter 8, Section 6).

Benzylidenehydantoin Sulfonylamino Acids

R.A. El-Sayed, *J. Serb. Chem. Soc.*, 2001, **66**(1), 17; *Chem. Abs.*, **134**, 252647.

5-Benzylidenehydantoin reacted with a large excess of chlorosulfonic acid, as

previously described (Chapter 6, Section 1.2.5), to yield the *para*-sulfonyl chloride (**18**) (Structures 18, 19).



18 R = Cl
19 R = Gly-OH, DL-Ala-OH, DL-Val-OH, L-Leu-OH, L-Phe-OH, L-Tyr-OH, L-Pro-OH

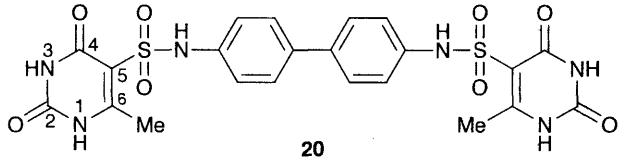
Attempted chlorosulfonation of 5-benzylidenehydantoin, using a mixture of chlorosulfonic acid (three equivalents) in excess thionyl chloride, gave a mixture of products, possibly involving initial chlorination of the amide group.

The sulfonyl chloride (**18**) was condensed with amino acids to yield the corresponding *N*-(benzylidinehydantoin sulfonyl) amino acids (**19**) and these were then converted into the dipeptide methyl esters using DCC (Chapter 4, Section 12.18).

A Study of the Technology of Diutsifon Synthesis

A.N. Shirshov, A.A. Muslinkin, V.S. Reznik and N.G. Pashkurov, *Phar. Chem. J.*, 2000, **34**(3), 132; *Chem. Abs.*, **134**, 193394.

Diutsifon (**20**) is an original drug recommended for the treatment of patients with leprosy or collagen disorders; it is also a general immunostimulant. In the first stage of the synthesis of diutsifon, 6-methyluracil was heated with hot excess chlorosulfonic acid–thionyl chloride to form 6-methyluracil-5-sulfonyl chloride (Chapter 6, Section 1.2.3). The chlorosulfonation stage was modified to increase the yield of the sulfonyl chloride from 64% to 70–75% using glass apparatus. In the second stage of the synthesis, the sulfonyl chloride was condensed with 4,4′-diaminodiphenyl sulfone to yield the drug (**20**) (Chapter 8, Section 1).

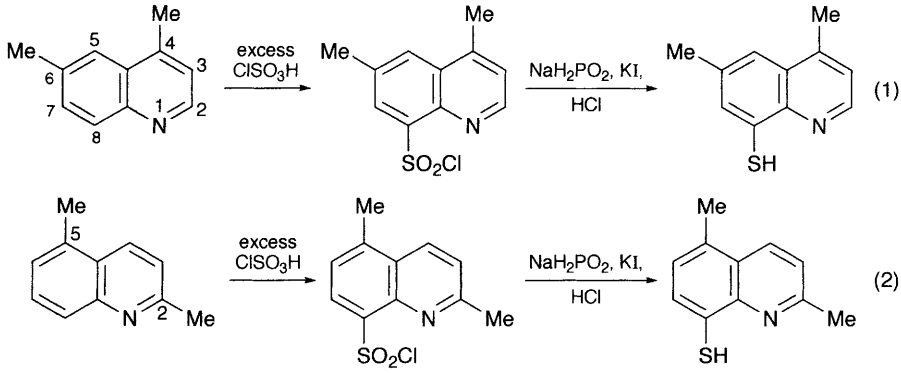


20

Synthesis of 4,6-Dimethyl- and 2,5-Dimethyl-8-mercaptoquinolines

J. Bankovskis, M. Circule, J. Asaks and D. Zaruma, *Latv. Khim. Z.*, 2000, (**2**), 97; *Chem. Abs.*, **134**, 178445.

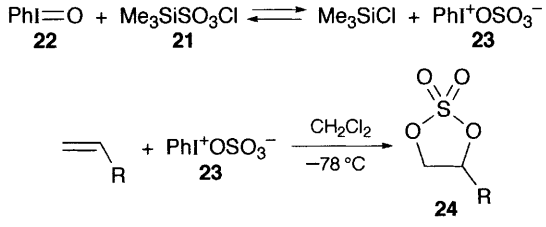
Reaction of 4,6-dimethyl- and 2,5-dimethylquinoline with warm excess chlorosulfonic acid afforded the corresponding -8-sulfonyl chlorides. The orientation of sulfonation is in agreement with previous results (Chapter 6, Section 1.1.5). The sulfonyl chlorides were then reduced to the 8-thiols by treatment with sodium hyperphosphite–potassium iodide reagent in hydrochloric acid (Equations 1 and 2).



An Improved Simple Synthesis of Cyclic Sulfates from Trimethylsilyl Chlorosulfonate

A.R. Bassindale, I. Katampe and P.G. Taylor, *Can. J. Chem.*, 2000, **78**(11), 1479; *Chem. Abs.*, **134**, 147156.

Trimethylsilyl chlorosulfonate can be prepared by reaction of tetramethylsilane with chlorosulfonic acid (Chapter 4, Section 12.8). The reaction of trimethylsilyl chlorosulfonate (**21**) with iodosobenzene (**22**) in dichloromethane at −78°C under nitrogen, followed by warming to RT, removal of solvent and trimethylsilyl chloride, yields phenyliodosulfate (**23**) (Equation 3). Phenyliodosulfate, without further purification, reacts with alkenes to give cyclic sulfates (**24**, 50–76% yield) (Equation 4).



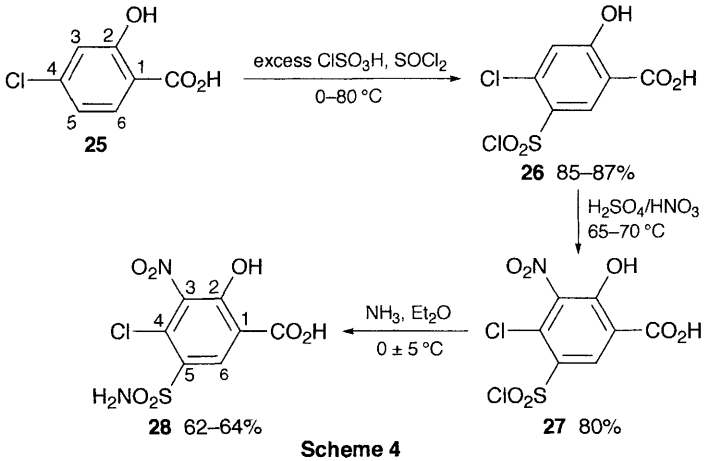
In the second reaction, if the trimethylsilyl chloride is not removed from the phenyliodosulfate then sultones are formed.

Synthesis and Diuretic Activity of 3-Nitro(amino)-4-chloro-5-sulfamoylsalicylic Acids and their Derivatives

V.A. Smirnov, *Pharm. Chem. J.*, 2000, **34**(4), 198; *Chem. Abs.*, **134**, 207581.

4-chlorosalicylic acid (**25**), by reaction with excess chlorosulfonic acid (5.2 equivalents), at 0 °C (2 hours), followed by heating with thionyl chloride at 80 °C (2 hours) afforded the 5-sulfonyl chloride (**26**) (Scheme 4). In the chlorosulfonation, a substantial excess of chlorosulfonic acid (at least five equivalents) is

required, otherwise the yield of the product falls off sharply (Chapter 4, Section 8.1).



Scheme 4

Nitration of the sulfonyl chloride (**26**) affords the 3-nitro derivative (**27**), which on ammonolysis, under very mild conditions, is converted into the sulfonamide (**28**). Determination of the diuretic activity of 4-chloro-5-sulfamoylsalicylic acid and its derivatives showed that electronic factors played a role in the activity. Thus the 3-nitro compound (**28**) was less potent than the corresponding 3-amino derivative. Esterification or hydrazinolysis of the carboxylic acid moiety also produced compounds with lower diuretic activity (Chapter 8, Section 1).

Preparation of Sulfonated Chitosan

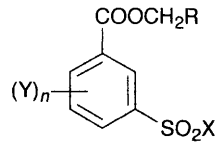
Y. Wu, B. Li, G. Wu, Z. Cao, J. Chen, *Guangzhou Huagong*, 2000, **28**(4), 99; *Chem Abs.*, **135**, 308769.

Chitosan was sulfonated by treatment with chlorosulfonic acid–formamide, in which the ratio of chitosan to formamide was 1 g:10 ml. Studies were made of the effects of the addition of chlorosulfonic acid, reaction temperature and time. The optimum conditions for the sulfonation were 4 ml of chlorosulfonic acid for 1 g of chitosan and a reaction temperature of 68 °C for 4 hours (see Chapter 5, Section 3.2).

Preparation of Halosulfonylbenzoate Esters

T. Hoshimiya and K. Yamada, *Jpn. Kokai*, JP 2001302612; *Chem Abs.*, **135**, 331261.

Halosulfonylbenzoate esters (**29**) are readily obtained by reacting halosulfonylbenzoyl halides with primary alcohols in the presence of bases.



29 R = alkyl, aryl or heteroaryl radical, X = halo, Y = substituent, n = 0–4

As an example, 3-chlorosulfonylbenzoyl chloride (prepared as described in Chapter 4, Section 8.1) was esterified by reaction with 1-decanol (one equivalent) in the presence of triethylamine at 25 °C for 1 hour to yield the corresponding ester (**29**; R = C_9H_{19}, X = Cl, Y = H) in 84% yield. In the absence of the base, no esterification occurred.

Subject Index

Numbers in bold type indicate the more important references.

Since its discovery in 1854, chlorosulfonic acid has demonstrated that it is a truly versatile reagent. It is widely used as a sulfonating and chlorosulfonating agent, particularly of organic compounds, and it provides useful synthetic intermediates for many branches of industry.

This book provides a detailed, up to date account of the reactions of chlorosulfonic acid with aliphatic, aromatic and heterocyclic compounds; reactions with elements and inorganic compounds are also discussed, along with the use of the reagent as a powerful acid catalyst and a halogenation and dehydrating agent. Finally, the commercial uses and manufacture of chlorosulfonic acid are reviewed.

The detailed coverage in this book, coupled with the many references to recent work, will ensure that it is welcomed as a reference by synthetic chemists in, for example, the pharmaceutical, agrochemical, plastic and detergent industries. Researchers and their students in academia will also find it a valuable addition to their bookshelves.

ISBN 0-85404-498-1