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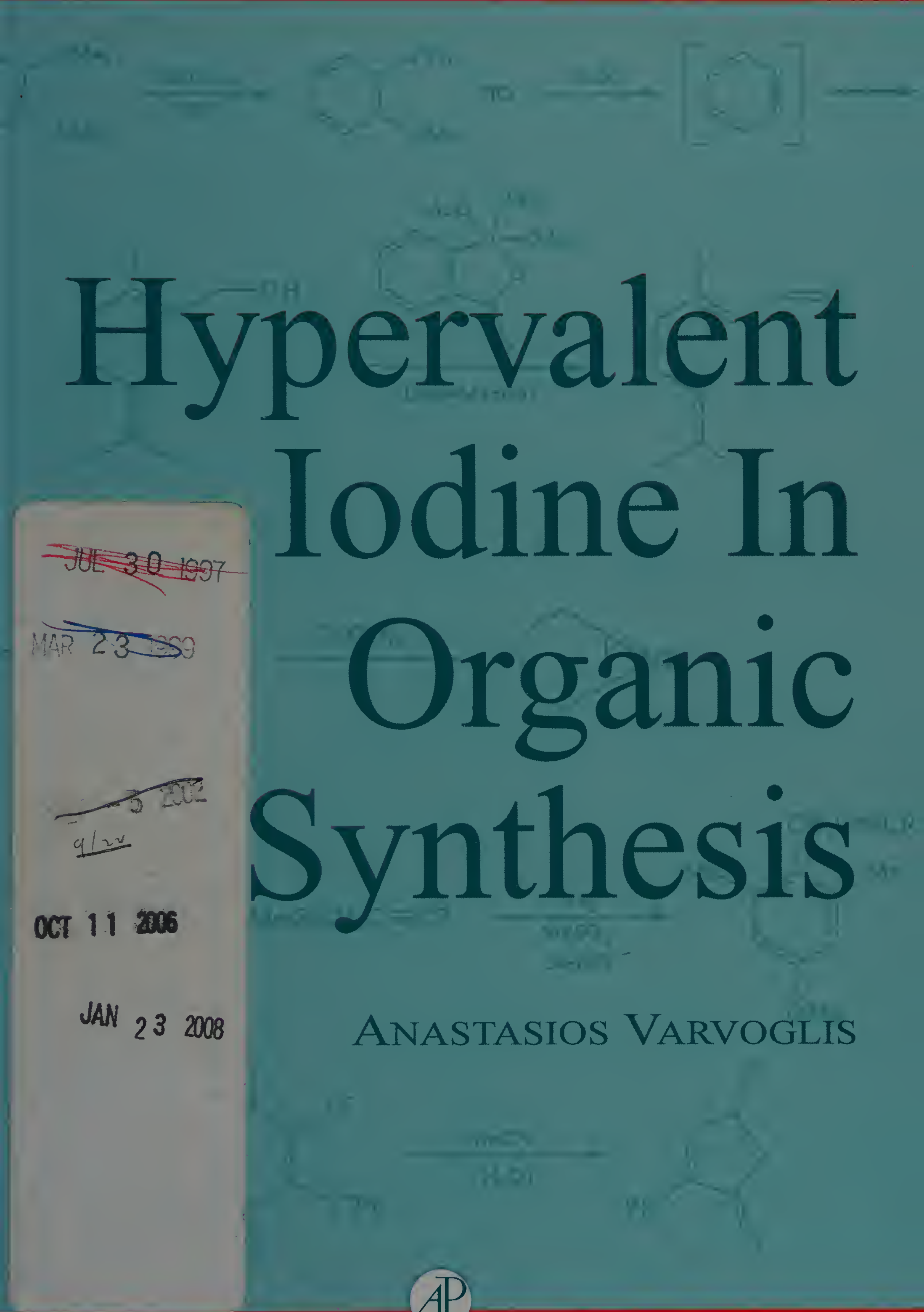

Hypervalent Iodine In Organic Synthesis

ANASTASIOS VARVOGLIS

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BEST SYNTHETIC METHODS

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Hypervalent Iodine in Organic Synthesis

A. Varvoglis
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Aristotelian University of Thessaloniki,
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Foreword

There is a vast and often bewildering array of synthetic methods and reagents available to organic chemists today. Many chemists have their own favoured methods, old and new, for standard transformations, and these can vary considerably from one laboratory to another. New and unfamiliar methods may well allow a particular synthetic step to be done more readily and in higher yield, but there is always some energy barrier associated with their use for the first time. Furthermore, the very wealth of possibilities creates an information-retrieval problem. How can we choose between all the alternatives, and what are their real advantages and limitations? Where can we find the precise experimental details, so often taken for granted by the experts? There is, therefore, a constant demand for books on synthetic methods, especially the more practical ones like *Organic Syntheses, Organic Reactions*, and *Reagents for Organic Synthesis*, which are found in most chemistry laboratories. We are convinced that there is a further need, still largely unfulfilled, for a uniform series of books, each dealing concisely with a particular topic from a *practical* point of view—a need, that is, for books full of preparations, practical hints and detailed examples, all critically assessed, and giving just the information needed to smooth our way painlessly into the unfamiliar territory. Such books would obviously be a great help to research students as well as to established organic chemists.

We have been very fortunate with the highly experienced and expert organic chemists, who, agreeing with out objective, have written the first group of volumes in this series, *Best Synthetic Methods*. We shall always be pleased to receive comments from readers and suggestions for future volumes.

A. R. K., O. M.-C., C. W. R.

Preface

An explosive growth in the field of organic hypervalent iodine chemistry has been witnessed over the last few years. Several individual compounds and a variety of classes with many members have emerged as useful and sometimes unique reagents for a plethora of transformations, most of which are of considerable synthetic utility.

This book, hopefully, will make organic chemists familiar with all aspects of reactivity and the obvious usefulness of these valuable yet readily available compounds.

Acknowledgement. I wish to thank Dr R. Wagih Awad, Dr A. Koumbis, Ms C. Gartagani and Mr D. Rigas for their help in the prepaparation of the manuscript. My thanks are extended to the University of Cyprus, where I spent the autumn of 1995 as a visiting professor; it was there that part of this book was completed.

Biographical sketch

Anastasios Varvoglis graduated from the University of Thessaloniki in 1961. He obtained his PhD from Cambridge University in 1967 and since 1974 has been Professor of Organic Chemistry at the University of Thessaloniki. He has published regularly in the field of hypervalent iodine for the last 25 years and is the author of three review articles and a book in this field.

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Abbreviations

Ac	acetyl
acac	pentane-2,4-dione-acetylacetone
aq.	aqueous
Bn	benzyl
BTI	[bis(trifluoroacetoxy)iodo]benzene
Bu	butyl
Bz	benzoyl
cat.	catalyst, catalytic
DCC	1,3-dicyclohexylcarbodiimide
DIB	(diacetoxyiodo)benzene
DM	Dess–Martin reagent
DMF	dimethylformamide
DMSO	dimethylsulphoxide
ether	diethyl ether
eq.	equivalent
GC	gas chromatography
HTI	[hydroxy(tosyloxy)iodo]benzene
IOB	iodosylbenzene
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance
Pr	propyl
PTFE	polytetrafluoroethylene
py	pyridine
Rf	perfluoroalkyl
r.t.	room temperature
sil	trialkylsilyl
TEBA	benzyl triethylammonium chloride
TEMPO	2,2,6,6-tetramethylpiperidine-*N*-oxyl
Tf	triflate, trifluoromethanesulphonate
THF	tetrahydrofuran
THP	2-tetrahydropyranyl
TLC	thin layer chromatography
Tol	*p*-tolyl
TPP	tetraphenylporphyrin
Ts	tosylate
Δ	heating

– 1 –

General Considerations

1.1 INTRODUCTION

The first organic compound of polyvalent iodine – (dichloroiodo)benzene, $PhICl_2$ – was prepared by C. Willgerodt, in 1885. However, it took some 50 years before its first reaction was announced and several more years for really useful synthetic applications. Similarly, the exceptional oxidizing properties of *o*-iodylbenzoic acid, known since 1893, were unveiled only in 1994. In the meantime, an explosive growth occurred in the field of polyvalent iodine, especially during the last 10 years. More than a dozen individual compounds have currently reached the status of reagent, and numerous members from various classes have emerged as valuable synthetic intermediates. The chemistry of hypervalent iodine compounds, as it is appropriate to name them, includes a wealth of important, sometimes unique, reactions, offering powerful synthetic tools. Today, their exclusion from the arsenal of the organic chemist is inexcusable.

The discussion in this book will be restricted essentially to derivatives of iodobenzene and its ring-substituted analogues, functionalized from iodine.

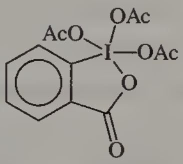
1.2 A NOTE ON CLASSES AND NOMENCLATURE

Several classes of hypervalent iodine compounds are known – some with few and some with many members. The large numbers of compounds, having a valency from 1 to 5, and being coordinated with 2–4 widely differing ligands – from elements to complex organic residues – makes a consistent nomenclature difficult; in fact, systematic names are often too long and hardly usable, even for simple and especially for cyclic compounds. In this book some IUPAC terms have been adopted, even though they are not yet widely accepted: iodanes for λ^3- and λ^5-compounds belonging to the families IL_3 and IL_5 (L = monovalent electronegative ligand); iodosylbenzene for PhIO; and iodylbenzene for $PhIO_2$. However, for other compounds simpler and more easily recognizable names are preferable, in line with current bibliography; for example, *o*-iodosylbenzoic acid for the cyclic 1,3-dihydro-1-hydroxy-3-oxo-1,2-benziodoxole (or 1-hydroxy-1,2-benziodoxoline-3(1*H*)-one) and Dess-Martin reagent for 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one.

The most important reagents can be divided in two broad categories: individual compounds and classes; those most frequently used are illustrated in Table 1.1.

TABLE 1.1

The commonest reagents of hypervalent iodine

	Formula	Abbreviation
a. Individual Compounds		
(dichloroiodo)benzene	$PhICl_2$	-
(diacetoxyiodo)benzene	$PhI(OAc)_2$	DIB
[bis(trifluoroacetoxy)iodo]benzene	$PhI(O_2CCF_3)_2$	BTI
iodosylbenzene	PhIO	IOB
[(hydroxy)(tosyloxy)iodo]benzene	PhI(OH)OTs	HTI
iodylbenzene	$PhIO_2$	-
Dess–Martin reagent		DM
b. Classes		
diaryliodonium salts	$Ar_2I^+ X^-$	
vinyl phenyl iodonium salts	$PhI^+CH{=}CHR\ X^-$	
alkynyl phenyl iodonium salts	$PhI^+C{\equiv}CR\ X^-$	
perfluoroalkyl phenyl iodonium salts	$PhI^+Rf\ X^-$	
iodonium ylides and dipoles	diverse formulas	

1.3 BONDING AND STRUCTURE IN HYPERVALENT IODINE

The concept of hypervalency refers to bonding in elements of Groups V–VIII of the periodic table. It is applied when these elements appear with a valence higher than the normal, or, more correctly, when their outer shell contains 10 or 12 electrons.

In iodanes of the IL_3 type the less electronegative group – usually a phenyl ring –

is bound to iodine by a normal covalent bond, lying in the equatorial position of a trigonal bipyramid. The other two ligands are at axial positions, attached, one to each lobe, to one doubly occupied 5p orbital of iodine. This arrangement results in a linear three-centre four-electron (3c-4e) bond system. In this way a single orbital of iodine participates to two 3c-4e bonds, called usually hypervalent; these are longer and weaker than the covalent bond. Molecules of this kind are T-shaped; the electronic formula for a typical member, (dichloroiodo)benzene, is depicted in Fig. 1.1.

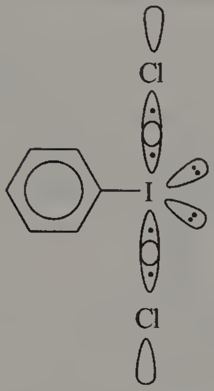


Fig. 1.1 The electronic structure of (dichloroiodo)benzene.

In compounds of hypervalent iodine most of the electron density is placed at the ends of the linear L-I-L triad, explaining why electronegative ligands stabilize iodanes. Among them, fluorine, chlorine, acyloxy and organosulphonyloxy groups, along with some nitrogen-containing groups, are the commonest.

In iodanes of the general formula PhILL$'$ one ligand may be significantly more electronegative than the other, so that such compounds become ionic. In diaryliodonium salts ($Ar_2I^+X^-$), for instance, both iodine–carbon bonds are equivalent, with covalent rather than hypervalent character; the triad C-I-C is bent, forming an angle of about 92°. Exceptional stability is conferred upon these compounds, some of which melt without decomposition above 200°. Strictly speaking, in purely ionic iodonium salts, such as $Ph_2I^+BF_4^-$, there is no hypervalent bonding; however, many members in this series, especially with halide anions, are not ionic, as evidenced by bond distances and their dimeric nature in the crystalline state, from X-ray crystallographic studies. This is why some authors prefer the symbolism $Ph_2I.X$; analogous representations are used for the essentially ionic [hydroxy(tosyloxy)iodo]benzene and other similar compounds.

Two orthogonal hypervalent bonds together with a covalent bond account for bonding in IL_5 iodanes. Depending on the ligands, square pyramidal, pseudo trigonal bipyramid or pseudo octahedral arrangements have been observed. In the crystalline state most λ^3- and λ^5-iodanes form secondary bonds leading to pseudo cyclic structures.

In compounds containing one or two formal double bonds, such as ylides of the general formula $PhI{=}NSO_2R$, and also iodosylbenzene or iodylbenzene, hypervalent bonding is different: here the interaction between two simply occupied orbitals of the bivalent ligand with a doubly occupied 5p atomic orbital of iodine results in the formation of a two-centre four-electron (2c-4e) hypervalent bond. This is highly polarized, so that zwitterionic rather than double-bond notations are nearer a correct assignment. However, for the sake of convenience the double bond notation is usually preferred, for example, $PhI{=}O$ rather than $PhI^+\text{-}O^-$ for iodosylbenzene. It is added that iodosyl and iodylbenzene are actually polymeric; by contrast, ylides of the general formula $PhI{=}CXY$ are monomeric. The electronic structure of iodosylbenzene is depicted in Fig. 1.2.

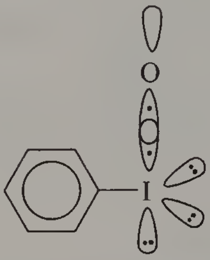


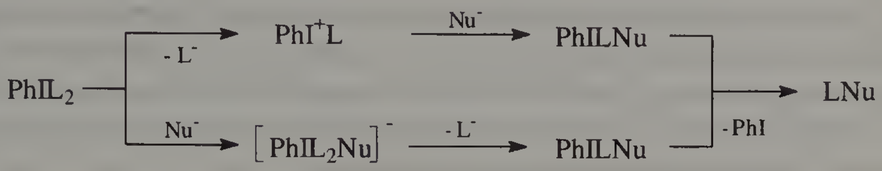
Fig. 1.2 The electronic structure of iodosylbenzene.

Both IL_3 and IL_5 iodanes may formally eliminate the equatorial ligand as a cation; in the resulting IL_2^- and IL_4^- species bonding is still hypervalent, with elongated weak bonds. These iodates have mostly iodine–chlorine or iodine–nitrogen bonds; although some of them are useful reagents, they will not be discussed here.

1.4 REACTIVITY PATTERNS

The rich chemistry of hypervalent iodine is primarily due to its strongly electrophilic character, in combination with the superleaving group ability of the phenyliodonio group. As a consequence, a diversified pattern of reactivity has been established leading sometimes to new, interesting and unsuspected outcomes. Iodine in both λ^3- and λ^5-iodanes is a good soft electrophilic centre which can be attacked by virtually any nucleophile. Depending on substrates and experimental conditions, new iodine species of varying stability are formed upon reaction with substrates ranging from non-functionalized hydrocarbons to complex natural products. The weak hypervalent bonds in these, sometimes isolable, intermediates are readily broken, resulting in reductive elimination of iodobenzene and formation of the end-products. In some instances the phenyl–iodine bond may also break.

The majority of reactions have been performed between compounds of the general formula $PhIL_2$ and nucleophiles (NuH or Nu^-), following either a heterolytic or a homolytic pathway. The former is more common and can be either monomolecular or bimolecular; the final products are often a combination of L with Nu, according to the simplified scheme:



In this mode, an umpolung of reactivity for the nucleophile occurs, leading to many useful transformations. More complex pathways are not unusual: these include addition to multiple bonds, vinylic and acetylenic substitution, rearrangements – some involving ring-expansion or ring-contraction – generation of reactive intermediates, etc. Solvent effects, especially solvent participation, may add new dimensions to reactivity.

Homolytic reactions are fairly numerous; indeed, some of the simplest transformations, such as dehydrogenation and halogenation, are free-radical processes; photochemical conditions or catalysts are not always necessary. For example, [bis(trifluoroacetoxy)iodo]benzene functions with electron-rich aromatics as a radical-cation generating reagent. Other preparatively useful examples of homolytic reactions include additions to multiple bonds, oxidation of alcohols – notably through alkoxy radicals – and azidation of several substrates. One single class of nucleophiles, alkenes, reacts in more than ten different ways with individual hypervalent iodine reagents; in combination with some otherwise unreactive reagents, new pathways open and new products are formed, so that the utility of hypervalent iodine is greatly expanded. A similar pattern of reactivity is observed in the less explored λ^5-iodanes, such as iodylbenzene and Dess–Martin reagent.

Apart from the above two major general reaction pathways, there are some further possibilities; for instance, [bis(trifluoroacetoxy)iodo]benzene reacts as an ambident electrophile and is attacked by hard nucleophiles at its carbonyl carbon, whereas iodylarenes may react similarly from carbon rather than iodine. Alkynyl iodonium salts are actually tetraphilic electrophiles, whereas iodosylbenzene reacts also as a nucleophile from oxygen. Diaryl iodonium salts serve as arylating reagents, mostly homolytically; other iodonium salts transfer groups such as perfluoroalkyl, vinyl, alkynyl or cyano to several nucleophiles in various ways.

Generally, hypervalent iodine reagents are often better than traditional reagents of similar reactivity, with respect to efficiency and chemoselectivity – sometimes even stereoselectivity. Unusual reactivity is another interesting feature which has often resulted in unexpected transformation. Examples of such reactions may be found in the oxidation of nitrogen-containing compounds, the Hofmann rearrangement in acidic conditions, the acetalization of carbonyl compounds in alkali, the remote functionalization of steroids, etc. Some unique transformations were effected in the field of steroids and carbohydrates. A feature not yet adequately exploited is that significant variations are possible within a class of compounds by slightly changing a ligand or a substituent in the benzene ring; in this way a fine-tuning of reactivity might eventually be realized.

The high reactivity of iodanes may be moderated by using cyclic analogues, which constitute considerably milder reagents, because of their less electrophilic character. An additional advantage for those coming from *o*-iodobenzoic acid is that the isolation procedure is simplified. A better idea about the diversity of transformations effected through hypervalent iodine reagents can be formed by inspection of the detailed table of contents as well as the index.

1.5 PRACTICAL ASPECTS

Most hypervalent iodine reagents are obtained from readily available starting materials, namely iodobenzene and ring-substituted analogues. Their preparation does not involve dangerous, demanding or time-consuming methods, as evidenced by the detailed procedures given in the next chapter. Some reagents are commercially available.

All hypervalent iodine reagents are solids – amorphous or crystalline – colourless and odourless. They are fairly stable at room temperature and insensitive to atmospheric oxygen and moisture. The usual precaution required upon storage is simply light-protection and sometimes refrigeration. Easy handling is therefore an important advantage, for example, in weighing accurately (dichloroiodo)benzene for chlorinations. Some compounds such as certain iodonium salts or dipoles are less stable and need not be isolated: they are used *in situ*.

Operational simplicity is an important feature in reactions of hypervalent iodine reagents. They are usually performed in non-complicated apparatus, often in open vessels, at room temperature; elevated or low temperature is seldom required and reaction times, as a rule, are quite short. Protection from humidity is not normally necessary; in fact, in several instances aqueous solvents are used; however, an inert atmosphere is often recommended. Most ordinary solvents are suitable, even when they are themselves reactive – as most are. Expensive catalysts are rarely required. After reaction, work-up procedures normally involve chromatographic separation, especially when iodobenzene is the main by-product. This drawback is offset by the possibility of collecting and recycling this relatively expensive starting material. Indeed, for large-scale preparations the high cost of hypervalent iodine reagents should be taken into account, although they compare favourably with other valuable reagents of similar reactivity. On the other hand, iodobenzene can be disposed of without problems, since it is environmentally acceptable because of its low toxicity and ready biodegradability. When compared to some highly toxic inorganic oxidants such as lead tetraacetate and thallium or mercury salts, iodine reagents are distinctly advantageous; in addition, they often produce higher yields.

It should be noted that on impact or heating in the absence of solvent, a mildly explosive character has been detected for some compounds. Among them, the following are the most frequently used: $PhI(OMe)_2$, PhIO, $PhIO_2$, $(PhI^+)_2O\ 2BF_4^-$, and *o*-iodylbenzoic acid.

This introductory chapter does not contain specific references. Information about bonding, structural (and spectral) properties can be found in a book about polycoordinated iodine [1] and three long chapters in a multiauthored work [2–4]. Review articles covering reactivity and synthetic aspects are numerous; among recent ones cited are those referring to alkenyl and alkynyl iodonium salts [5–7] and to [hydroxy(organosulphonyloxy)iodo]arenes [8]. Of interest also are reviews about carbon–carbon bond forming reactions [9] and synthetic applications to natural products [10]; literature coverage of the latest comprehensive review [11] is through the middle of 1995.

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Preparative Methods for Hypervalent Iodine Reagents

In most cases iodobenzene or some ring-substituted analogues, especially iodobenzoic acid, are the starting materials through which hypervalent iodine reagents are prepared. It is emphasized that most preparations are very convenient, so that it is not necessary to purchase commercially available compounds; these and their suppliers include:

(Diacetoxyiodo)benzene: Aldrich, Fluka, Lancaster, Merck
[Bis(trifluoroacetoxy)iodo]benzene: Aldrich, Fluka
[Bis(trifluoroacetoxy)iodo]pentafluorobenzene: Aldrich, TCI America
Iodosobenzene: ICN, TCI America
2-Iodosobenzoic acid: Aldrich, Fluka
[Hydroxy(tosyloxy)iodo]benzene: Aldrich
Diphenyliodonium-2-carboxylate: Lancaster
Diphenyliodonium chloride, bromide, and iodide: Aldrich, Lancaster
Perfluoroalkyl phenyliodonium salts: TCI America

Because of the multitude and diversity of iodonium salts and zwitterions, some of which are labile or are prepared for specific purposes, their preparative methods are discussed in Chapter 8, for diaryl iodonium salts and related compounds, Chapter 9 for perfluoroalkyl, alkenyl and alkynyl phenyliodonium salts and Chapter 10 for zwitterionic iodonium compounds. In addition, the preparation of some lesser known reagents, including 2-iodosylbenzoic acid, is given in Chapter 12.

2.1 [BIS(ACYLOXY)IODO]ARENES

Although several methods are available for the preparation of the title compounds, in practice the starting material is (diacetoxyiodo)benzene (DIB). The standard method for its preparation is direct oxidation of iodobenzene with either peracetic acid [1] or sodium perborate in acetic acid [2]. The first method appears to be preferable; it requires great care in maintaining temperature at exactly 40°C: at a lower temperature the reaction fails completely, whereas at a higher temperature overoxidation occurs. Also, the reaction fails with old samples of hydrogen peroxide which have lost their original titre. The perborate method is simpler and temperature control needs not be as strict; however, it is more expensive and the yield of DIB is lower. It is considered suitable for small scale preparations of (diacetoxyiodo) arenes.

(Diacetoxyiodo)benzene, DIB [1]

$$\mathrm{PhI} \xrightarrow[\mathrm{Ac_2O}]{\mathrm{H_2O_2}} \mathrm{PhI(OAc)_2}$$

A stirred mixture of acetic anhydride (305 ml) and 30% hydrogen peroxide (70 ml) was kept at exactly 40°C for 4 h; the use of a thermostated bath is strongly recommended. To the resulting peracetic acid solution, iodobenzene (52 g, 28.5 ml) was added with stirring over 15 min and the clear reaction mixture was kept overnight at room temperature. A part of DIB crystallized out and was collected; then ice–water (~ 400 ml) was added to the filtrate and a further crop of crystals was obtained. The combined material was washed with cold water and petroleum ether and was dried in a desiccator over sodium hydroxide to yield 55–65 g (67–79%) of crude DIB, m.p. 156–159°C (recrystallized from chloroform, m.p. 163–165°C); this purity is satisfactory in most cases.

DIB is stable in the air; it can be stored at room temperature for long periods, provided it is light-protected. It dissolves in several ordinary solvents, most of which react with it at elevated temperature. A study in some solvents, using iodometric titration for monitoring the loss of oxidation power of DIB with time, showed that benzene is one of the most inert: DIB remained unaltered in it at 25–50°C after 24 h. In contrast, in dimethylsulphoxide (DMSO) at 25°C 97% decomposed after 24 h. Acetone, methanol, methylene chloride, chloroform, acetic acid and acetonitrile are suitable solvents at room temperature even though they are reactive at elevated temperature [3]. Anyway, heating is rarely required in reactions with DIB and in such cases it is for short periods of time, so that the solvent reaction is unimportant.

[Bis(trifluoroacetoxy)iodo]benzene (BTI) [4]

$$\mathrm{PhI(OAc)_2} \xrightarrow{\mathrm{CF_3CO_2H}} \mathrm{PhI(O_2CCF_3)_2}$$

(Diacetoxyiodo)benzene (20 g) was dissolved in boiling trifluoroacetic acid (25 ml); on cooling to room temperature BTI crystallized out as colourless crystals of good purity (17 g, 60%). The product was washed with petroleum ether and dried in a desiccator over potassium hydroxide. A second crop was obtained by cooling at 0°C; this was contaminated with (diacetoxyiodo)benzene and should be collected separately; when a sufficient quantity accumulated from several batches, it was treated with trifluoroacetic acid as above. Complete removal of the solvent is not recommended because some decomposition occurs at elevated temperature; in the presence of acetic acid the oxygen-bridged *meso* compound $PhI(OOCCF_3)OI(OOCCF_3)Ph$ may also be formed. The filtrate is a mixture of trifluoroacetic acid and acetic acid which differ substantially in their boiling points, so that most of the more volatile (and expensive) trifluoroacetic acid (b.p. 74°C) may be recovered by fractional distillation.

Pure BTI is obtained by recrystallization from acetone–petroleum ether (m.p. 112–120°C with decomposition, depending on the rate of heating). It is soluble in several organic solvents, such as acetone, acetonitrile, chloroform, dichloromethane, ethanol and ether. Most of them react slowly with BTI, even at room temperature; nevertheless, since its reactions do not require heating and are completed in a short time, by-products from reactions with the solvent are minimal and do not pose a problem. The reagent is fairly stable and can be kept without refrigeration for a long period of time, with light protection.

Exchange reactions of DIB with practically any acid is the most convenient method for the preparation of [bis(acyloxy)iodo]benzenes.

[Bis(acyloxy)iodo]benzenes [5]

$$PhI(OAc)_2 \xrightarrow{RCO_2H} PhI(O_2CR)_2$$

A solution of DIB (6 g, 18.6 mmol) and the acid (37.2 mmol) in chlorobenzene (75 ml) was treated in a rotary evaporator to 50–55°C, until the solvent and acetic acid were completely evaporated. The residue obtained was essentially pure [bis(acyloxy)iodo]benzene, in nearly quantitative yield.

Alternative methods involved nucleophilic substitution at iodine in (dichloroiodo)benzene or BTI by the acyloxy group of silver or sodium carboxylates; the latter permits the preparation of mixed [bis(acyloxy)iodo]benzenes with two different acyloxy groups [6]. Also, heating of iodosylbenzene and an acid (molar ratio 1:2) in chloroform results in the formation of [bis(acyloxy)iodo]benzenes quantitatively. A stable (diformyloxyiodo)arene from

2-nitro-4-methyl-iodosylbenzene and formic acid has been prepared in this way in the old literature [7].

Direct oxidation of pentafluoroiodobenzene in fluorotrichloromethane resulted in the preparation of perfluoro DIB, $C_6F_5I(O_2CCF_3)_2$; the oxidant was trifluoroperacetic acid formed *in situ* from 91% hydrogen peroxide and trifluoroacetic anhydride [8]. Heating of $C_6F_5I(O_2CCF_3)_2$ with pentafluorobenzoic acid in carbon tetrachloride resulted in the formation of $C_6F_5I(O_2CC_6F_5)_2$ [9]. Similar methods have been applied for the preparation of [bis(trifluoroacetoxy)iodo]perfluoroalkanes, i.e. either oxidation of perfluoroiodides with trifluoroperacetic acid [10], or reactions of (dichloroiodo)perfluoroalkanes with silver trifluoroacetate [11].

2.2 (DIFLUOROIODO)- AND (DICHLOROIODO)ARENES

The most practical method for the preparation of (difluoroiodo)arenes is from (dichloroiodo)arenes on reaction with mercuric oxide and hydrofluoric acid.

(Difluoroiodo)arenes [12]

$$\mathrm{ArICl_2} \xrightarrow[\mathrm{HgO}]{\mathrm{HF}} \mathrm{ArIF_2}$$

The (dichloroiodo)arene (40 mmol) and finely ground yellow mercuric oxide (10.8 g, 50 mmol) were shaken in a polyethylene bottle with dichloromethane (100 ml). Hydrofluoric acid (48%, 10 ml) was added and the bottle shaken vigorously for about 1 min. The colour of the solution turned from bright yellow to nearly colourless. Then the solvent phase was carefully decanted. The residue was shaken with dichloromethane (50 ml) which was combined with the original solution. The reagent formed was used in this solution for fluorination. In order to find its titre, a portion (1 ml) was analysed by titration of the iodine liberated by reaction with aqueous potassium iodide. The yield was calculated to be in the range 60–90%.

Several (difluoroiodo)arenes are stable at room temperature; when they are pure, they melt without decomposition. However, they present difficulties in handling and usually their preparation *in situ* is preferable. They can be kept in PTFE or polyethylene containers but not in glass containers, since glass is slowly attacked.

The direct chlorination of iodoarenes is a very effective and convenient method to obtain (dichloroiodo)arenes in good yield; this approach was recommended for the purification of arenes. The method described in *Organic Syntheses* [13] is also suitable for a wide number of iodoarenes. An alternative new method involved the oxidation of iodoarenes with a mixture of sodium perborate and hydrochloric acid, in acetonitrile or carbon tetrachloride.

(Dichloroiodo)arenes [14]

$$\mathrm{ArI} \xrightarrow[\mathrm{NaBO_3 \cdot 4\,H_2O}]{\mathrm{HCl}} \mathrm{ArICl_2}$$

Sodium perborate tetrahydrate (770 mg, 5 mmol), was added to a stirred solution of the iodoarene (1 mmol) in a mixture of hydrochloric acid (20 ml) and either acetonitrile or carbon tetrachloride (20 ml); the latter was more effective for all three iodoanisoles. The mixture was stirred at room temperature for 2 h (with the exception of *p*-diiodobenzene which required 3 days) and then was diluted with water (100 ml). The resulting solid which separated was collected, washed with water and light petroleum and dried.

(Dichloroiodo)arenes are yellow crystalline compounds, heat- and light-sensitive. They are stable enough to be handled without special precautions and do not hydrolyse by moisture. Several of them can be kept for long periods of time under refrigeration without any alteration, whereas others should be used as rapidly as possible after preparation. In organic solvents they dissociate partially to iodoarenes and chlorine.

2.3 IODOSYLARENES

With the exception of cyclic '*o*-iodosylbenzoic acid' (Section 12.1), unsubstituted iodosylbenzene is normally the reagent of choice. The best methods for its preparation involve hydrolysis of either (dichloroiodo)- or (diacetoxyiodo)benzene. Both have been described but the latter is more convenient and has a better yield.

Iodosylbenzene [15]

$$\mathrm{PhI(OAc)_2} \xrightarrow[\mathrm{H_2O}]{\mathrm{NaOH}} \mathrm{PhIO}$$

Finely ground DIB (32.2 g, 10 mmol) was placed in a 250 ml beaker, and 150 ml of 3N sodium hydroxide was added over 5 min with vigorous stirring. The mixture was triturated with a spatula for 15 min in order to become homogeneous. After standing for 45 min, water was added (100 ml) with vigorous stirring and the solid collected on a Buchner funnel; it was returned to the beaker and triturated in water (200 ml), collected again, washed with water (3 × 200 ml) and dried by maintaining suction. Further purification was effected by triturating this solid in chloroform (75 ml). After air-drying, iodosylbenzene (18.7–20.5 g, 85–93%) was obtained, m.p. 210°C. HAZARD: the compound explodes at its m.p. In some reactions best results were obtained when it was well-crushed and kept over P_4O_{10} for 2–3 weeks. When left at room temperature for long periods of time, iodosylbenzene disproportionates to iodobenzene and iodylbenzene.

2.4 [HYDROXY(TOSYLOXY)IODO]BENZENE AND ITS ANALOGUES

The standard method for the preparation of [hydroxy(tosyloxy)iodo]benzene (HTI) is the reaction of (diacetoxyiodo)benzene (DIB) with *p*-toluenesulphonic acid hydrate.

[Hydroxy(tosyloxy)iodo]benzene, HTI [16]

$$\mathrm{PhI(OAc)_2} \xrightarrow[\mathrm{MeCN}]{\mathrm{TsOH.\,H_2O}} \mathrm{PhI(OH)OTs}$$

p-Toluenesulphonic acid monohydrate (7.61 g, 40 mmol) dissolved in a minimum amount of acetonitrile was added to a suspension of DIB (6.44 g, 20 mmol) in acetonitrile (45 ml) at room temperature. The reaction mixture was allowed to stand for a few hours; crystals of HTI separated (two crops may be collected) in a total yield of 93% (7.62 g). The crude product was washed with acetone (removes *p*-toluenesulphonic acid) and ether (removes acetic acid). It may be recrystallized from acetonitrile or methanol–ether; m.p. 140–142°C.

HTI is a stable crystalline compound, which may be stored at room temperature. It is slightly soluble in dichloromethane (5.3 mg/ml) and moderately soluble in water (1 g/42 ml); in most ordinary solvents it is practically insoluble and it usually enters into reactions from suspensions.

The preparation of HTI analogues, for example with a camphorsulphonyloxy group in the place of the tosyloxy group, was effected similarly [17]. Also, phenyl substituted analogues have been obtained by this procedure or through metathetical reactions between HTI and iodoarenes [18].

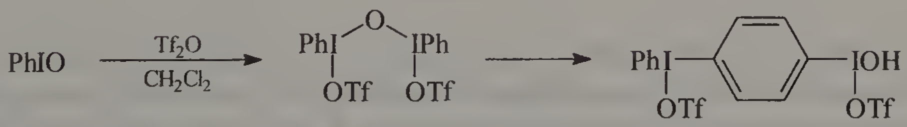
[Methoxy(tosyloxy)iodo]benzene was prepared by simply dissolving HTI in trimethyl orthoformate [19]:

$$\mathrm{PhI(OH)OTs} \xrightarrow[86\%]{\mathrm{HC(OMe)_3}} \mathrm{PhI(OMe)OTs}$$

An exchange reaction between HTI and some optically active alcohols (R*OH) was used for the preparation of compounds of the general formula PhI(OR*)OTs [20].

1,4-Bis(iodosyl)benzene reacted with triflic anhydride to afford a bis iodine (III) derivative [21]. DIB or iodosylbenzene, however, do not afford with triflic acid, or its anhydride, the expected analogues of HTI, although these are initially formed. The reaction of iodosylbenzene and triflic anhydride leads to two different products, depending on reaction time. When triflic acid was allowed to react with iodosylbenzene in dichloromethane for about 20 min the yellow μ-compound **1** (m.p. 100–110°C) was obtained; it was the same with the so-called Zefirov's reagent, which was originally prepared from DIB and triflic acid in chloroform. When the reaction time was extended to 12 h, then **1** isomerized to the slightly pale yellow compound **2** (m.p. 125–132°C). For preparative purposes the direct reaction of iodosylbenzene with triflic acid was preferable for **2**, since it was isolated in 94% yield.

μ-Oxo-bis[(trifyloxy)(phenyl)]iodine, 1 [22]



1 **2**

Triflic anhydride (1.17 g, 4.14 mmol) in dry dichloromethane (5 ml) was added slowly at room temperature to a stirred mixture of freshly prepared and carefully dried iodosylbenzene (1.77 g, 8.05 mmol), in dichloromethane (5 ml). The reaction was carried out in a flame-dried 50 ml three-neck flask under nitrogen. The solution became homogeneous after 5 min and a yellow solid precipitated after another 20 min. This was collected on a Schlenk filter under nitrogen, rinsed with dichloromethane (3 × 5 ml) and dried *in vacuo*, affording **1** (1.64 g, 93%), mildly air-sensitive but thermally stable.

1-[Hydroxy(trifyloxy)iodo]-4-[(phenyl)(trifyloxy)iodo]benzene, 2 [23]

$$\mathrm{PhIO} \xrightarrow[\mathrm{CH_2Cl_2}]{\mathrm{TfOH}} \mathbf{2}$$

To a stirred suspension of iodosylbenzene (10 mmol) in dry dichloromethane (20 ml) was slowly added, dropwise, triflic acid (3 g, 20 mmol) at 0°C. The reaction mixture was stirred for 4 h at room temperature, concentrated and dry ether was added to the residue. Compound **2** crystallized upon trituration, was washed with dry ether and dried *in vacuo*; it could be handled at room temperature without any special precaution.

2.5 REAGENTS OF IODINE (V)

The preparation of iodylbenzene has been described in *Organic Syntheses* from (dichloroiodo)benzene [24]; an alternative simpler method involved the direct oxidation of iodobenzene using aqueous hypochlorite and phase transfer catalysis.

Iodylbenzene [25]

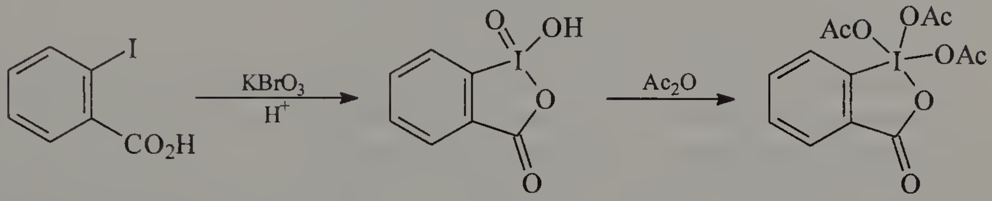
$$\mathrm{PhI} \xrightarrow[\text{cat.}]{\mathrm{HOCl}\,/\,\mathrm{H_2O}} \mathrm{PhIO_2}$$

Iodobenzene (1.01 g, 4.9 mmol) was dissolved in dichloromethane (75 ml) and stirred vigorously with hypochlorite solution (200 ml of commercial laundry bleach adjusted to pH 8.2 and containing 200 mg of tetrabutylammonium hydrogen sulphate) at room temperature for 45 min. The reaction mixture was allowed to stand for 1 h; then the precipitate was filtered to give crude iodylbenzene (0.69–0.94 g, 59–81%). Purification may be effected by crystallization from water or acetic acid.

HAZARD: the melting point of iodylbenzene (231–240°C) is also its decomposition point, accompanied by explosion. Generally, all iodylbenzenes are potentially explosive when heated; a violent decomposition of iodylbenzene (dry sample) has been induced by scraping with a spatula.

The Dess–Martin reagent was prepared in two steps from *o*-iodobenzoic acid which was first converted into the isolable '*o*-iodylbenzoic acid', of cyclic structure. The original procedure for the second step was substantially improved.

a. *1-Oxido-1-hydroxybenziodoxol-3*(1H)*-one (o-iodylbenzoic acid)* [26]
b. *1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3*(1H)*-one* [27,28]
(Dess-Martin reagent)



a. Potassium bromate (76 g, 0.45 mol) was added to a vigorously stirred mixture of 2-iodobenzoic acid (85.2 g, 0.34 mol) and sulphuric acid (730 ml of 0.73 M) over 30 min, in a 55°C bath. The mixture was warmed to 68°C with stirring for 3.6 h. The precipitate formed on cooling in an ice bath was filtered and washed with water (11 ml) and ethanol (2 × 50 ml) to give the intermediate *o*-iodylbenzoic acid (89 g, 93%) m.p. 232–233°C.

b. This compound (100 g, 0.235 mol) was added to a 1-l flask containing acetic anhydride (400 ml) and *p*-toluenesulphonic acid hydrate (0.5 g) and the mixture was stirred for 2 h in an oil bath at 80°C, with protection from humidity with a drying tube. The reaction mixture was cooled in an ice bath and the precipitate was filtered through a fritted glass funnel, followed by rinsing with anhydrous ether (5 × 50 ml). The resulting title compound (138 g, 91%) was quickly transferred to an argon flushed amber-glass bottle and stored in the cold (m.p. 134°C).

HAZARD: the intermediate *o*-iodylbenzoic acid is explosive on heating above 200°C and also upon impact; the Dess–Martin reagent explodes violently on heating under confinement, at 130°C.

The mono-acetylated form of the above *o*-iodylbenzoic acid, i.e. 1-acetoxy-1,2-benziodoxol-3(1*H*)-one-1-oxide, is probably the actual oxidizing species [28].

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– 3 –

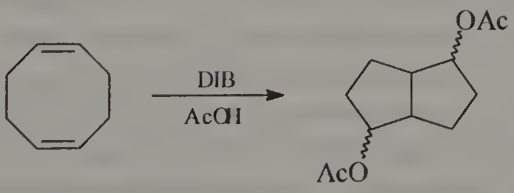
(Diacetoxyiodo)benzene

This is one of the most popular reagents of hypervalent iodine, used in 1939 in acetoxylations of ethylenic double bonds [1]. Apart from oxidations of a great diversity (diacetoxyiodo)benzene (DIB), has found applications in several other useful transformations, including α-functionalization of carbonyl compounds, carbon–carbon bond forming reactions, rearrangements, cyclizations, etc. Also, it is a good starting material for the preparation of other hypervalent iodine compounds. In several instances DIB is used in combination with other reagents.

3.1 ACETOXYLATION

Although some nucleophilic alkenes and cyclopentadiene [1] upon treatment with DIB readily added two acetoxy groups, generally isolated double bonds are inert under mild conditions. An interesting reaction of preparative importance was the intramolecular cyclization of 1,5-cyclooctadiene.

2,6-Diacetoxybicyclo[3.3.0]octane [2]



A 1-l oven-dried flask equipped with a reflux condenser and a drying tube was charged with DIB (100 g, 0.31 mol) and glacial acetic acid (300 ml). To this stirred mixture 1,5-cyclooctadiene (25 g, 0.23 mol) was added and the system was refluxed for 16 h. The reaction mixture was concentrated and the residue distilled to afford the title compound (29.1–30.5 g, 56–58%) as a pale liquid, b.p. 74–84°C (0.06 mmHg) as a mixture of three stereoisomers, the major of which was the di-*exo*-diacetate.

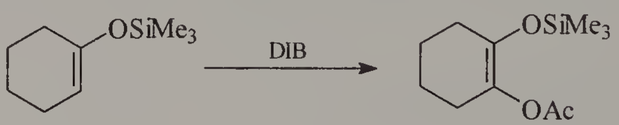
In the presence of strong acids the reactivity of DIB is enhanced, because of its dissociation to the more reactive cationic species:

$$PhI(OAc)_2 + H^+ \rightleftharpoons PhI^+OAc + AcOH$$

Using tetrafluoroboric acid, several unsaturated acids and nitriles were thus made reactive and were converted into acetoxy lactones [3]. Tosyloxy-, phosphoryloxy- and iodomethyl lactones as well as cyclic ethers resulting from analogous neighbouring group participation will be discussed in connection with other hypervalent iodine reagents.

Acetophenones, aliphatic and cyclic ketones were α-acetoxylated by DIB in acetic acid–acetic anhydride, in the presence of sulphuric acid, in moderate yield; some *β*-diketones were similarly acetoxylated at the methylene carbon. The more reactive trimethylsilyl ethers reacted at room temperature without acid catalysis, with retention of their silyl group; the products came either from substitution of the vinylic hydrogen or from bis acetoxylation of the double bond.

1-Trimethylsilyloxy-2-acetoxy-cyclohexene [4]

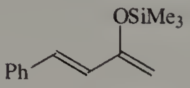
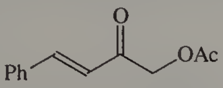
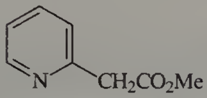
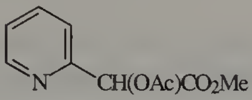
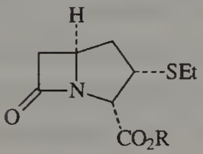
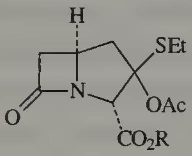


To a stirred solution of DIB (3.2 g, 10 mmol) in dichloromethane (40 ml) the silyl ether (1.7 g, 10 mmol) in dichloromethane (20 ml) was added at room temperature, under argon. After 6 h, the reaction mixture was concentrated and the residue extracted with pentane; the extract was concentrated and then distilled to give 1-trimethylsilyloxy-2-acetoxy-cyclohexene (1.78 g, 78%), b.p. 55°C (0.2 mmHg). A by-product (7%) was 1,2-diacetoxy-1-trimethylsilyloxy-cyclohexane.

Some acetoxylations of various substrates are listed in Table 3.1. It should be noted that the experimental conditions may vary widely; for example, allenic ethers reacted at – 78°C, whereas arylacetonitriles required reflux in acetonitrile and catalysis by benzoyl peroxide.

TABLE 3.1

Acetoxylations mediated by DIB

Substrate	Product	Yield (%)	Ref.
p-$ClC_6H_4COCH_3$	*p*-$ClC_6H_4COCH_2OAc$	56	[5]
		78	[4]
$H_2C{=}C{=}CHOR$	$HC{\equiv}CCH(OAc)(OR)$	63–68	[6]
$ArCH_2CN$	$ArCH(OAc)CN$	79–87	[7]
		90	[8]
		60	[9]
Ar_2Te	$Ar_2Te(OAc)_2$	89–97	[10]

An unusual type of acetoxylation occurred in acetanilides of the general formula 4-R-C_6H_4NHAc, where R was an electron donor; upon reaction with DIB they were converted into 3-acetoxy derivatives, after a complex sequence of events in which the acetoxy groups entered the aromatic ring as a nucleophile [11].

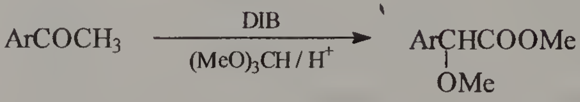
3.2 TRANSFORMATIONS OF CARBONYL COMPOUNDS

Apart from acetoxylation, carbonyl compounds undergo a variety of transformations with DIB in combination with alkali and methanol or trimethyl orthoformate. The nature of the substrates is often critical in determining the outcome of a reaction.

3.2.1 Ketones with acidic DIB

Many reactions of ketones were performed with methanolic DIB in either an acidic or alkaline environment. When DIB is dissolved in methanol (or other alcohols) an exchange with acetate takes place, so that the reacting species may be $PhI(OMe)OAc$ or $PhI(OMe)_2$; the latter is actually an isolable compound [12]. Oxidation of methanol at room temperature is negligible. Acetophenones react with DIB in methanol–sulphuric acid affording mixtures of α-methoxyacetophenones (minor products) and rearranged esters. A solvent change from methanol to trimethyl orthoformate combined with the use of two equivalents of DIB resulted in an efficient double transformation to rearranged methyl α-methoxyarylacetates.

Methyl α-methoxyarylacetates from acetophenones [13]

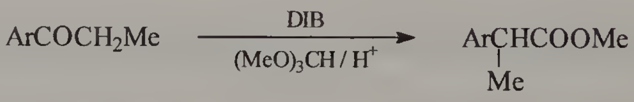


$$\mathrm{ArCOCH_3} \xrightarrow[\mathrm{(MeO)_3CH\,/\,H^+}]{\mathrm{DIB}} \mathrm{Ar\underset{\displaystyle OMe}{C}HCOOMe}$$

A mixture of DIB (70.8 g, 22 mmol), the acetophenone (10 mmol) and sulphuric acid (0.25 ml) in trimethyl orthoformate (30 ml) was stirred overnight at room temperature. Concentration was followed by treatment of the residue with saturated aqueous sodium bicarbonate, extraction with dichloromethane (3 × 50 ml), drying and concentration. The residue was purified by column chromatography on silica gel (benzene–petroleum ether, 4:1) to yield methyl α-methoxyarylacetates in 80–84% yield.

Propiophenones showed a different behaviour, under similar conditions, as shown below.

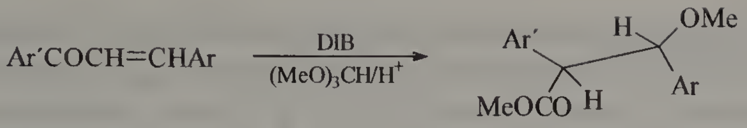
Methyl α-methylaryl acetates from propiophenones [14]



$$\mathrm{ArCOCH_2Me} \xrightarrow[\mathrm{(MeO)_3CH\,/\,H^+}]{\mathrm{DIB}} \mathrm{Ar\underset{\displaystyle Me}{C}HCOOMe}$$

Sulphuric acid (2 mmol) was added dropwise to a stirred solution of DIB (0.386 g, 1.2 mmol) and the propiophenone (1 mmol) in trimethyl orthoformate (3 ml), at room temperature. The mixture was stirred for 5–60 min at 0 or 60°C, quenched with water (10 ml) and extracted with ether (2 × 10 ml). The extract was washed with water (20 ml), dried and concentrated; the residue was purified by column chromatography (silica gel) or by distillation to give the pure methyl α-methylaryl acetates in 81–88% yield.

Under the same conditions 3-aroylpropionic acids were similarly converted cleanly into rearranged 2-arylsuccinates (~80%). Methoxylation accompanied by rearrangement occurred in chalcones which afforded diastereoselectively 2,3-diaryl-3-methoxypropanoates [15]:

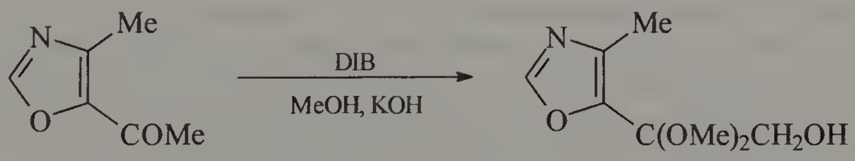


Some of these transformations were previously effected with the highly toxic thallium(III) nitrate; this and other heavy metal salts are unsuitable for the preparation of pharmaceuticals.

3.2.2 Ketones with DIB–methanol–potassium hydroxide

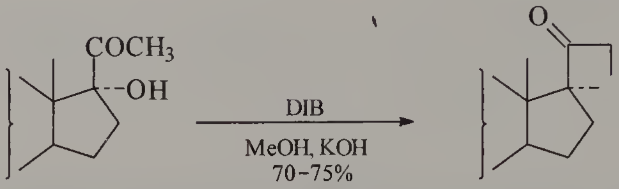
Enolizable ketones were converted directly into their α-hydroxy dimethyl acetals upon reaction with DIB and methanolic potassium hydroxide at room temperature. If, during work up, there was acid treatment, then α-hydroxyketones were directly obtained. Numerous examples are known for such transformation, e.g. with 3-pentanone, acetophenones, 2,6-diacetylpyridine [16], tropan-3-one [17], *β*-aminoketones of great structural variety [18], etc.; even a free radical reacted successfully in this way [19]. This conversion for an acetyl-oxazole served for the preparation of pyrimidine derivatives.

5-(2-Hydroxy-1,1-dimethoxyethyl)-4-methyloxazole [20]



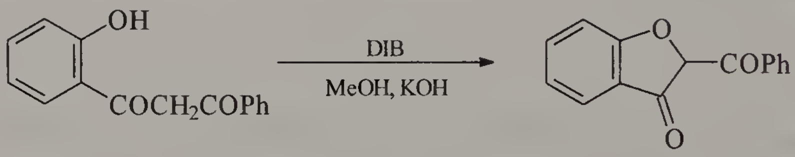
A solution of 5-acetyl-4-methyloxazole (12.5 g, 0.1 mol) in methanol (125 ml) was added dropwise to a stirred solution of potassium hydroxide (17.5 g, 0.31 mol) in methanol (250 ml) over 10 min at 0–5°C. After 5 min, DIB (36 g, 0.11 mol) was added in five portions over 10 min; stirring continued for 4 h at 0–5°C and the reaction mixture was left overnight at room temperature. Then, potassium carbonate was added to saturation and the mixture extracted with dichloromethane (5 × 75 ml). The extract was dried and concentrated; addition of benzene (HAZARD) and cooling afforded 5-(2-hydroxy-1,1-dimethoxyethyl)-4-methyloxazole (13 g, 69%), m.p. 63–64°C (from hexane–ether).

Some deviations from this normal route which involves an oxirane intermediate occurred in sterically hindered ketones. For example, 2,2,6,6-tetramethyl-4-piperidine underwent α-methoxylation (20%) [19], whereas cholestanone yielded a product of Favorski-type rearrangement [21]. In 17-acetylated steroids the reaction with DIB-MeOH-KOH was normal but in 17-hydroxy-17-acetyl-steroids intramolecular cyclization occurred with formation of oxetanones [22]:



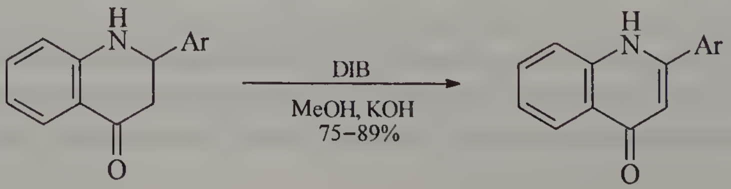
A relevant neighbouring group participation was noted in the oxidative cyclization of *o*-hydroxy-acetophenone [23] and *o*-hydroxy-dibenzoylmethane.

2-Benzoyl-coumarano-3-one from o*-hydroxy-dibenzoylmethane* [24]

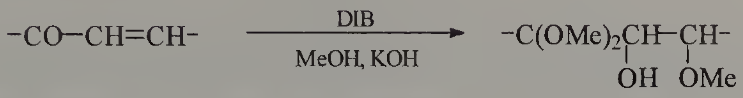


o-Hydroxy-dibenzoylmethane (1.2 g, 5 mmol) in methanol (20 ml) was added to a stirred solution of potassium hydroxide (1.68 g) in methanol (25 ml) at 0–5°C. DIB (1.77 g, 5.5 mmol) was added in small portions and stirring continued at 0–5°C for 1 h and at room temperature for 2 h. Concentration followed by addition of a saturated solution of ammonium chloride resulted in the separation of 2-benzoyl-coumarano-3-one (0.83 g, 70%), m.p. 300°C (from ethanol).

Although flavanones [25] and thioflavanones [26] gave normally under these conditions the expected α-hydroxy dimethyl acetals, their aza analogues, 2-aryl-tetrahydroquinolones, afforded dehydrogenation products [27]:

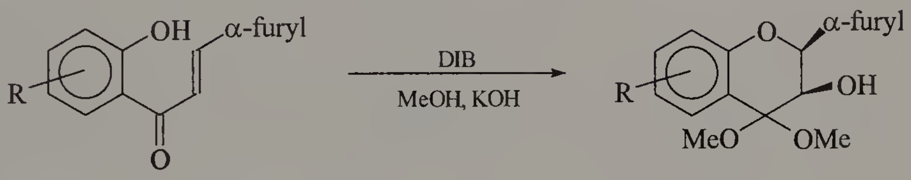


α,*β*-Unsaturated aldehydes and ketones are also reactive towards DIB-MeOH-KOH. Normally the double bond adds hydroxy and methoxy groups, with acetalization, according to the pattern:



$$-\mathrm{CO{-}CH{=}CH}- \xrightarrow[\text{MeOH, KOH}]{\text{DIB}} -\mathrm{C(OMe)_2}\underset{\mathrm{OH}}{\mathrm{CH}}{-}\underset{\mathrm{OMe}}{\mathrm{CH}}-$$

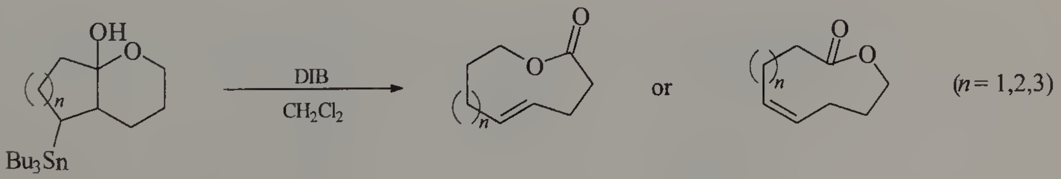
Chalcone, chromone, flavone, *trans*-cinnamaldehyde, cyclopentenone, etc. gave the corresponding products in satisfactory yields [28]. The oxidation of some disubstituted α,*β*-unsaturated cyclic ketones, however, gave predominantly hydroxylated products [29]. An interesting variation was the synthesis of *cis*-hydroxyflavanones from 2′-hydroxychalcones, e.g. [30]:



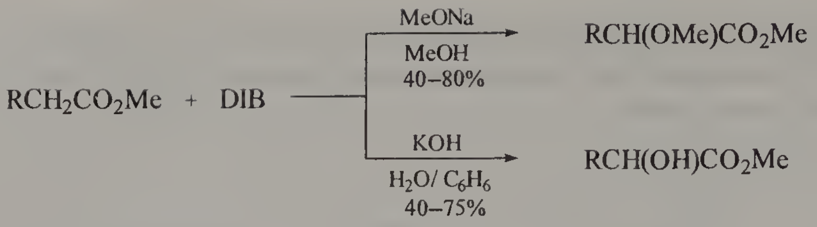
2-Hydroxychalcones with electron donating and relatively bulky substituents afforded directly cyclodehydrogenation products, i.e. flavones [31].

3.2.3 Other carbonyl compounds and esters

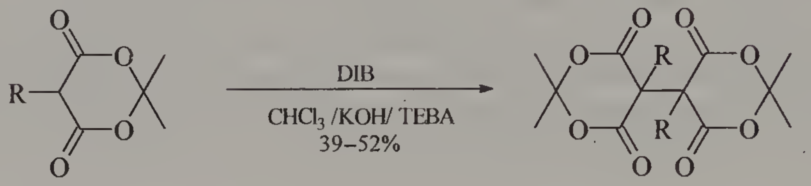
γ-Stannylated hemiacetals (lactols), obtained from cyclo-α,*β*-alkenones, on treatment with DIB underwent 1,4-oxidative fragmentation and were converted into unsaturated medium ring lactones [32]:



Esters of various types gave different products with DIB depending on the kind of base and solvent used, e.g. [33]:

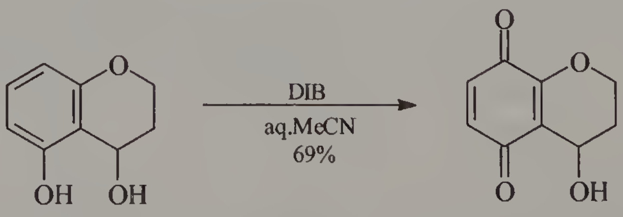

RCH$_2$CO$_2$Me + DIB
MeONa
MeOH
40–80%
RCH(OMe)CO$_2$Me
KOH
H$_2$O/ C$_6$H$_6$
40–75%
RCH(OH)CO$_2$Me

Oxidative coupling occurred in several isopropylidene-5-alkyl malonates (Meldrum's acid derivatives) on treatment with DIB under phase transfer catalysis [34]:


R
DIB
CHCl$_3$ /KOH/ TEBA
39–52%
R
R

3.3 PHENOLIC OXIDATION

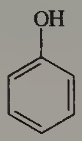
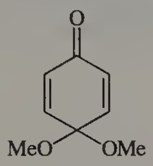
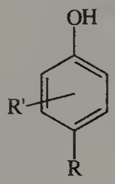
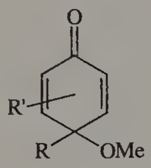
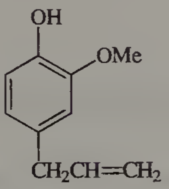
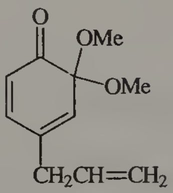
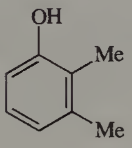
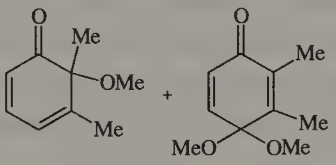
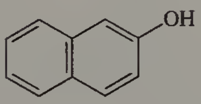
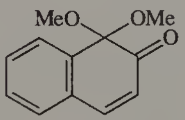
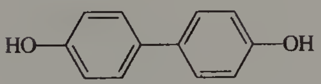
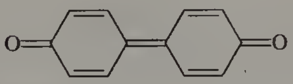
The use of hypervalent iodine reagents in oxidation of simple or complex phenols has been an exceptionally fertile area in synthetic transformations. A variety of products may result in this way involving mainly dehydrogenation and oxygenation, but also oxidative addition, with carbon–carbon or carbon–oxygen bond formation, inter- or intramolecularly. DIB and some analogues (Sections 4.3 and 4.7) are among the most widely used reagents. Several complex phenols were converted by DIB into *p*-benzoquinones, e.g. [35]:


OH
OH
DIB
aq.MeCN
69%
OH

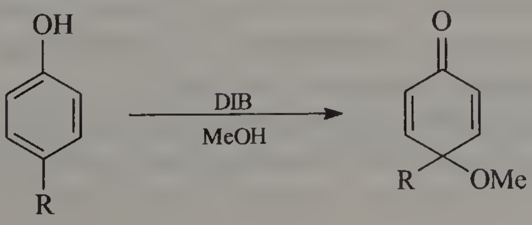
Nucleophilic solvents change the products, since they participate in phenolic oxidation, as amply demonstrated with methanol. A great number of phenols were converted in methanolic DIB into either quinol ethers or quinol acetals, i.e. 4,4-dimethoxy- or 4-alkyl-4-methoxy-cyclohexa-2,5-dienones, depending on the constitution of the substrate. Representative examples are collected in Table 3.2.

TABLE 3.2

Phenolic oxidation by DIB in methanol

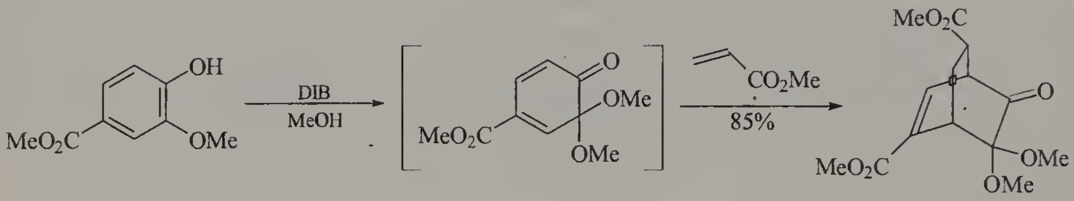
Substrate	Product	Yield (%)	Ref.
		68	[36]
		80–99	[36,37]
 OH OMe CH₂CH=CH₂	 O OMe OMe CH₂CH=CH₂	'high'	[38]
	 O Me OMe Me + O Me Me MeO OMe	1:4, 'high'	[38]
		78	[39]
		70	[40]

Oxidation of 4-substituted phenols by DIB in methanol [36]


OH
R
DIB
MeOH
O
R
OMe

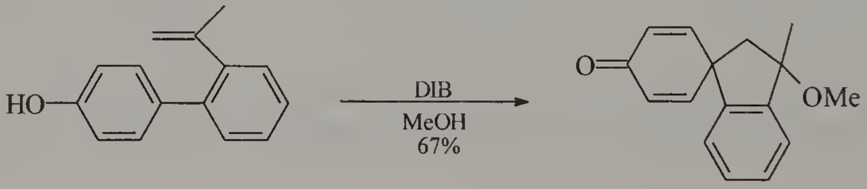
In a dry nitrogen flushed 100 ml flask sealed with a septum were placed the phenol (5 mmol) and dry methanol (10 ml). A solution of DIB (1.61 g, 5 mmol) in methanol (25 ml) was transferred via a double-ended needle to the stirred phenolic solution at room temperature over 40 min. After 40 min, the reaction mixture was concentrated and the residue was purified by column chromatography (silica gel, light petroleum to dichloromethane) to afford the title compounds in 65–99% yield.

o-Benzoquinone acetals are usually not very stable, tending to dimerize; they have been prepared *in situ*, in order to serve as dienes in inter- and intramolecular Diels–Alder reactions, for example, [41]:



Both *o*- and *p*-quinone acetals, also prepared *in situ*, reacted with 3-cyanophthalide affording hydroxy-anthraquinones [38].

Of special interest at present are phenolic compounds bearing suitable substituents which can undergo intramolecular cyclization induced by DIB. For example, whereas 4-hydroxybiphenyls normally gave in methanol the expected quinone ethers, when the aryl group had an *o*-alkenyl moiety, spiroannulated products resulted, with carbon–carbon bond formation [42]:



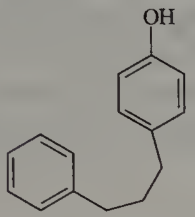
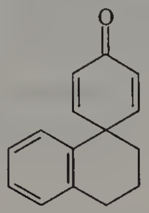
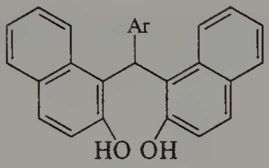
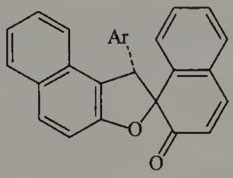
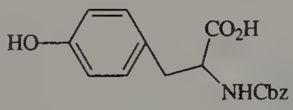
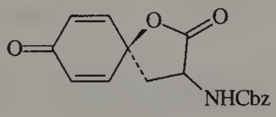
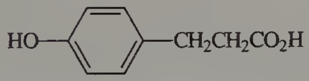
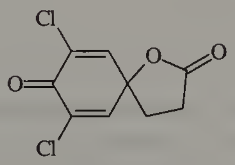
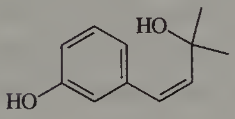
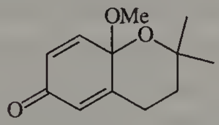
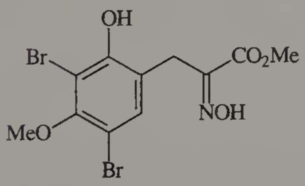
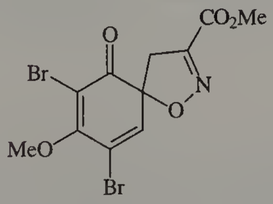
Further examples of such intramolecular cyclisations appear in Table 3.3.

In some cases DIB was uniquely effective in bringing about these oxidations. Its use has also been extended in natural product synthesis, especially in the field of alkaloids. In several instances it was used in trifluoroacetic acid, in which case it is equivalent to [bis(trifluoroacetoxy)iodo]benzene [49].

Phenols with strong electron acceptors (usually two) are converted by DIB into isolable phenyliodonium zwitterions or salts, which may rearrange spontaneously to iododiaryl ethers (Section 10.4.3).

TABLE 3.3

DIB-induced intramolecular cyclization of phenolic compounds

Substrate	Product	Yield (%)	Ref.
		30	[43]
		80	[44]
		68	[45]
		49[a]	[46]
		95[b]	[47]
		70	[48]

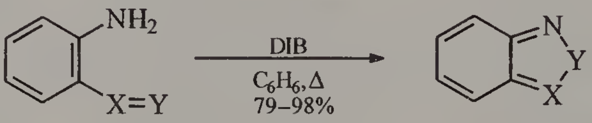
[a] With three eq. of DIB, in presence of NaCl. [b] In methanol.

3.4 OXIDATION OF NITROGEN COMPOUNDS

Most nitrogen-containing organic compounds are liable to oxidation on reaction with DIB. Simple *N-H* dehydrogenations constitute a major area of applications, often accompanied by further transformation.

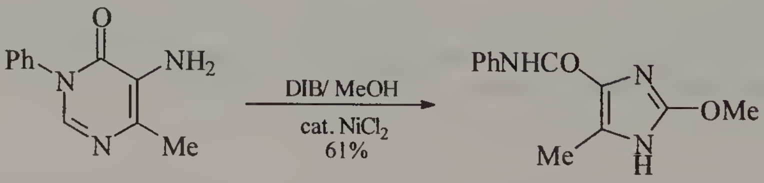
3.4.1 Amines

Anilines are readily oxidized by DIB, being converted either into azo compounds or into other products of condensation, in complex solvent-dependent reactions without much synthetic utility. Better results were obtained in some intramolecular cyclizations of 2,2′-diamino-diarylmethanes and 2,2′-diamino-diarylsulphones, which afforded the corresponding cyclic azo compounds (diazepines) [50,51]. More generally, intramolecular cyclizations of *ortho*-substituted anilines are known to occur on oxidation of several substrates, according to the following scheme [52]:

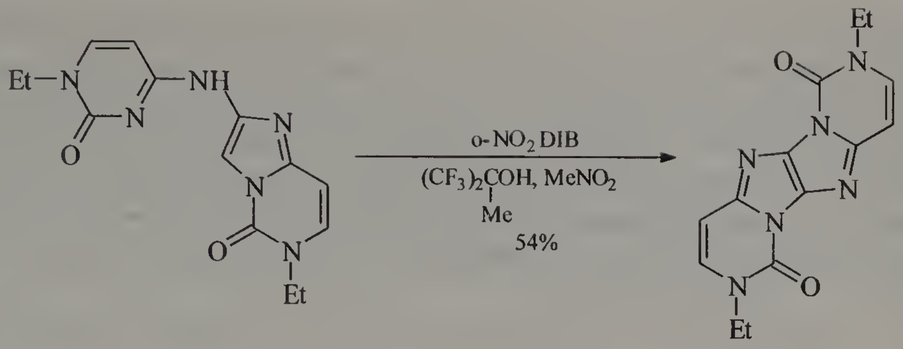


(X=Y is N(O)=O, N=NPh, PhC=O)

Analogous high-yield cyclizations were reported with 1-amino-2-nitro-derivatives of pyridines and isoquinolines, which gave the corresponding furoxans [53,54]. Anilines oxidized in the presence of indoles afforded Schiff's bases from 2- and/or 3-position in low yield [55]. An unexpected rearrangement occurred on treatment of 1-phenyl-4-methyl-5-aminopyrimidinone with DIB and catalytic amounts of nickel dichloride, resulting in the formation of an imidazole derivative [56]:



A range of interesting oxidative cyclizations could be effected only through DIB or its *o*-nitro analogue. Secondary amines in which nitrogen was linked with two nitrogen-containing rings gave in this way polycyclic heterocycles. Only solvents of very low nucleophilicity were suitable for these reactions, one of which is shown [57]:



A related oxidative cyclization of a complex indolic intermediate constituted a key step in the total synthesis of sporidesmin-A [58].

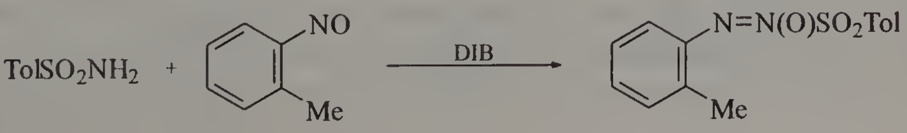
3.4.2 Amides and hydrazides

Amides of carboxylic and other acids react with DIB in various ways. Simple primary carboxamides, $RCONH_2$, and also peptidamides, undergo a facile Hofmann-type rearrangement affording amines with one less carbon atom. The same reaction has been applied using more potent hypervalent iodine reagents (Sections 4.4.1 and 7.4.1). A high yield preparation of urethanes was reported from amides and DIB in methanolic potassium hydroxide [59]:

$$RCONH_2 \xrightarrow[\text{MeOH, KOH}\atop 70\text{–}97\%]{\text{DIB}} RNHCOOMe$$

A related reaction accompanied by cyclization occurred with *ortho*-substituted benzamides (and also non-cyclic amides such as $RCH(CONH_2)_2$ [60]. Several compounds with a primary amino group, such as t-butylamine, *p*-toluenesulphonamide, ethyl carbamate, etc. were oxidized by DIB in presence of alkenes or nitroso compounds to give, respectively, aziridines or azoxy compounds.

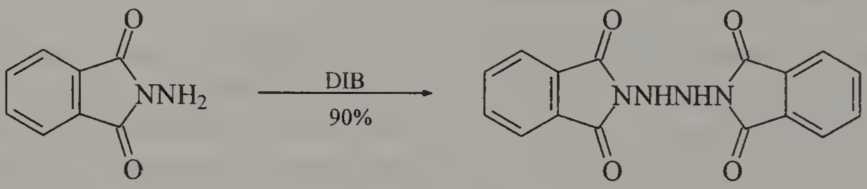
p-*Toluenesulphonyl*-NNO-*azoxy*-o-*toluene* [61]



The sulphonamide (0.171 g, 1 mmol) and 2-nitrosotoluene (0.121 g, 1 mmol) were stirred in dichloromethane (50 ml) at room temperature until a homogeneous solution was obtained. DIB (0.322 g, 1 mmol) was added and the resulting solution was stirred for 18 h. The reaction mixture was washed with cold saturated sodium bicarbonate solution (2 × 50 ml) and water (1 × 50 ml), dried and concentrated; the residue was purified by column chromatography (silica gel, hexane–chloroform, 7:3) to give p-toluenesulphonyl-*NNO*-azoxy-*o*-toluene (143 mg, 52%) m.p. 82–83°C.

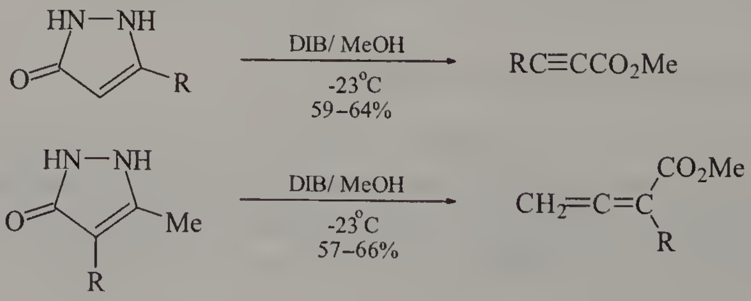
Other substrates which reacted with cyanamide and DIB included sulphides, sulphoxides and phosphines [62]. In all these oxidations formally, but not actually, nitrenes are involved, which give the corresponding ylides.

Also with DIB and nitrosobenzene *N*-phthalimidylamine gave the corresponding azoxy compound, whereas DIB alone converted it in a unique way into a tetrazane; further oxidation led to the *trans*-tetrazene [63]:



Other *N*-amino heterocycles upon oxidation with DIB were converted through nitrenes into aziridines [64].

Simple and complex hydrazides, with the general formula RCONHNHCOR, were readily dehydrogenated by DIB to the corresponding azo compounds, some of which were used as dienophiles for *in situ* Diels–Alder reactions [65,66]. Hydrazine itself in the form of its hydrate was similarly converted into diimide, NH = NH, which served for some *in situ* hydrogenations [67]. Further reactivity accompanied by solvent participation was observed in some cyclic derivatives of hydrazine, i.e. pyrazolones. At low temperature these underwent fragmentive loss of dinitrogen to give either methyl alkynoates or allenic esters [68]:



3.4.3 Amino acids

A specific cleavage reaction of NH_2-terminal tyrosyl dipeptides occurred upon their treatment with DIB in methanolic potassium hydroxide. Tyrosine itself was converted into 4-hydroxybenzyl cyanide (52%) under these conditions [69]. A related cleavage of tryptophan and several derivatives of it, including dipeptides, led to the formation of 3-methoxyindole [70]. Reserpine and also 2,3-dimethylindole reacted in the same way in the presence of alcohols, affording 3-alkoxyindolenines [71].

3.4.4 Carbonyl derivatives

Nitrogen-containing derivatives of carbonyl compounds are prone to facile oxidation by DIB. Under the proper conditions a geat variety of substrates afforded different types of products, as illustrated in Table 3.4.

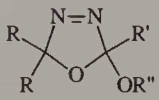
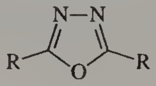
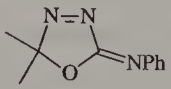
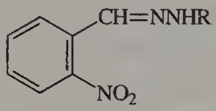
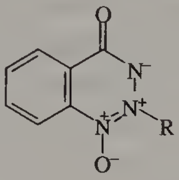
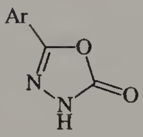
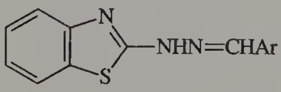
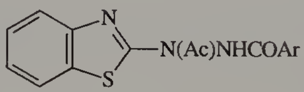
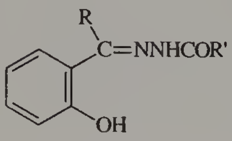
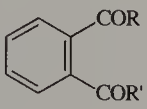
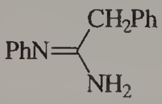
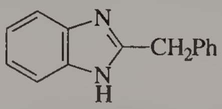
The reaction conditions were very simple, as usual, either at room temperature or at 0°C, in various solvents. Specific comments on Table 3.4 will be limited to a few cases. Deprotection of simple carbonyl derivatives to the parent ketone was achieved in a few minutes in non-acidic conditions for ketoximes, tosylhydrazones and semicarbazones; acetals were obtained from aldazines in alkaline environment, with sodium methoxide in methanol. Hydrazones from aldehydes gave *in situ* nitrilimines [83], whereas hydrazones from ketones were converted into diazo compounds, even from substrates with which other oxidants failed; for this transformation DIB may be considered as the reagent of choice. A useful extension was the *in situ* generation of diphenyldiazomethane from the hydrazone of benzophenone and its subsequent reaction with *N*-protected amino acids or phosphoric acid, affording benzhydryl esters in good yields [84,85]. An unusual reaction was the transformation of 2-hydroxyacetophenone acylhydrazones (and some analogues) to 1,2-diacyl and some tetraacyl benzenes [81,86]; here, DIB replaced the originally used lead tetraacetate. By comparing the two reagents, DIB had the following advantages: it provided a more generalized and simple route to these ketones, being less hazardous and toxic (but not less costly, as stated) than lead tetraacetate.

3.5 HYPERVALENT IODINE REAGENTS IN COMBINATION WITH AZIDO COMPOUNDS

DIB and some other hypervalent iodine reagents have been used in combination with sodium or trimethylsilyl azide to bring about interesting transformations in various types of reactants, involving either unstable iodine (III) species or the generation of free radicals. For the sake of a uniform presentation, all relevant results are discussed here together.

TABLE 3.4

Transformations of *N*-containing derivatives of carbonyl compounds mediated by DIB

Substrate	Product	Yield (%)	Ref.
$R_2C{=}NOH$	R_2CO	60–85	[72]
$R_2C{=}NNH_2$	R_2CN_2	~80	[73]
$R_2C{=}NNHTs$	R_2CO	87–93	[74]
$R_2C{=}NNHCONH_2$	R_2CO	70–82	[75]
$ArCH{=}NN{=}CHAr$	$ArCH(OR)_2$	50–95	[76]
$R_2C{=}NNHCOR'$		73–99^a	[77]
$RCH{=}NNHCOR$		48–70	[77]
$Me_2C{=}NNHCONHCOPh$		93	[77]
		75–82	[78]
$ArCH{=}NNHCO_2Bu^t$		47–67	[79]
	 N N(Ac)NHCOAr S	65–86	[80]
 R C=NNHCOR' OH		60–97	[81]
 CH2Ph PhN NH2		82	[82]

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[a] In alcohols (R"OH).

3.5.1 Alkenes and unsaturated compounds

Alkenes of various kinds reacted with DIB-Me_3SiN_3 in two main ways; one involved addition, whereas the other was a cycloaddition accompanied by fragmentation. The system DIB-Me_3SiN_3 consists of mixtures of non-isolable $PhI(OAc)N_3$ and $PhI(N_3)_2$, depending on the ratio of the reactants. Addition occurs mostly with cycloalkenes and aromatic vinyl compounds, including some heterocycles; all these afford α-azido-ketones regioselectively, i.e. the azide function is added to the carbon atom bearing fewer hydrogens.

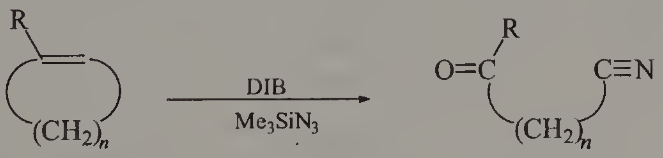
α-Azidoketones from alkenes [87]

$$ArCH{=}CH_2 \xrightarrow[Me_3SiN_3]{DIB} ArCOCH_2N_3$$

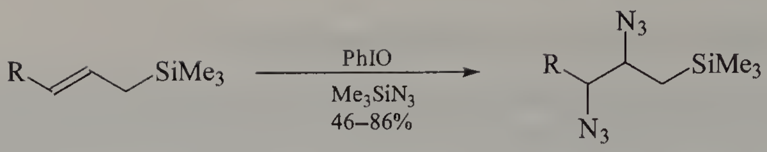
A solution of the alkene (10 mmol) and DIB (6.4 g, 20 mmol) in dry dichloromethane (250 ml) was cooled to − 20°C. To this a solution of trimethylsilyl azide (4.6 g, 40 mmol) in dichloromethane (50 ml) was added slowly. The homogeneous mixture was allowed to stand at − 20°C for 12–16 h and for a further 12 h at room temperature. The reaction mixture was washed with water and a saturated solution of sodium bicarbonate, dried and concentrated. The azidoketone was obtained by column chromatography (silica gel, petroleum ether–acetone, 9:1 or other suitable eluant).

The addition in this mode was successful with several substrates, some of which are shown in Table 3.5. An exception was noted in 1-cyanocyclohexene which added two azido groups.

The fragmentation mode was observed mostly in electron-rich cyclic alkenes, including steroids, which afforded ω-formyl nitriles [89]:



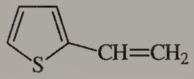
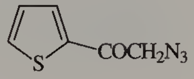
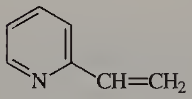
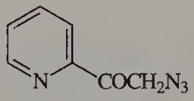
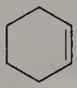
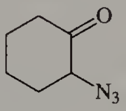
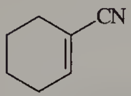
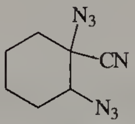
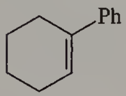
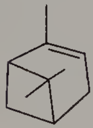
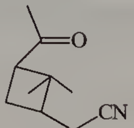
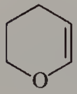
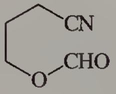
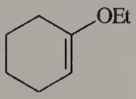
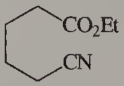
The system PhIO-AcOH-NaN_3, in contrast to the previous one, gave with alkenes 1,2-diazides in fair yields, either at room temperature or at 35–50°C; the addition lacked stereoselectivity [90].


R
SiMe3
PhIO
Me3SiN3
46–86%
N3
R
SiMe3
N3

Steroids with a double bond at C_5-C_6 were transformed eventually to 7α-azido allylic derivatives [91]. The reaction of PhIO-Me_3SiN_3 with allylsilanes at – 78°C

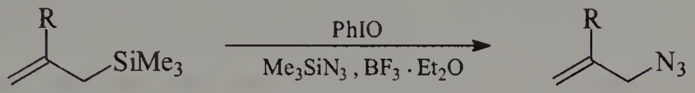
TABLE 3.5

Addition to and fragmentation of alkenes by DIB-trimethylsilyl azide

Alkene	Product	Yield %	Ref.
$ArCH{=}CH_2$	$ArCOCH_2N_3$	42–90	[87]
trans-$PhCH{=}CHPh$	$PhCOCH(N_3)Ph$	56	[87]
		57	[87]
		45	[87]
		95	[88]
		50	[88]
	$PhCO(CH_2)_4CN$	66	[89]
		65	[89]
		61	[88]
		56	[88]

gave 1,2-diazides in good yields; the addition of tetrabutylammonium fluoride to the products induced elimination of hydrazotic acid resulting in the formation of allyl azides [92]. Allyl azides were also prepared directly from allyl silanes.

Allylazides from allylsilanes [93]

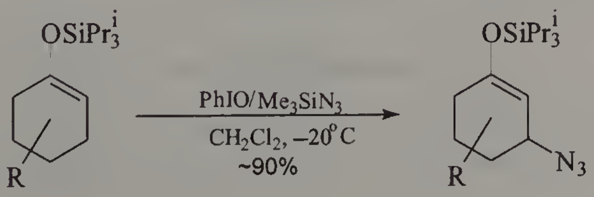


To a suspension of iodosylbenzene (264 mg, 1.2 mmol) and trimethylsilyl azide (138 mg, 1.2 mmol) in dichloromethane was added boron trifluoride ethereate (0.148 ml, 1.2 mmol) at −78°C, under nitrogen. After 30 min of stirring a solution of allylsilane (1.2 mmol) in dichloromethane was added dropwise and stirring was continued for 2 h at −78°C. The reaction mixture was quenched with a cold aqueous solution of sodium bicarbonate and extracted with dichloromethane. Concentration and column chromatography of the residue (silica gel, hexane–ethyl acetate, 7:1) afforded allylazides in good yield. For example, $CH_2{=}C(Me)CH_2SiMe_3$ gave $CH_2{=}C(Me)CH_2N_3$ (82%) and 3-trimethylsilylcyclohexene gave 3-azidocyclohexene (64%). A minor by-product of the reaction was in some cases a rearranged β-trimethylsilyl ketone.

3,4-Dihydro-2*H*-pyran and related glycals underwent with PhIO-Me_3SiN_3 either allylic azidation or addition to the double bond (*trans* azido adducts), depending on the conditions [94,95]. (CAUTION: it has been reported that $PhI(N_3)_2$ formed *in situ* in the presence of moisture is explosive, even in dichloromethane solution; therefore, all glassware should be flame-dried and exhaustively flushed with nitrogen).

3.5.2 Carbonyl compounds and their derivatives

Silyl enol ethers undergo primarily β-azidation, as the following equation illustrates [96]:



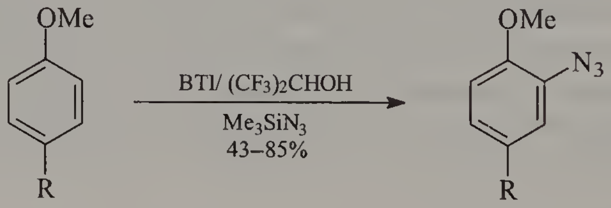
Under these conditions many triisopropyl enol ethers, and also 1-methoxycyclohexene and 3,4-dihydro-2*H*-pyran, afforded similarly their 3-azido derivatives, in high yield [96,97].

Direct 1,2-bis azidation of triisopropylsilyl enol ethers was possible when catalytic amounts of 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) were used, at – 45°C. The reaction under these conditions was often highly stereoselective, since only one (*trans*) adduct was obtained. In contrast to the other bis azidations of alkenes, which proceed ionically or through cycloaddition, this addition is a free radical process [98]. A radical pathway occurred also when cyclohexene was treated with PhIO-Me_3SiN_3-TEMPO; the yield of 1,2-bis azide was doubled (80%) in relation to the system PhIO-AcOH-NaN_3 (in both cases the *trans* adduct prevailed).

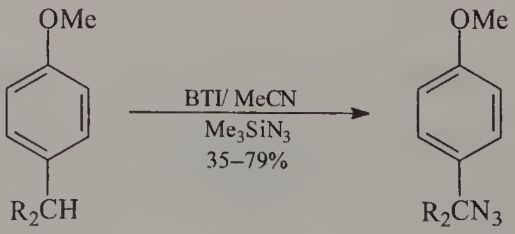
1,4-Addition occurred in 2-trimethylsilyloxy-furan upon treatment with PhIO-BF_3-Me_3SiN_3, with direct formation of 5-azidofuranone [99]. Some β-diketones and β-ketoesters underwent α-azidation by PhIO-Me_3SiN_3 [100].

3.5.3 Aromatics

The azide function can enter electron-rich aromatic rings; for such reactions another more potent system is suitable, i.e. [bis(trifluoroacetoxy)iodo]benzene (BTI) in hexafluoro-2-propanol. Most substrates had at least one methoxy group and the azide group was attached regioselectively to its *ortho*-position, e.g. [101]:



Some other aromatics azidated in this way included 1,2,3-trimethoxybenzene (at *C*-5), naphthalene (at *C*-1), mesitylene, etc. Mechanistic studies have shown that azide reacts as a nucleophile with aryl cation radicals formed through electron abstraction by BTI. With *p*-alkylanisoles bearing at least one benzylic proton, BTI and Me_3SiN_3 in acetonitrile gave sp^3-*C*-substitution products, homolytically. Among the R groups were not only alkyls but also cyano, nitro and others [102].

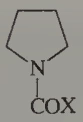
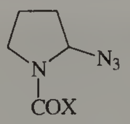
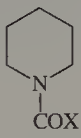
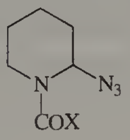
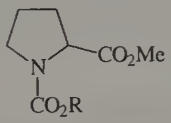
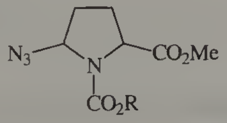
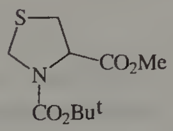
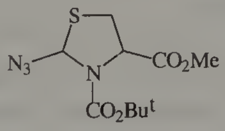


3.5.4 Amines

A variety of amines underwent substitution by the azido group, using the system PhIO-Me_3SiN_3. Some examples arc illustrated in Table 3.6. The azides were normally too unstable to be purified and some of them were used *in situ* for further transformation; for example, 1-dimethylaminonaphthalene gave either a monoazide or a diazide, which were converted with Me_2AlCl-$Bu_3SiCH_2CH{=}CH_2$ into the corresponding *N*-butenyl compounds [103]. In certain cases the initially formed azides underwent elimination of hydrazotic acid resulting in dehydrogenation of the substrate, e.g. *N*-benzyl-2,5-dihydro-pyrrole was converted directly into *N*-benzyl-pyrrole (95%) [103].

TABLE 3.6

Azidation of *N*-containing compounds by IOB-trimethylsilyl azide

Substrate	Product	Yield (%)	Ref.
Me_3N	$Me_2NCH_2N_3$	95	[103]
$ArNMe_2$	$ArN(CH_2N_3)Me$	~95	[103]
		~75	[104]
		~30	[104]
(X= OMe. OPh, Ph, NPh_2, etc.)			
		~70	[105]
		'100'	[105]

3.6 DIB AND SODIUM AZIDE IN COMBINATION WITH OTHER REAGENTS

3.6.1 Azido-phenylselenylation of alkenes

The tertiary system DIB–sodium azide–diphenyl diselenide was efficient for the azido-phenylselenylation of double bonds. The reaction proceeded with complete anti-Markovnikov regioselectivity, due to the ready decomposition of the $PhI(N_3)_2$ intermediate to the azido free radical [106,107]. Excellent yields were reported for glycals [108].

Azido-phenylselenylation of unsaturated compounds [106]

$$RCH{=}CH_2 \xrightarrow[\text{PhSeSePh}]{\text{DIB/ NaN}_3} RCH(SePh)CH_2N_3$$

A mixture of the unsaturated compound (5 mmol), diphenyl diselenide (936 mg, 3 mmol), sodium azide (78 mg, 12 mmol) and DIB (225 mg, 7 mmol) in dichloromethane (20 ml) was stirred at room temperature for 10–12 h. The reaction mixture was poured into 10% aqueous sodium bicarbonate solution and extracted with dichloromethane. The organic layer was washed with brine, dried and concentrated and the residue was purified by flash chromatography (silica gel, petroleum ether–ether) to give 1-azido-2-phenylselenylalkanes in 62–82% yield.

Not only alkenes but also other unsaturated substrates were similarly converted into *vic*-azidophenylselenyl derivatives, e.g. 3,4-dihydro-2*H*-pyran (74%), methyl methacrylate (75%), etc. Tri-*O*-methyl-D-glycal and tri-*O*-acetyl-D-glycal also gave the expected products: the former two stereoisomers in a 4:6 ratio for *cis* and *trans*, and the latter another two in the reverse ratio.

3.6.2 Transfer of the phenylthio(phenylseleno) group to aldehydes and ethers

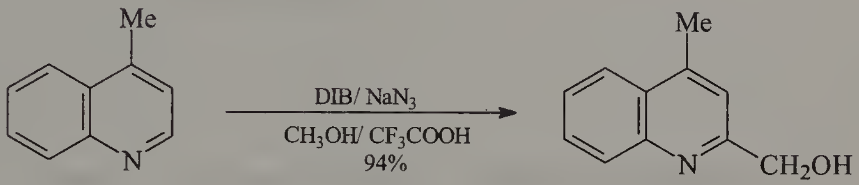
DIB in combination with sodium azide and diphenyl disulphide or diphenyl diselenide can replace the methinic hydrogen of aliphatic, aromatic and heteroaromatic aldehydes by the phenylthio or phenylseleno group. The corresponding esters were obtained in moderate (for unsaturated aldehydes) to very good yields [109]:

$$RCHO \xrightarrow[\substack{\text{PhYYPh/ CH}_2\text{Cl}_2 \\ 35\text{–}93\%}]{\text{DIB/ NaN}_3} RC(YPh)O \qquad (Y = S, Se)$$

An analogous α-substitution occurred with some ethers, either cyclic such as THF or aliphatic such as t-butyl methyl ether; for example, the latter afforded using diphenyl diselenide the mixed acetal of formaldehyde (t-BuOCH$_2$SePh, 90%). In contrast to aldehydes, ethers also served as solvents.

3.6.3 Functionalization of lepidine

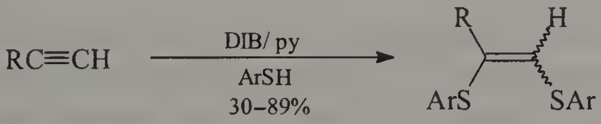
Lepidine (4-methylquinoline) was found to react with alcohols and DIB-NaN$_3$ in trifluoroacetic acid, producing 2-hydroxyalkyl derivatives. Here, the azide radical abstracts an α-hydrogen from the alcohol, generating new radicals (C·H$_2$OH, CH$_3$C·HOH, etc.) which are the reactive species, e.g. [110]:



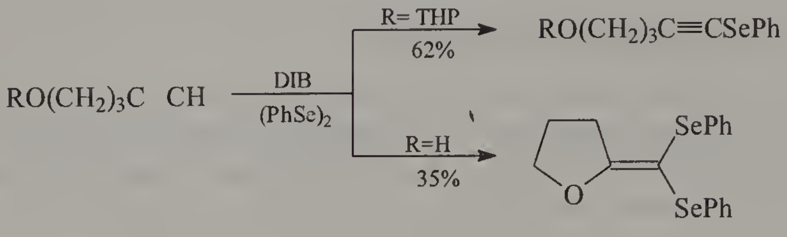
With more DIB at reflux, the corresponding aldehyde was obtained. Not only alcohols but also ethers (THF, 1,4-dioxane), formamide and alkyl iodides formed the appropriate carbon-centred free radicals which gave with lepidine the expected 2-substituted lepidines.

3.7 TRANSFORMATIONS OF ALKYNES INVOLVING THIOPHENOLS AND DIPHENYL DISELENIDE

The oxidation of thiols to disulphides by DIB proceeds through the intermediacy of PhI(SR)$_2$, which are homolytically converted into iodobenzene and dialkyl disulphides. These intermediates from 2,3,5,6-tetrafluoro-thiophenol yielded with various terminal alkynes adducts as mixtures of *E* and *Z* isomers of varying composition [111]:



Terminal alkynes reacted in a different way with DIB and diphenyl diselenide, yielding phenyl alkynyl selenides in varying yield, from 81%, for phenylselenyl phenylacetylene, to 15% for trimethylsilyl phenylselenyl acetylene. It is noteworthy that whereas a protected alcohol (4-pentynol) gave the expected product, the unprotected afforded a furan derivative [112]:



(THP= tetrahydropyranyl)

3.8 PHOTOCHEMICAL REACTIONS WITH IODINE

The combination of DIB with some substrates and subsequent photolysis of the intermediates formed constitute a good way to generate simple or functionalized free radicals, through which interesting products may result.

3.8.1 Oxidation of alcohols *via* alkoxy radicals

Of great synthetic importance is the generation of alkoxy radicals from alcohols: DIB reacts first with elemental iodine to form acetyl hypoiodite which in the presence of an alcohol is converted into alkyl hypoiodite; upon irradiation with visible light the alkoxy radical is generated:

$$\mathrm{PhI(OAc)_2} + \mathrm{I_2} \longrightarrow \mathrm{PhI} + 2\,\mathrm{AcOI}$$

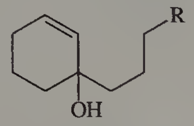
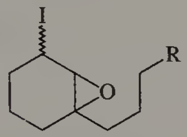
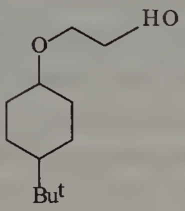
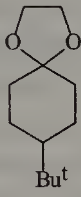
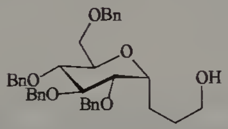
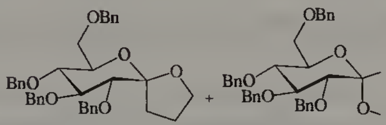
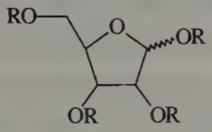
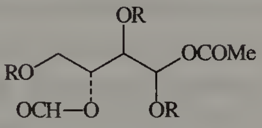
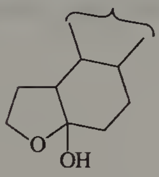
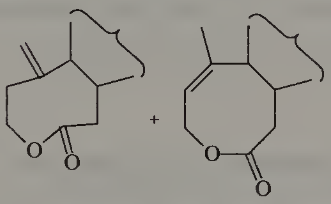
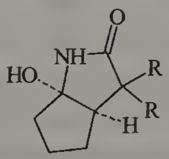
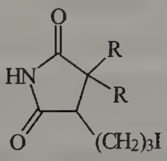
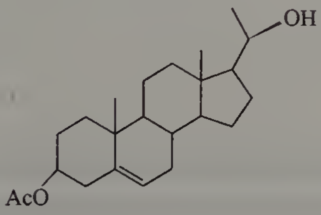
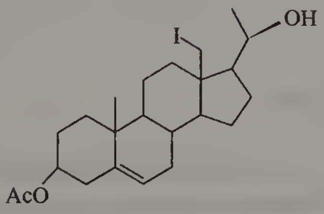
$$\mathrm{AcOI} + \mathrm{ROH} \longrightarrow \mathrm{AcOH} + \mathrm{ROI}$$

$$\mathrm{ROI} \xrightarrow{h\nu} \mathrm{RO}^{\bullet} + \mathrm{I}^{\bullet}$$

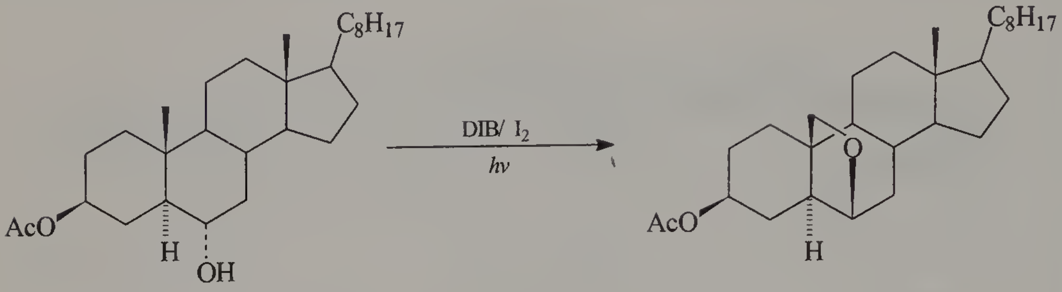
Oxidation of alcohols with this system is considered to be the best method available for the generation of alkoxy free radicals, not only for good yields of the final products but also for avoiding the use of toxic metals such as lead (in lead tetraacetate) and mercury (in mercuric oxide). A great number of substrates (1°, 2° and 3° alcohols, cyclic hemiacetals and carbohydrates) have undergone useful and sometimes unexpected transformation, which may involve cyclization, functionalization and fragmentation (often leading to ring expansion). Depending on the substrate, the products may contain iodine. Some representative examples are shown in Table 3.7, and a procedure follows.

TABLE 3.7

Photochemical reactions of DIB-iodine with alcohols

Substrate	Product	Yield (%)	Ref.
a. Cyclization			
		72–85	[113]
		85	[114]
		51+17	[115]
b. Fragmentation			
		up to 91	[116]
		85(1:1)	[117]
		~60	[118]
c. Functionalization			
		61	[119]

6β,19-Epoxy-5α-cholestan-3β-yl acetate [120]



A solution of the steroid (50 mg, 0.12 mmol) in cyclohexane (10 ml) containing DIB (40 mg, 0.12 mmol) and iodine (28 mg, 0.11 mmol) was irradiated with two 100 W tungsten-filament lamps for 50 min at 40°C. The reaction mixture was poured into water and extracted with ether; the organic layer was washed with aqueous sodium thiosulphate and then water, dried, concentrated and the residue was purified by column chromatography on silica gel (hexane–ethyl acetate, 9:1) to give 6β,19-epoxy-5α-cholestan-3β-yl acetate (45 mg, 90%) m.p. 114–115°C.

A special case from Table 3.7 (last entry) is the functionalization of the C_{13} methyl group in the pregnane series from both stereoisomeric alcohols which eventually retain their hydroxy function. In some instances reactions were performed in the presence of oxygen, with fragmentation and formation of peroxylactones from lactols [121]. Other unusual transformation can be found in the steroid field, in tricyclic alcohols and in alcohols related to natural products [122–124]. Some interesting transformations involving ring fragmentation [125] and ring-enlargement [126] were performed without irradiation.

3.8.2 Oxidation of nitrogen compounds

Hydrogen abstraction under conditions similar to those in Section 3.8.1 may occur also from nitrogen compounds, with formation of amidyl free radicals. The results vary, depending on the substrate; for example, 6-amino derivatives of steroids were converted into *N*-substituted pyrrolidines [127]. Medium-sized lactams underwent transannular cyclization to bicyclic lactams [128], and bicyclic carbinolamides afforded mainly β-fragmentation products (Table 3.7).

3.8.3 Oxidation of acids

In solution, DIB and carboxylic acids enter an equilibrium with formation of acetic acid and [bis(acyloxy)iodo]benzenes (Section 2.1). In some instances these need not be isolated; upon irradiation of a mixture of DIB and an acid, a homolytic cleavage of the iodine–oxygen bond occurs and the very unstable acyloxy radicals formed are decarboxylated to the less unstable alkyl radicals:

$$\mathrm{PhI(OAc)_2 + 2\,RCOOH \rightleftharpoons PhI(OOCR)_2 + 2\,AcOH}$$

$$\mathrm{PhI(OOCR)_2} \xrightarrow{h\nu} \mathrm{Ph\dot{I}OOCR + RCO\dot{O}}$$

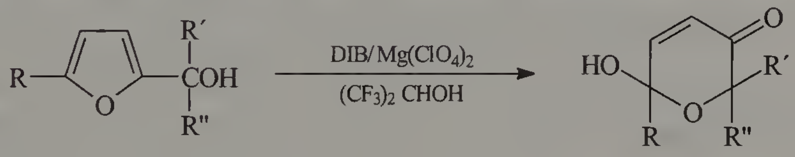
$$\mathrm{RCO\dot{O}} \longrightarrow \mathrm{\dot{R} + CO_2}$$

These radicals have been involved in several synthetic applications. Since for such reactions stable [bis(acyloxy)iodo]benzenes are preferable, all relevant results are discussed together in Section 4.8.1.

3.9 MISCELLANEOUS REACTIONS

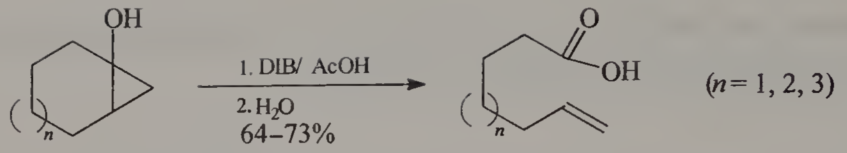
3.9.1 Oxidation of furyl and bicyclic alcohols

Alcohols are practically inert towards DIB at room temperature and react very slowly at elevated temperature, unless they possess special features. Thus, oxidation due to the presence of furan ring occurred in a series of furyl alcohols which with DIB alone or better in combination with magnesium perchlorate (in a molar ratio 1:2) were converted into pyran-3(6*H*)-ones [129].



The best yields, up to 99%, were obtained in hexafluoro-isopropanol but acetonitrile and methanol were also satisfactory. The role of the salt was to enhance the formation of the radical species involved bringing about a significant increase in reaction yield; furan and 2,5-dimethylfuran in methanol were converted into 2,5-dimethoxy-2,5-dihydrofurans. The use of $\mathrm{PhI(py^+)_2 2TfO^-}$ in acetonitrile–water provided better results [130].

Another interesting transformation of alcohols was effected using bicyclic 1-alkanols with a fused cyclopropane ring, which were cleaved oxidatively to alkenoic acids [131]:



A substantial improvement in yield (84–96%) was achieved by using the *O*-trimethylsilyl derivatives of the above alcohols. DIB was superior in these oxidations to lead tetraacetate. It is noted that 1-silyloxy-bicyclo[n.1.0]alkanes ($n = 4$–7) on treatment with iodosylbenzene-tetrabutylammonium fluoride were converted into mixtures of cyclic unsaturated ketones (Section 5.2.1).

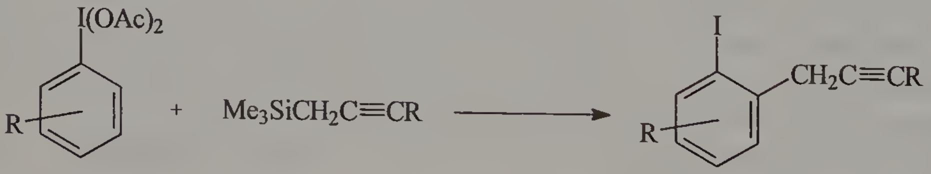
3.9.2 Oxidation of sulphur compounds

Compounds of sulphur(II) undergo the expected oxidations with DIB: thiols to disulphides and sulphides to sulphoxides. Thiols form initially unstable iodine(III) intermediates which react with alkynes (Section 3.7). With some sulphides, DIB proved to be uniquely efficient, for example in the oxidation of thioxanthone [132]. The best conditions for high yields involved the use of acetic acid as solvent and catalytic amounts of sulphuric acid; no heating was required and the reaction was completed in about 5 minutes [133].

3.9.3 Reactions with propargylsilanes

Propargylsilanes (alkynylsilanes, silylalkynes) reacted with DIB and several of its ring-substituted analogues in an unusual way: the eventual transformation involved the formation of *o*-iodopropargylarenes. Apart from its mechanistic interest, this constitutes a synthetically useful reaction.

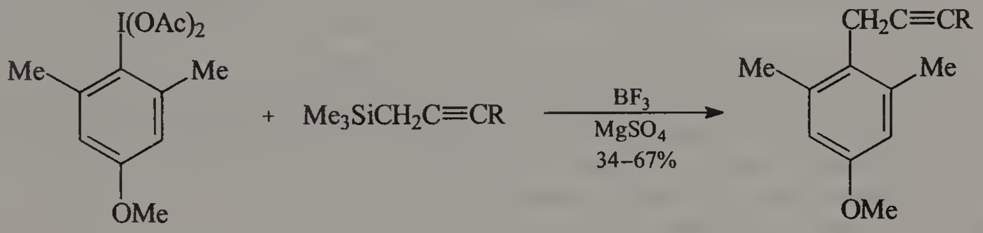
o-*Iodopropargylarenes* [134]



A 20 ml, oven-dried two-necked flask fitted with a nitrogen balloon and a rubber septum was charged with the (diacetoxyiodo)arene (0.3 mmol), the propargylsilane (0.36–0.6 mmol), anhydrous magnesium sulphate (100 mg) (dried previously at

100°C for 3 h under vacuum) and freshly distilled dichloromethane (2 ml). With stirring at −20°C, freshly distilled boron trifluoride etherate (0.037 ml, 0.3 mmol) was added dropwise. After the appropriate time the reaction mixture was quenched with water and extracted with hexane. The organic extracts were washed with brine, dried and concentrated to give an oily residue which was purified by preparative TLC. The yields of *o*-iodopropargylarenes were in the range 51–90%.

Instead of DIB, iodosylbenzene underwent the same reaction, with better yields in some instances. Also, propargylgermanes and stannanes could replace the silanes. *Ipso* substitution products resulted in some *p*-methoxy-substituted DIBs on treatment with two equivalents of propargylsilanes:



Competition between this deiodinative pathway and the normal *ortho* substitution was observed in the reaction of *p*-methoxy-DIB with 3-trimethylsilylpropene [135].

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– 4 –

[Bis(acyloxy)iodo]benzenes

This chapter is divided into two parts. The first part deals with [bis(trifluoroacetoxy)iodo]benzene, a powerful oxidant and a versatile electrophile with many synthetic applications; emphasis is given on reactions not realized by its acetoxy analogue, as discussed in previous chapters. In the second part are examined some reactions of its perfluoro analogue and mainly reactions common for a number of [bis(acyloxy)iodo]benzenes coming from a wide range of carboxylic acids.

Part A: Reactions with [bis(trifluoroacetoxy)iodo]benzene

4.1 TRANSFORMATIONS OF ALKYNES

In contrast to (diacetoxyiodo)benzene, [bis(trifluoroacetoxy)iodo]benzene, (BTI) reacts in aqueous solvents with both terminal and non-terminal alkynes affording eventually α-hydroxyketones and 1,2-diketones, respectively. The primary reaction of terminal alkynes leads to the formation of alkynyl phenyliodonium salts, which are not isolable under the experimental conditions but have been prepared by other routes (Section 9.1.3); these are hydrolysed *in situ* to α-hydroxymethyl ketones, through the intermediacy of their *O*-trifluoroacetates, which sometimes may be isolated as by-products.

α-Hydroxymethyl ketones from terminal alkynes [1]

$$\mathrm{RC{\equiv}CH} \xrightarrow[\mathrm{MeCN/\ H_2O}]{\mathrm{BTI}} \mathrm{RCOCH_2OH}$$

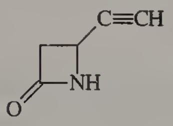
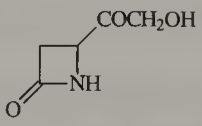
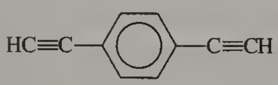
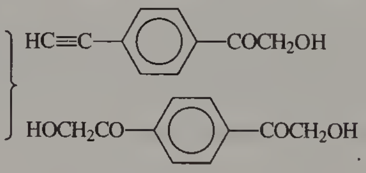
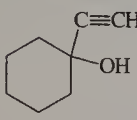
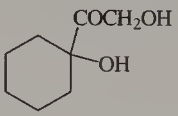
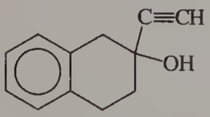
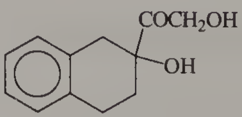
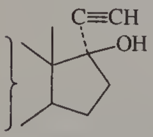
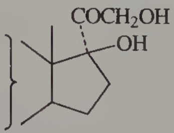
The terminal alkyne (or a propargylic alcohol, i.e. ethynyl carbinol)(1 mmol) was added dropwise to a solution of BTI (516 mg, 1.2 mmol) in chloroform, or a mixture of 1,2-dichloroethane–acetonitrile–water (4 ml, 80:10:1). The mixture was stirred at reflux for 10 h, cooled to room temperature and partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane and the combined extract was washed with saturated sodium chloride solution, dried over magnesium sulphate and concentrated. The residue, a mixture of α-hydroxyketone and its *O*-trifluoroacetate, was passed through a dry silica gel column with ethyl acetate to hydrolyse the ester. The eluate was concentrated and purified by column chromatography on silica gel (benzene–ethyl acetate, 5:1).

Ethynyl groups attached to various skeletons were generally oxidized to the hydroxyacetyl functionality. The reaction was useful in the synthesis of natural products and analogues with a dihydroxyacetone side chain, e.g. adriamycin and corticosteroids. Some examples are given in Table 4.1.

Non-terminal diarylacetylenes have been oxidized by BTI to α-diketones; good yields were obtained only from precursors containing electron donating groups or halogens [3]:

TABLE 4.1

Oxidation of ethynyl compounds by BTI

Substrate	Product	Yield (%)	Ref.
$C_6H_{13}C{\equiv}CH$	$C_6H_{13}COCH_2OH$	78	[1]
$PhC{\equiv}CH$	$PhCOCH_2OH$	82	[1]
$RCOCH(R)CH(R')C{\equiv}CH$	$RCOCH(R)CH(R')COCH_2OH$	47–55	[2]
		82	[1]
		39 39	[3]
		77	[1]
		76	[1]
		53–60	[1]

$$\mathrm{ArC{\equiv}CAr'} \xrightarrow[\mathrm{CHCl_3/H_2O,\ \Delta}]{\mathrm{BTI}} \mathrm{ArCOCOAr'}$$

The triple bond was also converted into the 1,2-diketo-function by iodosylbenzene (Section 5.1.3), whereas cleavage occurred by perfluoro-DIB (Section 4.7).

4.2 TRANSFORMATIONS OF KETONES

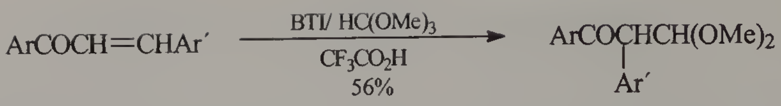
BTI is suitable for the direct hydroxylation of ketones. Aliphatic, aromatic and heterocyclic ketones in acetonitrile–water and trifluoroacetic acid afforded α-hydroxymethyl ketones (in the range of 70%), whereas α-methylene ketones, such as propiophenone, gave less satisfactory yields.

α-Hydroxymethyl ketones from methyl ketones [4]

$$\mathrm{RCOCH_3} \xrightarrow[\mathrm{H^+}]{\mathrm{BTI}} \mathrm{RCOCH_2OH}$$

The ketone (5 mmol) was added to a stirred solution of trifluoroacetic acid (0.77 ml, 10 mmol), water (5 ml) and acetonitrile (25 ml); BTI (4.3 g, 10 mmol) was added and the solution was refluxed for 2–4 h. When the reaction was completed, the reaction mixture was partitioned between dichloromethane (125 ml) and water (25 ml). The aqueous phase was extracted with dichloromethane (3 × 25 ml) and the combined extracts washed with a saturated solution of sodium bicarbonate (3 × 25 ml) and dried. The filtered solution was concentrated and the residue was triturated with cold hexanes to yield the product; column chromatography was not always necessary for purification.

Enol acetates seem to be more reactive than ketones, since a steroidal substrate gave the corresponding α-trifluoroacetoxy-ketone at room temperature [5]. Chalcones with DIB in trimethyl orthoformate and acid give normally rearranged methoxypropanoates (Section 3.1). However, a substituted chalcone with BTI yielded a different product which was an intermediate in the synthesis of homopterocarpin [6]:



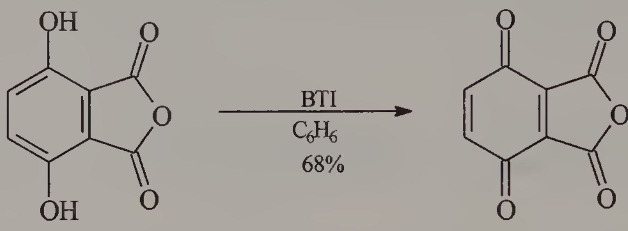
$$\mathrm{ArCOCH{=}CHAr'} \xrightarrow[\mathrm{CF_3CO_2H}\ \ 56\%]{\mathrm{BTI/\ HC(OMe)_3}} \mathrm{ArCO}\underset{\mathrm{Ar'}}{\underset{|}{\mathrm{C}}}\mathrm{HCH(OMe)_2}$$

Such products are normally obtained with [hydroxy(tosyloxy)iodo]benzene (Section 7.3.5), which, however, did not work in this particular case.

4.3 PHENOLIC OXIDATION

4.3.1 Phenols to quinones

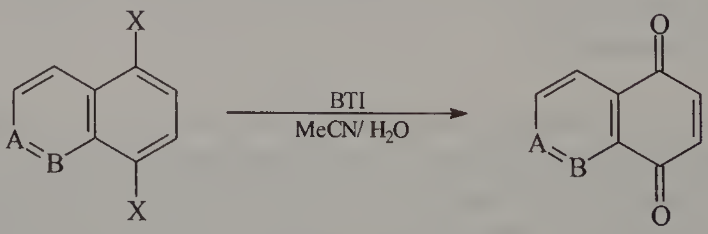
Although phenolic oxidations have been performed successfully with DIB (Section 3.3), BTI was the reagent of choice for difficult cases, as the one shown below [7]:



In this and other related 1,4-dihydroxy benzene derivatives several oxidants failed to react; even fuming nitric acid gave a trace of the quinone.

A route involving 1,4-dihydroxybenzene intermediates has been suggested for the oxidation of several naphthols and naphthylamines, and also hydroxy- and aminoquinolines and isoquinolines.

1,4-Naphthoquinones and their aza analogues [8]



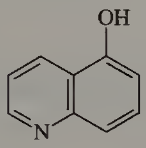
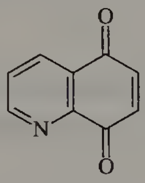
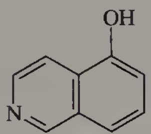
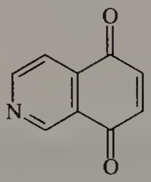
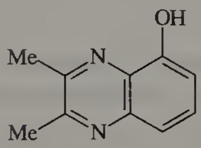
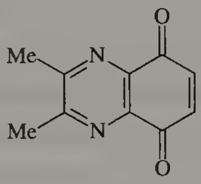
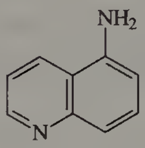
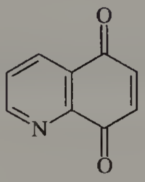
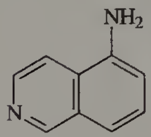
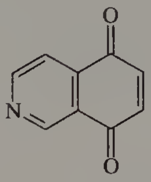
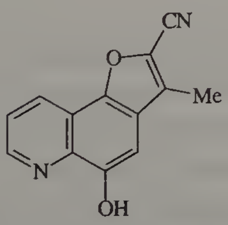
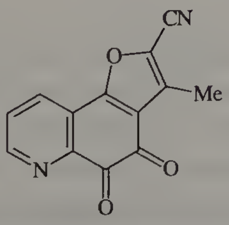
(A=B is CH—CH, CH=N or N=CH ; X is H, OH or NH_2)

A solution of the substrate (1 mmol of 1-naphthol or 5-hydroxyisoquinoline or 8-aminoquinoline, etc.) in acetonitrile–water (2:1, v/v) was added dropwise to a solution of BTI (946 mg, 2.2 mmol) in the same solvent system under nitrogen at 0°C. The mixture was stirred for 2 h and, after evaporation of volatiles, the quinones were obtained in crude form and purified by column chromatography. Examples of such quinones are collected in Table 4.2.

Similar oxidations have been performed with *p*-alkoxyphenols which were neatly

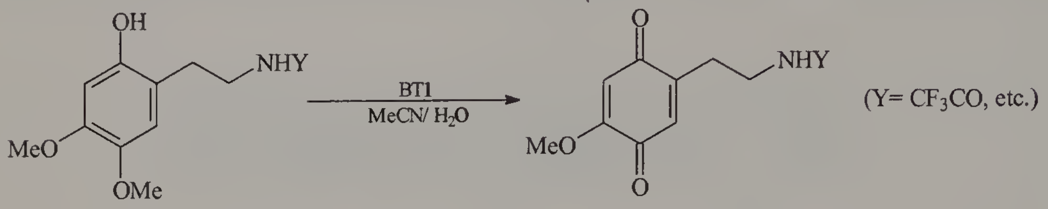
TABLE 4.2

BTI oxidation of aza-1-naphthols and aza-1-naphthylamines

Substrate	Product	Yield (%)	Ref.
		88	[8]
		80	[8]
		70	[8]
		85	[8]
		46	[8]
		78	[9]

converted into 1,4-benzoquinones. The use of potassium carbonate was beneficial when precursors contained an acid-sensitive group. The regioselectivity of the reaction was remarkable, with excellent yields; by contrast, other oxidants such as Fremy's salt gave predominantly 4-alkoxy-1,2-benzoquinones [10].

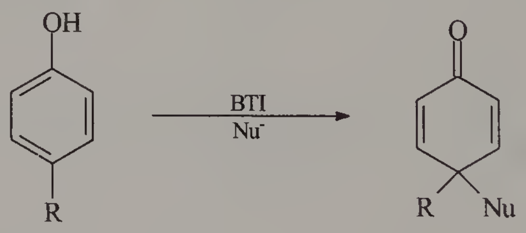
N-Protected 2-aminoethyl-3,4-dimethoxyphenols afforded similarly the corresponding 1,4-benzoquinones, in aqueous acetonitrile, in high yield [11]:



Both BTI and DIB have been used in key-steps involving phenolic oxidation to quinone imines in the total synthesis of (±)-dynemicin A [12].

4.3.2 Oxidation involving carbon–oxygen and carbon–fluorine bond formation

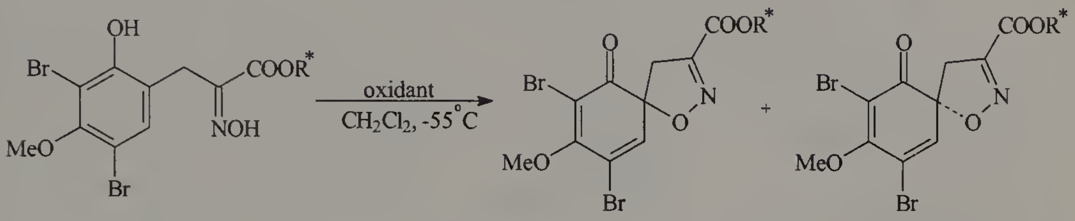
In the previous reaction when the solvent was changed to acetonitrile–methanol, quinone monoacetals were formed. Both products were used for the synthesis of 5-oxygenated indoles [11]. This type of transformation also occurred using DIB (Section 3.3); however, the use of BTI activated 4-alkyl phenols which reacted not only with methanol but also with other nucleophiles, simple ones such as water and fluoride, or more complex, according to the general scheme:



With water, the reaction was carried out in aqueous acetonitrile at 0°C, but the products (*p*-quinols) were formed in moderate yield; better results were obtained with silylated phenols, especially with their tripropylsilyl ethers [13]. For fluorination, pyridinium polyhydrogen fluoride was the source of fluoride; this system was effective with a variety of substrates, including a phenolic steroid [15]. As with DIB, intramolecular cyclizations were also performed on several occasions.

Representative examples of such phenolic transformations are illustrated in Table 4.3.

By using a chiral α-oximino ester, an efficient asymmetric induction at the γ-position to the carbalkoxy group was noted; with several hypervalent iodine reagents, this substrate gave products with varying degrees of yield and diastereoisomeric selectivity, as illustrated in the following scheme, where R is (−)-8-phenylmenthyl [17]:



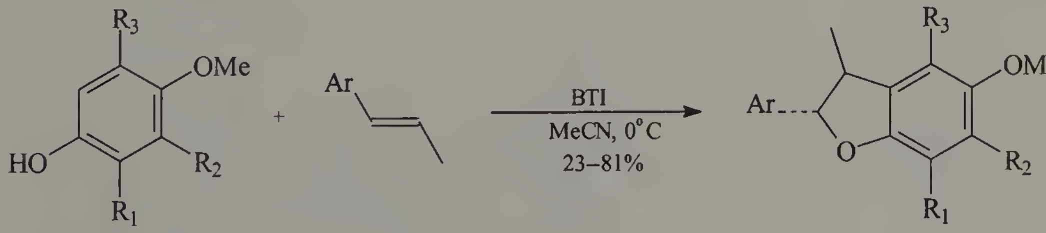
oxidant	yield	diastereoisomeric excess %
DIB	31	33
BTI	88	67
PhIO/ (+)-CSA	70	82
PhIO/ (-)-CSA	87	82

(CSA is camphorsulphonic acid)

N-Acetyltyramines of the general formula 4-$HOC_6H_4CH_2CH_2NHCOR$, reacted with BTI in two ways, depending on the solvent. When this was an alcohol or acetic acid, the expected quinol ethers or esters were obtained, whereas in trifluoroethanol heterocyclic *spiro*-cyclohexadienones were formed [18].

4.3.3 Oxidation involving carbon–carbon bond formation

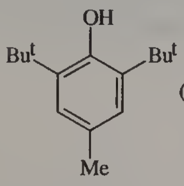
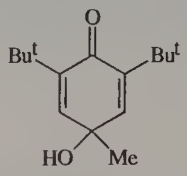
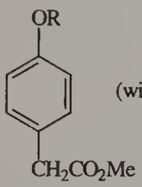
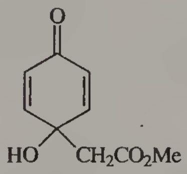
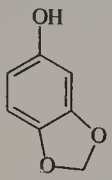
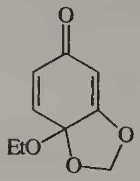
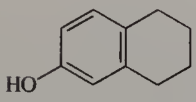
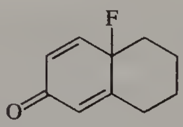
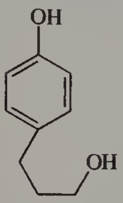
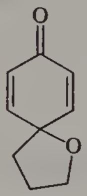
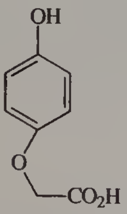
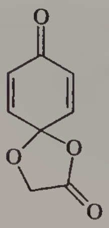
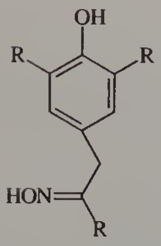
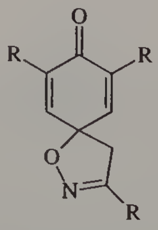
Several oxidations of this kind were performed inter- and intramolecularly. In the first case with 4-methoxyphenols and electron-rich styrenes or propenylbenzenes, dihydrobenzofuran derivatives were formed [19]:



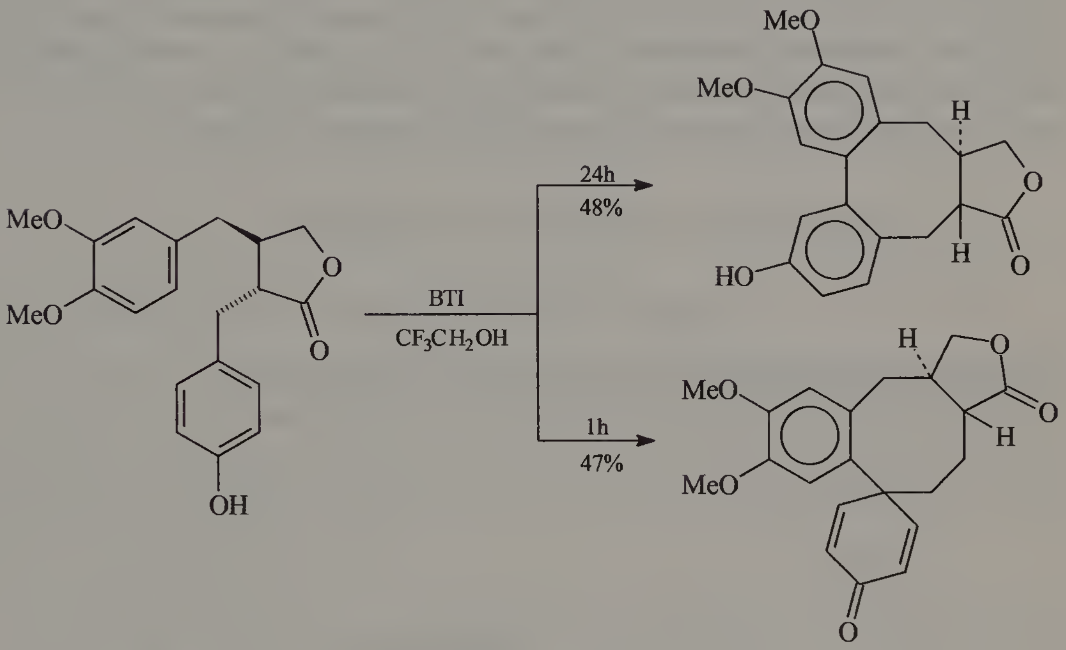
Many examples of this reaction were reported; the same products were also obtained electrochemically but the use of BTI, apart from the obvious handling convenience,

TABLE 4.3

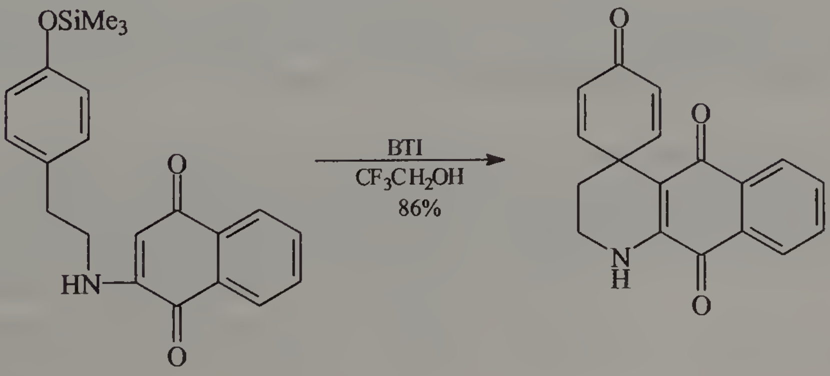
4,4-Disubstituted cyclohexa-2,5-dienones from BTI oxidation of phenols

Substrate	Product	Yield (%)	Ref.
Intermolecularly			
 (with H_2O)		78	[13]
 (with H_2O)		R= H, 27 R= Pr_3Si, 59	[13]
 (with EtOH)		99	[14]
 (with F^-)		66	[15]
Intramolecularly			
		59	[14]
		80	[14]
		(52–93)	[16]

had in several substrates the added advantage of better yield. The products obtained in this way were useful as units in neolignan-derived natural products. A related intramolecular oxidation was effected in a substituted dibenzylbutyrolactone which in trifluoroethanol afforded as major products two cyclooctane derivatives, depending on reaction time [20]:

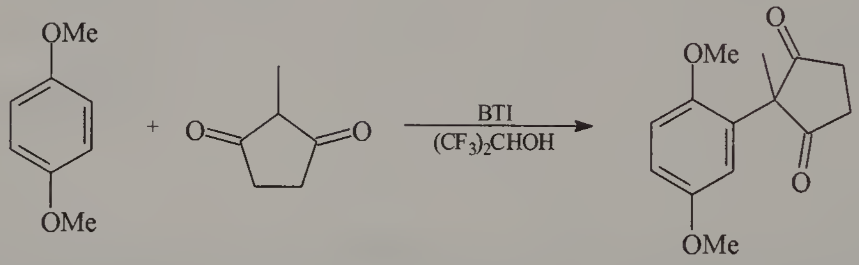

MeO
MeO
OH
O
O
BTI
CF_3CH_2OH
24h
48%
1h
47%
MeO
MeO
HO
H
H
O
O
H
O
O
H
MeO
MeO
O

Not only phenols but also their *O*-silyl derivatives and phenol ethers reacted similarly. In *O*-silylated phenols bearing an aminoquinone moiety at their *para*-position BTI oxidation resulted in the formation of cyclized products in high yield [21]:


$OSiMe_3$
HN
O
O
BTI
CF_3CH_2OH
86%
O
O
O
N
H

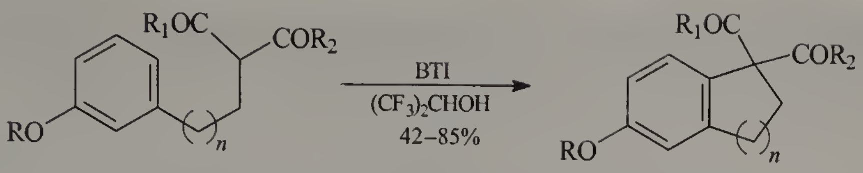
Several analogues of the above substrate bearing a quinoline-5,8-dione or 2-methylbenzofuran-4,7-dione or other heterocyclic moiety afforded similarly the corresponding azacarbocyclic spirodienones in good yield. This type of oxidative cyclization was a crucial step in a synthesis of discorhabdin C. Aminoquinone analogues bearing an *ortho* or *meta* phenolic hydroxyl or trimethylsilyloxy group gave with BTI 2,3-dihydro-1*H*-azepine systems [22]. Generally, oxidative coupling of related intramolecular processes has been reported in several instances in alkaloid syntheses; although the yields were low, often no other oxidant was suitable. *p*-Substituted phenol ethers in the presence of *β*-dicarbonyl compounds underwent oxidative nucleophilic substitution; in this way several aromatic substrates reacted with 2-methylcyclopentanedione, 2-methylcyclohexanedione and 3-acetylbutyrolactone in hexafluoro-2-propanol to give arylated carbonyl compounds.

2-(2,5-Dimethoxyphenyl)-2-methyl-1,3-cyclopentanedione [23]



To a stirred solution of the aromatic substrate (13.8 mg, 0.1 mmol) and the *β*-dicarbonyl compound (6.6 mg, 0.5 mmol) in hexafluoro-2-propanol (0.5 ml) was added BTI (43 mg, 0.1 mmol) at room temperature under nitrogen. The reaction mixture was stirred for 15 min and then concentrated; the residue was purified by column chromatography (silica gel, hexane–ethyl acetate) to give 2-(2,5-dimethoxyphenyl)-2-methyl-1,3-cyclopentanedione (16.5 mg, 66%), m.p. 165–166°C.

Other nucleophiles such as trimethylsilyl azide or trimethylsilyl acetate reacted in the same way and the azido or acetoxy group was similarly introduced to the aromatic substrate. Phenol ethers incorporating a *β*-diketonic moiety at the *meta*-position underwent an analogous intramolecular aromatic alkylation [24]:



(n=1 or 2 ; R=Me, $MeOCH_2$ or Bu^tMe_2Si; R_1,R_2= Me, Et)

4.4 OXIDATION OF NITROGEN COMPOUNDS

4.4.1 Degradation of carboxamides to amines

With some exceptions, BTI is considered to be the best choice for the Hofmann type degradation of carboxamides to primary amines. Generally, treatment of an aliphatic primary carboxamide with BTI in aqueous acetonitrile (at an acidic pH 1–3), followed by addition of hydrochloric acid delivers the corresponding amine hydrochloride in excellent yield.

Conversion of amides into amines [25]

$$RCONH_2 \xrightarrow[\text{(ii) HCl}]{\text{(i) BTI, MeCN/ }H_2O} RNH_3^+Cl^-$$

BTI (1.73 g, 4 mmol) was dissolved in acetonitrile (6 ml) and water (6 ml) was added. The amide (4 mmol) was added to this solution which was stirred at room temperature for about 6 h. The reaction mixture was diluted with water (75 ml), concentrated hydrochloric acid (8 ml) was added and the mixture was extracted with ether (75 ml). The aqueous layer was concentrated to give a residue which was dried *in vacuo* and purified by recrystallization, to give the hydrochloric salt of the amine.

Some precautionary measures for the effective use of BTI have been advised: they include protection of BTI from light and its storage under nitrogen , the use of glass-distilled water in the reaction medium, and the exclusion of chloride ions from the starting amide (if it is prepared from an acyl chloride).

The rearrangement occurred with complete retention of configuration in the migrating group in two cases, but with complete racemization in another. The range of substrates that react with BTI includes a great variety of amides; some representative examples are illustrated in Table 4.4.

TABLE 4.4

Rearrangement of primary amides to amines induced by BTI

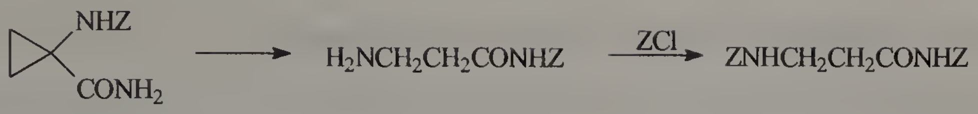
$RCONH_2 \rightarrow RNH_2$

R	Yield (%)	Ref.	R	Yield (%)	Ref.
C_2H_5	85	[25]	1-naphthylCH_2	85	[25]
C_5H_{11}	92	[25]	$AcNHCH(CH_2Ph)$	79	[25]
Me_3C	92	[25]	$ArSO_2(CH_2)_5$	40–76	[26]
cyclobutyl	69–78	[25]	$ArCO(CH_2)_5$	38–70	[27]
1-adamantyl	85	[25]	Z-$NHCH(CO_2H)CH_2$	38–87[a]	[28]
3-cyclohexenyl	75	[25]	$MeCONHCH(Pr^i)$	82	[29]
$HO_2CCH_2CH_2$	81	[25]	$(HO)_2P(O)CH_2CH_2$	56	[30]
			$HO_2CCH(OAc)CH_2$	82	[31]

[a] Z is carbobenzoxy ($OCOCH_2Ph$).

Besides simple aliphatic amides, cycloalkane carboxamides, amides of arylalkanoic acids, and amides bearing a carboxylic, carbethoxy, or another secondary or tertiary carboxamido group, were all converted readily into amines. The presence of isolated double bonds did not interfere; however, amides with an α-double bond gave mainly carbonyl compounds. Alkyl isocyanates may be isolated under appropriate conditions, because they hydrolyse more slowly than they are formed. The use of BTI has the advantage over DIB that the trifluoroacetic acid liberated helps the reaction in two ways: it protonates the amine, which then cannot react with any alkyl isocyanate present affording unwanted dialkylureas, and also it catalyses the hydrolysis of isocyanates. Aromatic amides are not suitable substrates because the amines formed are further oxidized by BTI. Similarly, amides of the $ArSO_2(CH_2)_5CONH_2$ type with a polyalkylated benzene ring gave poor yields of the amine, due to ring-oxidation. It is noted, that the normal Hofmann rearrangement failed completely with any member of this family of amides. For aliphatic amides with long chains (C_{12} to C_{21}), the use of [hydroxy(tosyloxy)iodo]benzene appears to be preferable (Section 7.4.1).

Numerous applications, especially in peptide chemistry, have taken advantage of this reactivity of BTI towards amides and peptidic amides [32]. Here it may be added that *N*-protected aminocyclopropanic amides underwent ring-opening in their reaction with BTI (two equivalents); the *β*-amino amide formed was obtained quantitatively on addition of benzyloxycarbonyl chloride ($Z = PhCH_2OCO$) [33]:



4.4.2 Transformations of *N*-methoxyamides

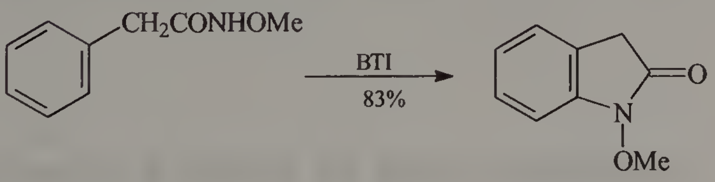
Treatment of aliphatic *N*-methoxyamides with BTI resulted in the formation of an intermediate, RCON(I^+Ph)Me, which in the presence of arenes (benzene, anisole) in excess underwent arylation to give *N*-aryl-*N*-methoxy-amides.

N-*Aryl*-N-*methoxyamides from* N-*methoxyamides* [34]

$$\text{RCONHOMe} + \text{ArH} \xrightarrow{\text{BTI}} \text{RCON(Ar)OMe}$$

A solution of the methoxyamide (2 mmol) in chloroform (5 ml) was added to a stirred solution of BTI (2.6 mmol) in chloroform (10 ml) at 65°C over 3 min under argon. After 3 min stirring, the reaction mixture was poured into saturated aqueous sodium bicarbonate solution, extracted with dichloromethane and dried. Concentration and chromatographic purification afforded *N*-aryl-*N*-methoxyamides in yields in the range 64–82%. With anisole a mixture of *o*- and *p*-isomers was obtained (29% and 53%, respectively).

An analogous intramolecular transformation was also successful, as illustrated in the following cyclization [34]:

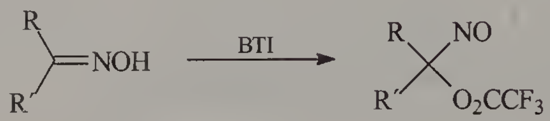


However, some more complex *N*-methoxyamides, rather unexpectedly, afforded 1,5-benzodiazonine derivatives [35].

4.4.3 Oxidation of other nitrogen compounds

In contrast to the plethora of reactions between DIB and *N*-containing compounds, BTI has so far limited applications. Among them, its reactivity with oximes is of interest, because several products are formed, depending on the substrate [36]. Aromatic oximes were converted directly into ketones in good yield, whereas aliphatic ketoximes gave isolable intermediates, i.e. 1-nitroso-1-trifluoroacetoxyalkanes.

1-Nitroso-1-trifluoroacetoxyalkanes from oximes [37]



To a suspension of the oxime (1 mmol) in dichloromethane (10 ml) was added a solution of BTI (430 mg, 1 mmol) in dichloromethane (10 ml) at 0°C; an intense blue colour was immediately developed and the oxime was consumed after a few minutes of stirring. The reaction mixture was washed with water, the organic layer dried for 2 h, and, after concentration, the residue was chromatographed (silica gel, hexanes–chloroform) to give the title compounds as oils. It is essential to perform the separation as quickly as possible, because the products are readily converted in solution into ketones. The yields of isolated 1-nitroso-1-trifluoroacetoxyalkanes ranged between 44% and 67%, e.g. the compound from the oxime of cyclohexanone was obtained in 53% yield.

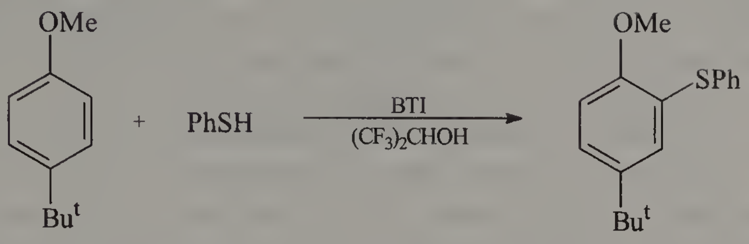
With BTI mixtures of aldazines aromatic aldoximes gave their di-*N*-dioxides and benzonitrile oxides; sterically hindered precursors such as 2,4-dichlorobenzaldoxime and mesitylaldoxime afforded predominantly nitrile oxides.

Efficient dehydrogenation occurred in some N-H containing compounds of various types, e.g. in hydrazine derivatives to azo compounds accompanied by cyclization [38] and in tetrahydroquinoxaline derivatives to quinoxalines [39].

4.5 TRANSFORMATIONS OF SULPHUR COMPOUNDS

Thiophenols are normally oxidized by BTI to disulphides. However, when they were treated with BTI in the presence of a phenol ether, sulphenylation of the latter occurred with formation of diaryl sulphides.

Sulphenylation of p-*t-butylanisol* [40]



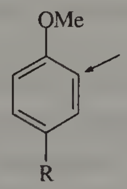
To a stirred solution of the phenol ether (20.7 mg, 0.126 mmol) and thiophenol (27.8 mg, 0.252 mmol) in hexafluoro-2-propanol (1 ml) was added BTI (81 mg, 0.189 mmol), at room temperature, under nitrogen. The reaction mixture soon turned green, due to the formation of a radical cation. After 30 min of stirring the solution was concentrated and the residue purified by column cromatography (silica gel, hexane–ethyl acetate) to give the title compound (23 mg, 67%) as an oil.

Dialkoxybenzenes were very reactive and gave bis sulphenylated products. 1,4-Dimethoxynaphthalene underwent sulphenylation with thiophenols having electron-withdrawing groups such as *p*-nitrothiophenol (87%), whereas those with electron-donating groups gave products in low yield. A selection of the numerous substrates sulphenylated by thiophenol are shown in Table 4.5.

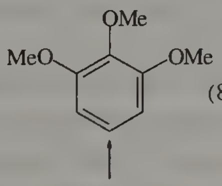
By using BTI and trimethylsilyl thiocyanide in hexafluoro-2-propanol, phenol ethers were thiocyanated efficiently [41] (see Section 6.4.5 for an aternative method). Simple sulphides are readily oxidized by BTI, as expected; diaryl

TABLE 4.5

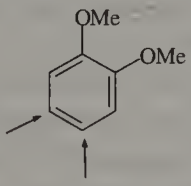
Activated aromatics sulphenylated by thiophenol- BTI (at the site indicatedby an arrow) (yield, %) [40]



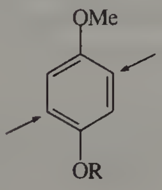
(62–70)



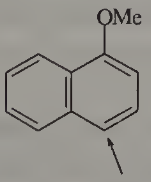
(88)



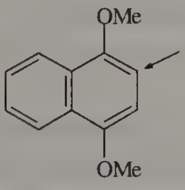
(88)



(68–75)



(81)

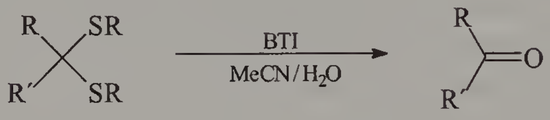


(62)

sulphides can give their sulphoxides or sulphones, depending on the relative amounts of reactants and the temperature. For example, diphenylsulphide with 1 equiv. of BTI in chloroform at 20°C gave the sulphoxide (88%), whereas with 4 equiv. of BTI at 63°C the sulphone (91%) was produced; thianthrene was transformed exclusively to its *trans*-disulphoxide (93%). Dibenzylsulphide was converted predominantly into benzyl trifluoroacetate [42].

BTI is a very efficient reagent for the regeneration of aldehydes and ketones from their dithiacetals. As usual, reaction conditions are very mild, with yields impressively high. A great variety of substrates have in this way undergone dethioacetalization, so that BTI has become the reagent of choice for this transformation. The fate of the sulphur-containing moiety has not been identified.

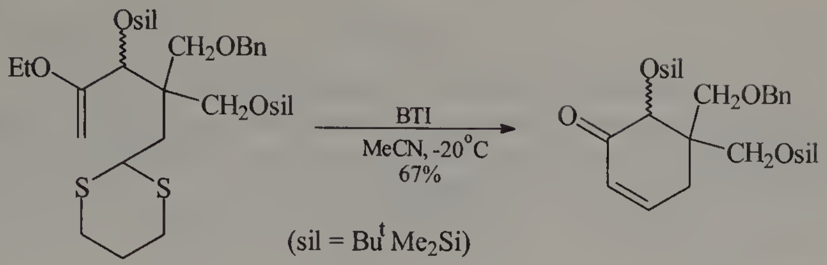
Conversion of dithiacetals into carbonyl compounds [43]



BTI (645 mg, 15 mmol) was added to a stirred solution of dithiacetal (10 mmol) in either methanol–water (9:1) or acetonitrile–water (9:1) (10 ml), at room temperature. After 1–10 min the reaction was completed; the solution was then poured into a saturated aqueous solution of sodium bicarbonate (20 ml) and extracted with ether (3 × 20 ml). After drying and concentration, the residue was purified by flash chromatography (silica gel, hexanes–ethyl acetate) to give the carbonyl compound in up to 97% yield.

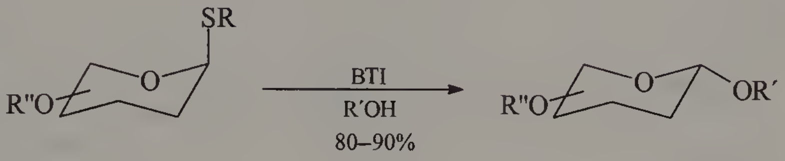
In contrast to other methods, functional groups such as esters, amides, nitriles, alkenes, alkynes, etc. were unaffected, under these conditions. In pure methanol, ethanol or ethylene glycol, thioacetals were converted to acetals. The use of [bis(trichloroacetoxy)iodo]benzene gave equally good results [44]. Generally, since trichloroacetic acid is ~3 times cheaper than trifluoroacetic acid on a mole basis, [bis(trichloroacetoxy)iodo]benzene may be an alternative to BTI.

Some substrates incorporating an enolic ester functionality and a 1,3-dithiane ring reacted in an unexpected way, when their dethioacetalization was attempted, affording aldol-type condensation products e.g. [45]:



(sil = Bu^tMe_2Si)

Thioglycosides reacted in an analogous way with BTI and alcohols to give *O*-alkyl glycosides in high yields [46]:



A high degree of stereoselectivity was also noted, involving inversion, i.e. *β*-substrates afforded mainly *α*-products and *vice versa*. It is remarkable that among several oxidants BTI gave the best results, with ratios of stereoisomers up to 30:1.

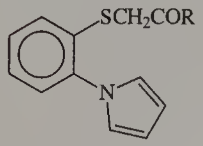
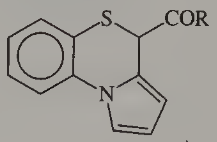
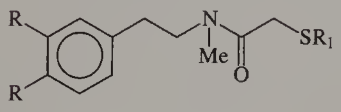
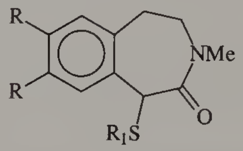
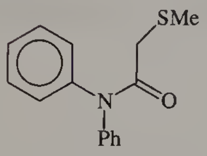
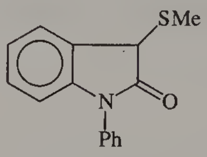
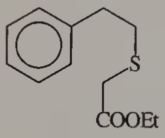
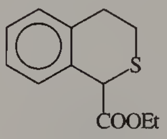
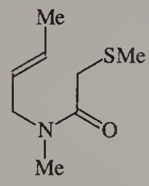
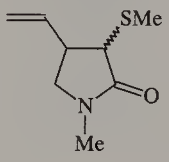
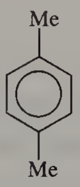
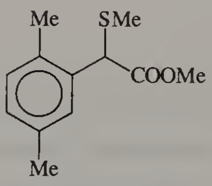
BTI is a useful reagent for Pummerer-type reactions of *α*-acyl sulphides. Instead of being separately oxidized to their sulphoxides, the sulphides were converted *in situ* into sulphonium salts; these subsequently reacted with added aromatics or intramolecularly to afford various products. These reactions were performed in boiling 1,2-dichloroethane and some results are illustrated in Table 4.6.

Diaryl diselenides were oxidatively cleaved by BTI to form selenenyl trifluoroacetates, $CF_3COOSeAr$. This reaction served for the preparation of selenosulphonates which resulted in good yield when BTI was added to a mixture of sodium sulphinate and diaryl diselenide [49]:

$$ArSO_2Na \quad + \quad Ar'SeSeAr' \xrightarrow[\text{CH}_2\text{Cl}_2,\ 0\,^{\circ}\text{C} \\ 62\text{–}83\%]{\text{BTI}} ArSO_2SeAr'$$

TABLE 4.6

Pummerer-type reaction of α-acetylsulphides with BTI

Substrate	Product	Yield (%)	Ref.
		57–64	[47]
		56–61	[47]
		63	[48]
		74	[48]
		63	[48]
MeSCH$_2$COOMe + 		80	[48]
MeSCH$_2$COOMe + MeOH	MeSCH(OMe)COOMe	48	[48]

4.6 MISCELLANEOUS TRANSFORMATIONS

4.6.1 Iodination of aromatics

The formation of unstable trifluoroacetyl hypoiodite on reaction of BTI with elemental iodine has been used for aromatic iodination. This method has some advantages over other methods, since it is carried out at room temperature and work up is convenient.

Aromatic iodination [50]

$$\mathrm{PhI(O_2CCF_3)_2} + \mathrm{I_2} \longrightarrow 2\,\mathrm{CF_3CO_2I} + \mathrm{PhI}$$

$$\mathrm{ArH} + \mathrm{CF_3CO_2I} \longrightarrow \mathrm{ArI} + \mathrm{CF_3CO_2H}$$

A suspension of the arene (10 mmol), iodine (2.54 g, 10 mmol) and BTI (4.73 g, 11 mmol) in carbon tetrachloride (15 ml) was stirred at room temperature for 15 min to 5 h. Iodoarenes of poor solubility were isolated by simple filtration, otherwise, after concentration, the residue was chromatographed on a short column of silica gel (hexanes) to give the iodoarene in high yield.

Substrates iodinated in this way included simple aromatics and also thiophenes [51] and a porphyrin [52].

4.6.2 Trifluoroacetoxylation and hydroxylation of various substrates

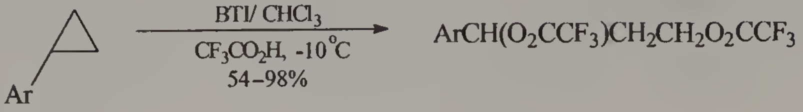
Reactions of this type are relatively few, in comparison to those of DIB. Alkyl benzyl ethers afforded benzaldehyde and alkyl trifluoroacetates in a potentially useful reaction for the deprotection of benzylated alcohols under oxidative conditions, since trifluoroacetates are hydrolysed very easily [53]:

$$\mathrm{C_8H_{17}OCH_2Ph} \xrightarrow[\substack{\mathrm{CF_3CO_2H/CHCl_3}\\ 72\%}]{\mathrm{BTI}} \mathrm{C_8H_{17}O_2CCF_3} + \mathrm{PhCHO}$$

An analogous reaction occurred with oxiranes which underwent mainly carbon–oxygen bond cleavage, with formation of α-hydroxyketones. In some instances by-products arising from carbon–carbon bond cleavage were also formed; in triphenyloxirane this mode dominated and the sole product was the hydroxyketone $\mathrm{Ph_2C(OH)COPh}$ (80%) [54].

Alkyl iodides upon oxidation by BTI in presence of lithium perchlorate afforded alkyl perchlorates in a reaction where trifluoroacetate competed with perchlorate [55]; α-iodoketones were directly converted into α-hydroxyketones [56]. This transformation gave better yields than an analogous hydroxylation of ketones directly with BTI (Section 4.2).

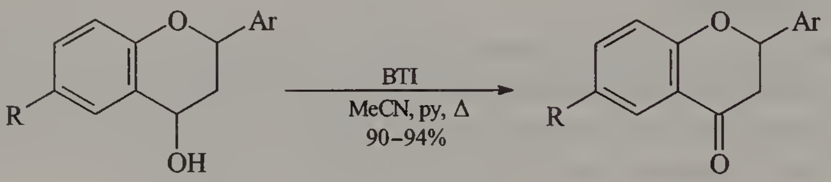
Alkenes formed bis trifluoroacetates of glycols in their reaction with BTI; with phenylated alkenes rearranged products dominated, e.g. tetraphenylethylene was converted into triphenylacetophenone (93%) [57]. Mono- and bis-arylated cyclopropanes gave 1,3-bis-trifluoroacetoxypropanes [58]:


Ar
BTI/ CHCl3
CF3CO2H, -10°C
54–98%
ArCH(O2CCF3)CH2CH2O2CCF3

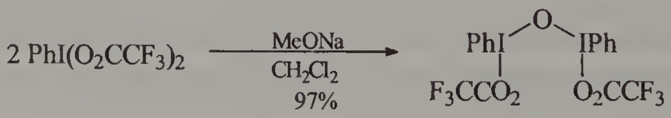
The aliphatic iodane $C_3F_7I(O_2CCF_3)_2$ was reactive towards alkenes; for example, with 1-hexene it gave 1,2-bis-trifluoroacetoxy-hexane (68%); with cyclohexene the quantitative formation of *trans*-1-iodo-2-trifluoroacetoxy adduct occurred, at 0°C [59].

4.6.3 Other oxidations

Simple alcohols are not oxidized readily by BTI; however, flavonols in the presence of pyridine in boiling acetonitrile gave flavanones in excellent yields [60]:


O
Ar
R
OH
BTI
MeCN, py, Δ
90–94%
O
Ar
R
O

In several instances BTI has been used for the preparation of other hypervalent iodine compounds, such as iodonium salts and zwitterions. Of special interest is its reaction with hard nucleophiles which attack the carbonyl carbon rather than iodine, with eventual formation of a *meso*-compound [61]:


2 PhI(O2CCF3)2
MeONa
CH2Cl2
97%
O
PhI
IPh
F3CCO2
O2CCF3

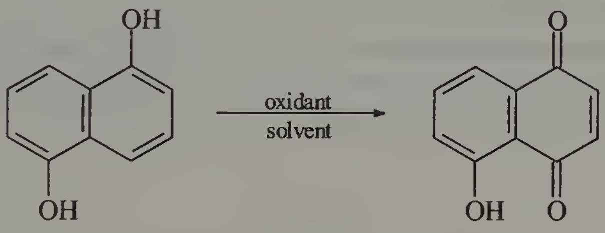
The oxidative properties of this stable compound have not been explored in detail but it appears that they are more pronounced than those of BTI. For example, 9,10-dihydroanthracene was oxidized to anthraquinone (68%) at room temperature, whereas the use of BTI required heating and the product was anthracene in low yield.

Part B: Reactions with [bis(acyloxy)iodo]arenes

Apart from oxidations of special nature, the main characteristic of this class of compounds, including DIB and BTI, is their thermal or photochemical decomposition which in conjunction with suitable reagents leads to interesting synthetic applications.

4.7 OXIDATIONS

When [bis(acyloxy)iodo]arenes have electron-withdrawing groups either in the phenyl ring or in the acyloxy moiety, their oxidizing power increases generally. In a comparative study of the conversion of 1,5-dihydroxy-naphthalene to juglone, the following yields were obtained, under similar conditions [62]:



oxidant :	DIB	PhIO	BTI	$C_6F_5I(O_2CCF_3)_2$	$C_6F_{13}I(O_2CCF_3)_2$
yield % :	26	47	58	76	91

The strong oxidant $C_6F_5I(O_2CCF_3)_2$ brought about the cleavage of acetophenones to the corresponding benzoic and other acids under mild conditions; cyclohexanone was similarly converted into adipic acid (with 3 equivalents of oxidant) and dimedone to 3,3-dimethylglutaric acid [63]. A related cleavage occurred under more drastic conditions with alkynes which were converted into acids [64]. The same reagent was useful also for bond formation: exceptionally high yields were reported in some phenolic oxidations leading to the formation of a dihydro-oxepin ring during the synthesis of some alkaloids [65].

Compounds of phosphorus (III) are readily oxidized by [bis(acyloxy)iodo]-benzenes; in this way, the reaction with triphenylphosphine led to the formation of acid anhydrides at room temperature:

$$PhI(O_2CR)_2 + Ph_3P \xrightarrow[-PhI]{CHCl_3} (RCO)_2O + Ph_3PO$$

Although the reaction was very clean (quantitative by NMR), most anhydrides were isolated in moderate yield because of difficulties in the isolation procedure [66].

4.8 HOMOLYTIC ALKYLATION AND ARYLATION

Carbon-centred free radicals may be formed readily either directly from [bis(acyloxy)iodo]arenes, thermally or photochemically, or from added precursors such as alkyl iodides, acids and alcohols, mediated by DIB, BTI or a [bis(acyloxy)iodo]arene. Table 4.7 presents approaches applied for the generation of free radicals in this way.

Decarboxylation of acids is of special interest, since the free radicals produced may combine with iodine, heteroaromatic bases or electron-deficient alkenes affording useful products in clean reactions.

4.8.1 Alkyl iodides from acids

This is a modified Hunsdiecker reaction which avoids some of the difficulties associated with the use of heavy metals, i.e. troublesome work up procedures and the need to use an excess of toxic oxidant. For this transformation there is no need to convert the acid into its $PhI(O_2CR)_2$ derivative, since it is formed *in situ* using DIB.

TABLE 4.7

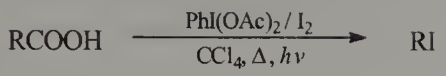
Generation of carbon-centred free radicals through [bis(acyloxy)iodo]arenes[a]

$ArI(O_2CR)_2 \xrightarrow[\text{or } h\nu]{\Delta} R^{\bullet}$
$ArI(O_2CR)_2 + RCO_2H \xrightarrow[\text{or } h\nu]{\Delta} R^{\bullet}$
$PhI(OAc)_2 + RCO_2H + I_2 \xrightarrow{h\nu} R^{\bullet}$
$PhI(OAc)_2 + RCO_2H + RI \longrightarrow R^{\bullet}$
$ArI(O_2CR)_2 + ROOCCOOH^{b} \xrightarrow{h\nu} R^{\bullet}$
$ArI(O_2CCO_2R)_2 \xrightarrow{h\nu} R^{\bullet}$
$PhI(OAc)_2 + NaN_3 + RCH_2OH \longrightarrow R^{\bullet}$

[a] For references, see text.

[b] In these cases $R^{\cdot}$ comes from an alcohol; for the oxidation of ROH to $RO^{\cdot}$, see Section 3.8.1.

Conversion of acids to alkyl iodides [67]

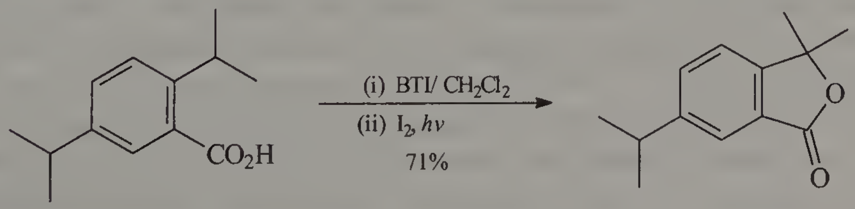


$$\text{RCOOH} \xrightarrow[\text{CCl}_4,\ \Delta,\ h\nu]{\text{PhI(OAc)}_2\ /\ \text{I}_2} \text{RI}$$

A solution or suspension of the acid (1 mmol) in carbon tetrachloride (75 ml) containing DIB (0.55 mmol) and iodine (0.5 mmol) was irradiated with two 100 W tungsten-filament lamps for 45 min at reflux temperature. Another portion of DIB (0.55 mmol) was then added and irradiation was continued for 45 min at reflux. The reaction mixture was washed with dilute sodium thiosulphate and water, concentrated and chromatographed (silica gel column, 9:1 hexanes–ethyl acetate) to afford the alkyl iodide. Several steroidal acids with the carboxyl group attached at a 1° or 2° carbon atom gave the corresponding iodides in good yields. Acids with a 3° α-*C* instead of the iodide afforded alkenes; similarly, alkenes were formed with a fivefold excess of DIB in the presence of cupric acetate. Aromatic acids also underwent iododecarboxylation, in moderate yields; very effective was the otherwise difficult transformation of 1,8-naphthalenedicarboxylic acid to 1,8-diiodonaphthalene (80%) [68]. Cubyl and homocubyl iodides were also prepared in excellent yield [69].

4.8.2 Synthesis of lactones from aromatic acids

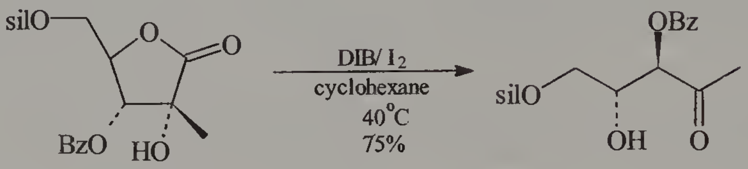
The oxidative radical cyclization of *o*-alkyl and *o*-arylbenzoic acids by BTI and iodine, photochemically, was a good way to prepare γ- and δ-lactones from these acids. The experimental conditions were similar to those mentioned in the previous Section but milder, since no heating was required and the amount of iodine was 0.1 equiv. in respect to BTI. In the following example, a small amount of an iodinated δ-lactone was also formed [70]:



Generally, this methodology was superior to an analogous approach using lead tetraacetate.

4.8.3 Fragmentation of α-hydroxylactones

Not only acids but also α-hydroxylactones (γ- and δ-) when submitted to the system DIB-iodine underwent oxidative decarboxylation, accompanied by β-fragmentation. This reaction took place under non-photochemical conditions in various solvents, at 20–58°C. The substrates – mainly sugar derivatives – eventually yielded, after a mechanistically interesting route, β-iodo or α,β-unsaturated compounds. An example follows [71]:



4.8.4 Alkylation of heteroaromatic bases (substitution)

The possibility to alkylate a variety of nitrogen-containing heterocycles, using hypervalent iodine reagents to induce the generation of free radicals, has considerable synthetic utility and potential. The combination of three kinds of reactants, i.e. heterocycle, iodine reagent and the radical source has resulted in a wide area of applications, extending to the synthesis of *C*-nucleosides. These reactions follow the general pattern [72]:

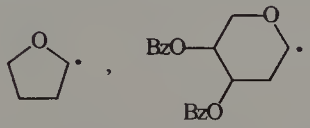
$$\text{Het}-\text{H} + \text{R}^{\bullet} \xrightarrow[-\text{H}^{\bullet}]{\text{H}^{+}} \text{Het}-\text{R}$$

The presence of a strong acid such as trifluoroacetic acid is beneficial, because the protonated heterocycles possess increased reactivity. Satisfactory yields were also obtained using BTI in the absence of added acid, which was, however, produced from BTI. An idea about the applicability of this methodology can be formed from Table 4.8.

DIB, BTI and perfluoro-DIB were suitable precursors; the last was most effective under photochemical conditions, whereas DIB and BTI were used either thermally or photochemically; for DIB, best results were obtained with added trifluoroacetic acid, photochemically. Not only alkyl but other more complex free radicals could also be introduced, notably acyl radicals. Products derived from acids bearing sugar moieties were obtained in low to moderate yield. In the case of acetonides complete retention of the initial configuration was observed. This high diastereoselectivity

TABLE 4.8

Radical decarboxylative alkylation of heteroaromatic bases mediated by [bis(acyloxy)iodo]arenes

The reaction partners	
Free radicals	Heteroaromatic bases[a]
a. From $PhI(O_2CR)_2$:	4-X-pyridines
1-adamantyl, C_6H_{11}, $PhCH_2CH_2$	(X = Me, Ac, CN, CO_2Me, etc.)
b. From RCO_2H:	methyl nicotinate
1-adamantyl, C_6H_{11}, C_4H_9, Me_2CH,	quinolines
Me_3C, $PhOCH_2$, PhCO,	phthalazine
$CH_2{=}CHOCH_2CH_2$	benzothiazole
, etc.	
c. From RO_2CCO_2H:	
(-)-menthyl, (-)-bornyl, etc.	
d. From RI:	
C_4H_9, Me_2CH, C_6H_{11}	

[a] Alkylation α- or γ- to nitrogen; for references, see text.

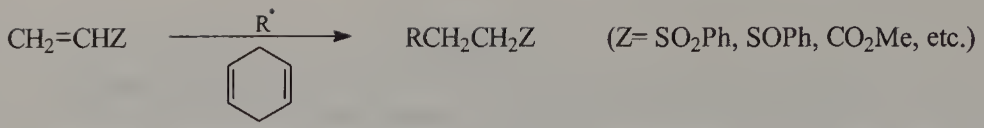
was assigned to the non-planarity of the free radical. However, benzyl and benzoyl protected sugar acids showed less pronounced diastereoselectivity, with ratios of $\alpha:\beta$ isomers only 3:2. The use of such substrates is of special importance for the synthesis of unnatural *C*-nucleosides [73–77].

4.8.5 Alkylation of electron-deficient alkenes (addition)

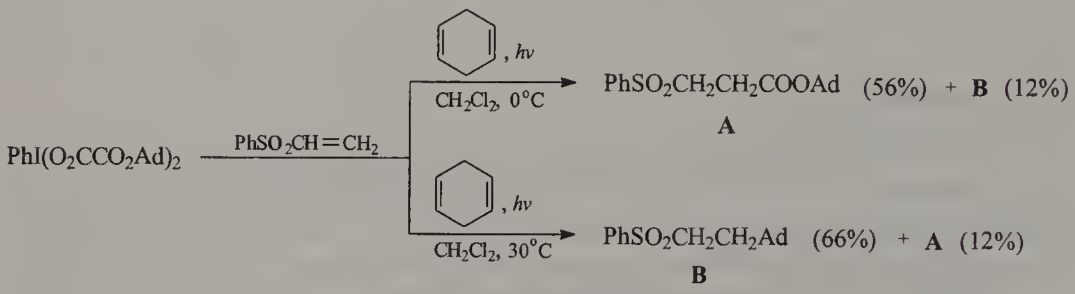
In this category the source of free radicals were either [bis(acyloxy)iodo]benzenes or [bis(alkoxyoxalyloxy)iodo]benzenes of the following kind:

$PhI(O_2CR)_2$; R = 1-adamantyl, 2-tetrahydrofuranyl, several cycloalkyl, benzoylated α- and β-2-deoxy-ribopyranyl, (*L*)-MeCH(OAc) $PhI(O_2CCO_2R)_2$; R = 1-adamantyl, ethyl, 2-phenylethyl, (−)-menthyl, cycloalkyl, 3-butenyl, 1-methyl-3-butenyl.

When these compounds were treated photochemically with electron-deficient alkenes in the presence of an excess of 1,4-cyclohexadiene, serving as hydrogen donor, reductive addition products were obtained according to the generalized scheme [78]:



Yields ranged from 40 to 90%; the best coming from precursors producing tertiary and secondary free radicals. Divinyl sulphone gave either mono- or bis-adducts according to the ratio of reactants. The use of [bis(alkoxyoxalyloxy)iodo]benzenes permitted the generation not only of alkyl radicals but also of alkoxycarbonyl radicals, simply by changing the reaction conditions, notably the temperature (also the solvent and concentration). In this way $PhI(O_2CCO_2Ad)_2$ reacted with phenyl vinyl sulphone to give mixtures of two products, A and B. The selectivity was better with some other $PhI(O_2CCO_2R)_2$:


PhI(O2CCO2Ad)2
PhSO2CH=CH2
, hν
CH2Cl2, 0°C
PhSO2CH2CH2COOAd (56%) + B (12%)
A
, hν
CH2Cl2, 30°C
PhSO2CH2CH2Ad (66%) + A (12%)
B

Eventually, the use of $p\text{-}MeC_6H_4I(O_2CAd)_2$ gave the best results for the addition of 1-adamantyl (Ad) and hydrogen to phenyl vinyl sulphones [78].

4.8.6 Further alkylations involving the 1-adamantyl free radical

In addition to the reactions discussed in the previous section, the free radical produced photochemically from $PhI(O_2CAd)_2$ reacted with alkyl or aryl or cyclic disulphides to afford the corresponding adamantyl sulphides in good yield [79]:

$$PhI(O_2CAd)_2 + RSSR \xrightarrow[\substack{CH_2Cl_2 \\ 61\text{–}80\%}]{h\nu} AdSR$$

Neat thermolysis of some $ArI(O_2CAd)_2$ produced the adamantyl ester of adamantyl carboxylic acid, AdCOOAd, in up to 56% yield, when Ar was duryl [80].

4.8.7 Arylation and aroyloxylation

The thermal decomposition of $PhI(O_2CAr)_2$ leads to the formation not only of aryl· but also of carboxyaryl free radicals. In the presence of aromatics these radicals cause arylation and to a lesser degree aroyloxylation; for example, with $PhI(O_2CPh)_2$ and 1,4-dichlorobenzene a mixture of 2,5-dichlorobiphenyl (52%) and 2-benzoyloxy-1,4-dichloro-benzene (7%) were formed [81].

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– 5 –

Iodosylbenzene

Iodosylbenzene or iodosobenzene, PhIO (hereafter abbreviated IOB) is formally the anhydride of the non-isolable acid $PhI(OH)_2$, with which it is in equilibrium in water, where it is slightly soluble:

$$PhIO + H_2O \rightleftharpoons PhI(OH)_2$$

IOB is actually polymeric and sometimes is written as $(PhIO)_n$. It depolymerizes readily in alcohols and acids, where it dissolves forming isolable compounds, $PhI(OR)_2$ and $PhI(O_2CR)_2$, respectively. The polymeric character of IOB makes it less suitable as oxidant than other hypervalent reagents, mainly because of its insolubility in ordinary sovents. Its utility is, however, greatly enhanced when it is used with catalysts, notably boron trifluoride or some metal complexes.

5.1 REACTIONS WITH UNSATURATED COMPOUNDS

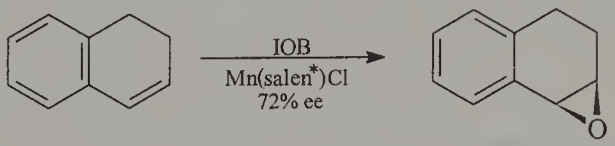
5.1.1 Alkenes

5.1.1.1 Epoxidation

Simple alkenes do not normally react with IOB, unless there is catalysis by metal porphyrins or related metal complexes, in which case epoxidation occurs [1,2]. A great deal of work has been done in this field, especially with the relatively simple catalyst Fe(TPP)Cl (TPP is tetraphenylporphyrin); in some instances this approach can be used advantageously in comparison with other well-known methods of epoxidation. The Fe(TPP)Cl catalysed IOB epoxidation of alkenes is stereospecific, with *cis* substrates being considerably more reactive than *trans*. Several alkenes underwent efficient epoxidation with this system, e.g. cyclooctene (84% of epoxide), norbornene (67% *exo*-epoxide, accompanied by 3% of the *endo*-isomer) and

1,3-cyclohexadiene (93% of monoepoxide) [3]. Pentafluoroiodosylbenzene and modified catalysts (other metal or ligand) can improve considerably the yield and selectivity of the reaction; for example, with polymer-bound Fe(2,6-diClTPP) cyclooctene afforded its epoxide in 93% yield, with a catalyst turnover of 7900 [4].

The design of more sophisticated porphyrins allowed shape-selective epoxidations as well as asymmetric induction [5]. Instead of porphyrins, chiral ligands are also useful in such cases, as the following example illustrates [6]:

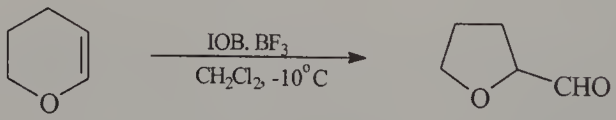


Although most of these numerous studies were of mechanistic rather than synthetic interest, in special cases the potential utility of catalytic epoxidations using IOB should be considered.

IOB alone epoxidizes some electron-deficient alkenes, in a reaction where its oxygen attacks the substrate nucleophilically. An example of this type was with tetracyanoethylene which was converted into its epoxide (74%); similarly, ketenes formed unstable α-lactones which polymerized [7].

5.1.1.2 *Rearrangements*

The electrophilic character of iodine in IOB is greatly increased by the addition of boron trifluoride, probably because of the *in situ* formation of the monomeric dipole $PhI^+OBF_3^-$. Some cycloalkenes reacted with $IOB.BF_3$ undergoing ring-contraction, for example cyclohexene gave formylcyclopentane (60%), and 3,4-dihydro-2*H*-pyran gave tetrahydrofurfural [8]:



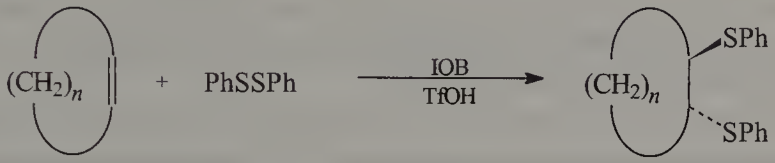
The yield of this transformation (36%) was increased to 80% by using the adduct of IOB and sulphur trioxide (2:1) (Section 12.2.31). A related transformation was the rearrangement of *trans*-stilbene to diphenylacetaldehyde (80%) [8].

5.1.1.3 *Sulphenylation, methoxylation and chlorination*

IOB in the presence of triflic acid (TfOH) is converted into another reagent (Section

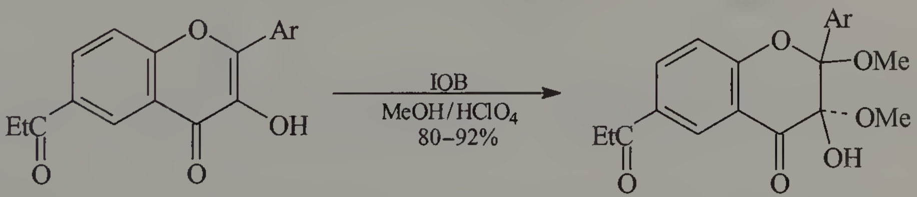
2.4). There is no need to isolate this compound in order to effect addition of diphenyl disulphide (and dimethyl disulphide) to alkenes; in this way *trans*-1,2-bis-phenylthio (and methylthio) adducts were formed from cycloalkenes and 1-hexene.

trans-1,2-Bis phenylsulphenylation of alkenes [9]



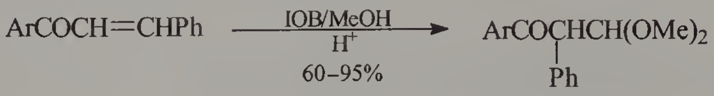
To a stirred suspension of IOB (110 mg, 0.5 mmol) in dichloromethane (20 ml) was added triflic acid (0.044 ml, 0.5 mmol) at 0°C. After 2 h at room temperature, a solution of diphenyl disulphide (238 mg, 1.09 mmol) in dichloromethane (6 ml) was added dropwise at 0°C. After 2 h at room temperature, the alkene (5 mmol) was added at 0°C and the mixture was stirred for 12 h. The reaction mixture was poured into water and extracted with ether. The organic layer was washed with water, dried and concentrated to an oil from which iodobenzene was removed *in vacuo* at 70–80°C. Purification was effected using preparative centrifugal TLC; yields of bis phenylsulphides were near 90%.

Such additions of nucleophiles to non-activated double bonds mediated by hypervalent iodine compounds are also possible in other cases (Section 3.5). This umpolung of reactivity is due to the formation of an adduct with hypervalent iodine which renders this intermediate highly electrophilic. In this way 6-propionylflavonols gave 1,2-dimethoxy-adducts in methanol–perchloric acid [10]:



Hemiacetals of the same kind have also been obtained using [hydroxy (tosyloxy)-iodo]benzene (Section 7.1.2). A variation of bis methoxylation occurred in styrene which with IOB and catalytic amounts of boron trifluoride (or triflic acid) in the presence of methanol gave the rearranged dimethylacetal of 2-phenylethanal,

$PhCH_2CH(OMe)_2$ (80%) [11]. Similarly, rearranged dimethylacetals were obtained from chalcones [11]:



$$\mathrm{ArCOCH{=}CHPh} \xrightarrow[60\text{–}95\%]{\mathrm{IOB/MeOH},\ \mathrm{H^+}} \mathrm{ArCO}\underset{\mathrm{Ph}}{\underset{|}{\mathrm{C}}}\mathrm{HCH(OMe)_2}$$

All these reactions are analogous to those previously effected using thallium nitrate in methanol; however, they gave better yields and, more importantly, the use of the toxic thallium salt was avoided.

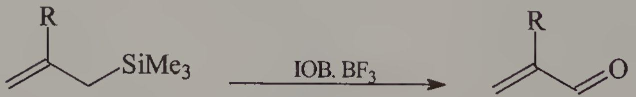
Some solid-state reactions have been reported for the chlorination of alkenes. For example, styrene upon reaction with a mixture of IOB and hydrogen chloride-treated silica gel gave the dichloro adduct (65%); since no solvent was present, it was essential to use efficient crushing and grinding [12].

5.1.2 Alkenylsilanes

Alkenylsilanes (silylalkenes) are very reactive towards $IOB.BF_3$, forming initially iodonium salts, which in some cases are isolable (Section 9.1.2). Normally, at room temperature and in several solvents elimination prevails and alkynes are formed directly; from substrates with an *E*-configuration further treatment with base was required for complete elimination [13].

2-Substituted allylsilanes on treatment with $IOB.BF_3$ (2 equivalents) in dioxane afforded conjugated enals.

Conjugated enals from allylsilanes [14]



To a stirred suspension of the allylsilane (1 mmol) and IOB (2 mmol) in dry dioxane [Caution] (250 ml) was added boron trifluoride etherate (142 mg, 1 mmol) dropwise at room temperature, under nitrogen. After 2 h, cold aqueous sodium bicarbonate was added and the mixture was extracted with ether. The extract was washed with brine and dried. Evaporation left a residue which was purified by preparative TLC, to give the title compounds (63–72%).

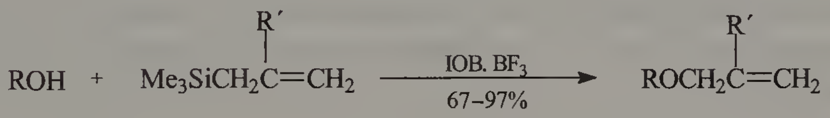
The side chain R in these enals contained functionalities such as a double bond, or an acetoxy group, which were unaffected. The reaction proceeds again through a vinyl iodonium intermediate which serves as a reactive allyl cation. In this way the umpolung of allylsilanes is achieved and, indirectly, the reactivity of allyl halides is considerably increased.

In the reaction of allylsilane with activated arenes a Friedel–Crafts monoalkylation occurred, with formation of allylarenes [15]:

$$\mathrm{Me_3SiCH_2CH{=}CH_2} \xrightarrow[\substack{\text{(ii) ArH}\\ 75\text{–}95\%}]{\text{(i) IOB. BF}_3} \mathrm{ArCH_2CH{=}CH_2}$$

The allylation was successful with benzene, toluene, *p*-xylene, anisole, etc. Thiophene gave an equimolar mixture of 2- and 3-allyl thiophenes (82%); by changing the order of addition of reagents in anisole (it normally gave a 1:4 mixture of *o*:*p*-allylated products), *o*-allyl-iodobenzene was also formed (36%).

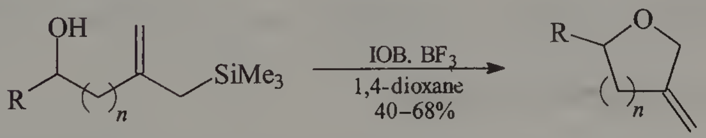
Oxygen nucleophiles, especially alcohols (and an acid) also reacted with the system allylsilane–IOB.BF$_3$. The allylation of several alcohols (in large excess, often serving as solvents) afforded their allyl ethers in good yields [16]:



$$\mathrm{ROH} + \mathrm{Me_3SiCH_2}\overset{\overset{\large R'}{|}}{\mathrm{C}}\mathrm{{=}CH_2} \xrightarrow[67\text{–}97\%]{\text{IOB. BF}_3} \mathrm{ROCH_2}\overset{\overset{\large R'}{|}}{\mathrm{C}}\mathrm{{=}CH_2}$$

(R=Me, Et, PhCH$_2$, MeOCH$_2$CH$_2$)

The allylation of alcohols was applied to the intramolecular cyclization of hydroxyallylsilanes which were converted into 5- and 6-membered *β*-methylene cyclic ethers [17]:



Allylsilanes also reacted with IOB-trimethylsilyl azide to give allylazides (Section 3.5.1).

5.1.3 Alkynes

IOB in the presence of catalytic (1%) amounts of the ruthenium compound RuCl$_2$(Ph$_3$P)$_3$ becomes a very effective oxidant. Among various substrates, it oxidized internal alkynes to *α*-diketones and cleaved terminal alkynes to acids.

From a synthetic point of view, alkynyl ethers and alkynyl amines were readily converted into the corresponding esters and amides.

N,N-*Dimethylamides of α-ketoacids from alkynylamines* [18]

$$\mathrm{RC{\equiv}CNMe_2} \xrightarrow[\text{Ru cat.}]{\text{IOB}} \mathrm{RCOCONMe_2}$$

To a suspension of IOB (5.72 g, 26 mmol) in dichloromethane (50 ml) was added the catalyst $RuCl_2(Ph_3P)_3$ (96 mg in 25 ml of dichloromethane). The substrate (10 mmol) in dichloromethane (25 ml) was then added at once. After stirring for 90 min, excess IOB was filtered out, the solvent was evaporated and the residue purified by column chromatography (silica gel, dichloromethane, then ether) to give the *N,N*-dimethylamides in 44–84% yield.

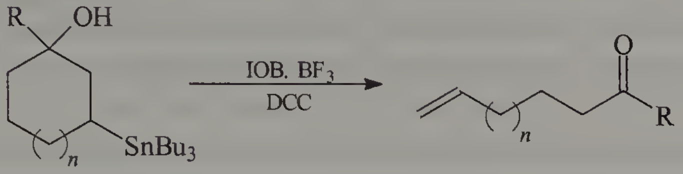
A shorter reaction time (15 min) was required for the analogous conversion of alkynyl ethers, which gave the corresponding esters of α-ketoacids in an average 60% yield [18].

5.2 REACTIONS WITH ALCOHOLS AND CARBONYL COMPOUNDS

5.2.1 Alcohols and silyl ethers

IOB alone can oxidize some alcohols, but catalysed oxidations are much more efficient. Thus, in the presence of $RuCl_2(PPh_3)_2$ primary aliphatic alcohols were oxidized cleanly to aldehydes, at room temperature; the use of *m*-iodosylbenzoic acid instead of IOB considerably increased the yields; for example, hexanal was formed from hexanol quantitatively (by GC) [19]. Another catalytic system involved the use of simple lanthanide salts such as ytterbium triacetate [20]. Cyclic γ-stannyl alcohols, readily available from cyclic vinyl ketones and Bu_3SnLi, underwent oxidation accompanied by carbon–carbon bond cleavage (Grob fragmentation), when treated with $IOB.BF_3$ and DCC. The products were unsaturated aldehydes or ketones.

Unsaturated carbonyl compounds from γ-stannylalcohols [21]

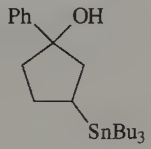
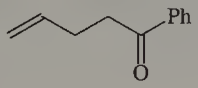
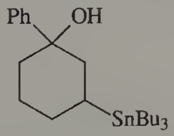
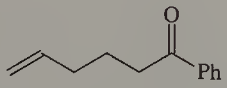
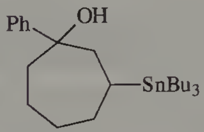
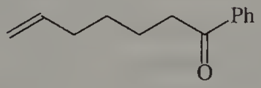
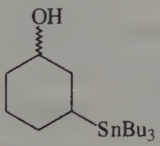
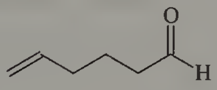
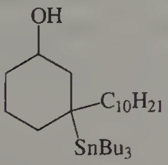
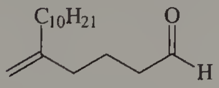
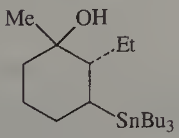
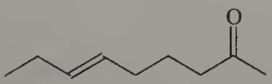


(n = 1, 2)

To a solution of DCC (295 mg, 0.12 mmol) in dichloromethane (0.5 ml) was added boron trifluoride ethereate (170 mg, 0.12 mmol) and the mixture was stirred for 1 h

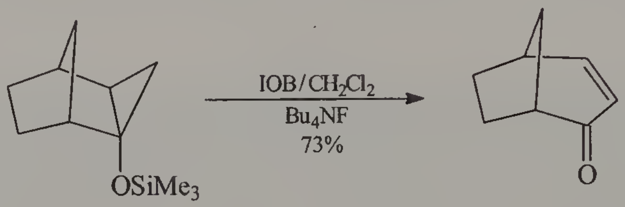
TABLE 5.1

Unsaturated carbonyl compounds by oxidative fragmentation of γ-tributylstannyl alcohols induced by IOB.BF_3/ DCC [21]

Substrate	Product	Yield (%)
		63
		81
		86
		71, from *cis* 74, from *trans*
		18
		67

at room temperature. Then, it was added to a suspension of the substrate (0.1 mmol) and IOB (264 mg, 0.12 mmol) in dichloromethane (0.5 ml) at 0°C and the mixture was stirred for 1–5 h. The reaction mixture was treated with brine and extracted with dichloromethane. The organic layer was dried and concentrated; the crude product was purified by preparative TLC to afford the title compounds, as shown in Table 5.1. The reaction proceeded stereospecifically, when appropriate.

The *O*-silyl derivatives of some tertiary bicyclic or tricyclic alcohols with a cyclopropane moiety upon treatment with IOB, followed by addition of tetrabutylammonium fluoride, underwent oxidation with ring expansion and formation of α,β-unsaturated ketones, for example [22]:

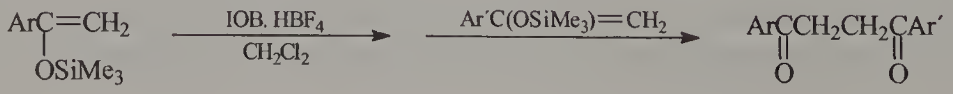


A different reactivity was observed in similar compounds upon DIB oxidation (Section 3.9.1).

5.2.2 Silyl enol ethers

Silyl enol ethers are quite reactive towards IOB-boron trifluoride (or tetrafluoroboric acid) and can be considered as valuable starting materials for several reactions of synthetic importance. Of special interest is their use for carbon–carbon bond formation: 1,4-diketones and unsaturated ketones are the products of such reactions; further, they can be transformed to α-hydroxy, methoxy or trifyloxy ketones. With tetrafluoroboric acid IOB forms a yellow solution containing the highly electrophilic $\text{PhI}^+\text{OH BF}_4^-$, stable up to 0°C. This species reacts readily with silyl ethers of several ketones, notably acetophenones, at −78°C, forming an unstable iodonium ion ($\text{ArCOCH}_2\text{I}^+\text{Ph}$) which with another silyl ether affords 1,4-diketones.

Butane-1,4-diones [23]

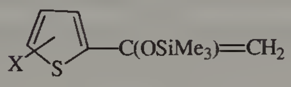
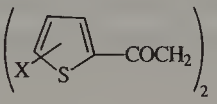
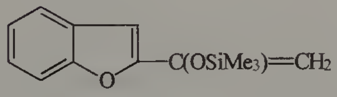
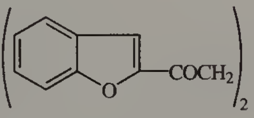
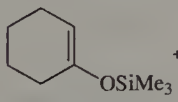
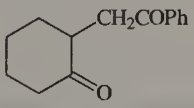
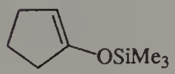
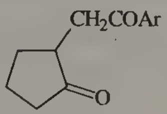
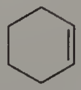
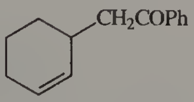
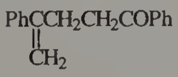


$$\text{Ar}\underset{\text{OSiMe}_3}{\text{C}}{=}\text{CH}_2 \xrightarrow[\text{CH}_2\text{Cl}_2]{\text{IOB. HBF}_4} \xrightarrow{\text{Ar}'\text{C(OSiMe}_3){=}\text{CH}_2} \text{Ar}\underset{\underset{\text{O}}{\|}}{\text{C}}\text{CH}_2\text{CH}_2\underset{\underset{\text{O}}{\|}}{\text{C}}\text{Ar}'$$

To a stirred suspension of IOB (220 mg, 1 mmol) in dichloromethane (5 ml) was added tetrafluoroboric acid in dimethyl ether (0.2 ml) at −50°C. The mixture was warmed to 0°C until formation of a yellow solution and then cooled to −78°C. To this the first silyl enol ether (1 mmol) was added with stirring. The cold reaction mixture was then added to a stirred solution of the second silyl enol ether (1 mmol) in dichloromethane (5 ml) at room temperature. After 10 min stirring, the reaction mixture was poured into water (50 ml) and extracted with dichloromethane (2 × 10 ml). The organic extract, after drying and concentration, yielded the crude diketone which was purified by column chromatography on silica gel (hexanes–ethyl acetate). When a silyl enol ether was treated with $IOB.BF_3$ in the ratio 1:2, then the

TABLE 5.2

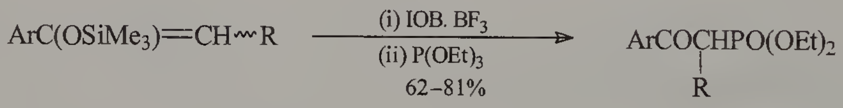
Butane-1,4-diones and γ,δ-unsaturated ketones from silyl enol ethers upon reaction with IOB/ HBF_4 and a carbon nucleophile

Precursors	Product	Yield (%)	Ref.
a. For symmetrical 1,4-diones			
$ArC(OSiMe_3){=}CH_2$	$(ArCOCH_2)_2$	43–62	[23]
$Bu^tC(OSiMe_3){=}CH_2$	$(Bu^tCOCH_2)_2$	55	[23]
 (X= H, 4-Me, 5-Cl)		50–56	[24]
		63	[24]
b. For unsymmetrical 1,4-diones			
 + $PhC(OSiMe_3){=}CH_2$		50	[25]
 + $ArC(OSiMe_3){=}CH_2$		30–75	[25]
$ArC(OSiMe_3){=}CH_2$ + $Ar'C(OSiMe_3){=}CH_2$	$ArCOCH_2CH_2COAr'$	27–51	[25]
c. For unsaturated ketones			
$PhC(OSiMe_3){=}CH_2$ + 		90	[25]
$PhC(OSiMe_3){=}CH_2$ + $PhC(Me){=}CH_2$	 $\underset{\underset{CH_2}{\|}}{PhC}CH_2CH_2COPh$	59	[25]
$PhC(OSiMe_3){=}CH_2$ + $Me_3SiCH_2CH{=}CH_2$	$CH_2{=}CHCH_2CH_2COPh$	63	[25]

symmetrical butane-1,4-diones were formed in good yields. Diketones obtained by these methods are shown in Table 5.2. Some of these products were also obtained using other hypervalent iodine reagents in better yield (Sections 6.4.3 and 12.3).

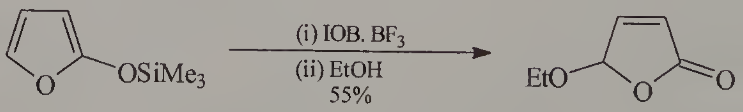
The iodonium ion formed on reaction of the silyl enol ether of acetophenone also reacted with alkenes or allylsilanes, providing a good approach for the preparation of γ,δ-unsaturated ketones as exemplified in Table 5.2. An interesting deviation from this reactivity occurred with 2,3-dimethyl-2-butene which afforded a dihydrofuran derivative [25]. Another group of useful α-functionalization of carbonyl compounds effected through their silyl enol ethers involved carbon–oxygen bond formation. Water, methanol, and trimethylsilyl triflate served as nucleophiles in order to convert the iodonium intermediates ($\mathrm{RCOCH_2I^+Ph}$) into, respectively, α-hydroxy-, α-methoxy- or α-trifyloxyketones. Not only α-hydroxyacetophenones but also several other α-hydroxyketones (ketols) were obtained in this way, as illustrated in Table 5.3, which also contains examples of α-methoxy- and α-trifyloxyketones.

A catalytic route using a manganese (III) complex has been developed for α-hydroxylation of ketones avoiding the use of water or a protic solvent; mixtures of α-hydroxyketones and their silyl derivatives were formed in excellent yield. By using a chiral pyrrolidine-based manganese (III) complex as catalyst, asymmetric oxidation was effected, with enantiomeric excess varying from 14 to 62% [30]. Another kind of α-functionalized ketones resulted from silyl enol ethers which after the addition of IOB.$\mathrm{BF_3}$ were treated with triethyl phosphite; α-ketophosphonates were obtained in this way [31]:



$$\mathrm{ArC(OSiMe_3){=}CH{\sim}R} \xrightarrow[\text{(ii) P(OEt)}_3\ \ 62\text{–}81\%]{\text{(i) IOB. BF}_3} \mathrm{ArCO}\underset{\mathrm{R}}{\mathrm{CH}}\mathrm{PO(OEt)_2}$$

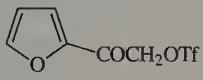
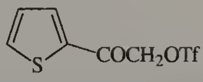
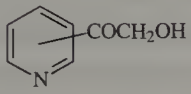
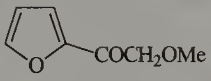
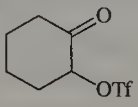
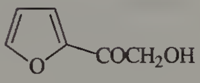
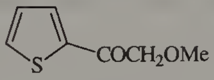
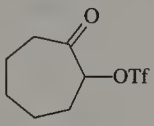
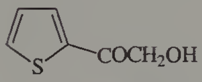
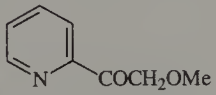
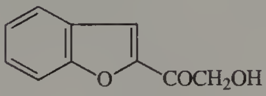
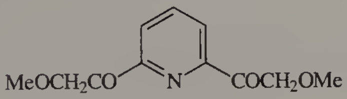
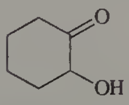
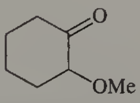
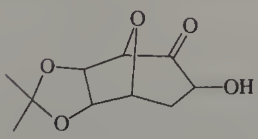
2-(Trimethylsilyloxy)furan may be considered as a special silyl enol ether; in its reaction with IOB.$\mathrm{BF_3}$, followed by addition of ethanol, γ-functionalization occurred, with formation of 5-ethoxy-2(5*H*)-furanone [32]:



Similar functionalization was noted by using acetic acid or *p*-toluenesulphonic acid

TABLE 5.3

α-Functionalized ketones from silyl enol ethers[a]

α -Hydroxy ketones	α -Methoxy ketones	α -Ketotriflates
$ArCOCH_2OH$ (65–70%)	$ArCOCH_2OMe$ (68–78%)	$ArCOCH_2OTf$ (53–77%)
$PhCOCH(OH)Me$ (74%)	$PhCOCH(OMe)Me$ (75%)	 (70%)
Bu^tCOCH_2OH (83%)	Bu^tCOCH_2OMe (85%)	 (69%)
 (2-,62%; 3-,54%)	 (60%)	 (64%)
 (78%)	 (54%)	 (74%)
 (50%)	 (70%)	
 (59%)	 (71%)	
 (80%)	 (78%)	
 (67%)	$PhCOCH_2OEt$ (80%)	
	$PhCOCH_2OPr^i$ (45%)	

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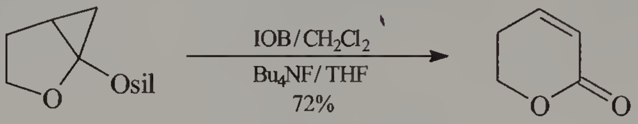
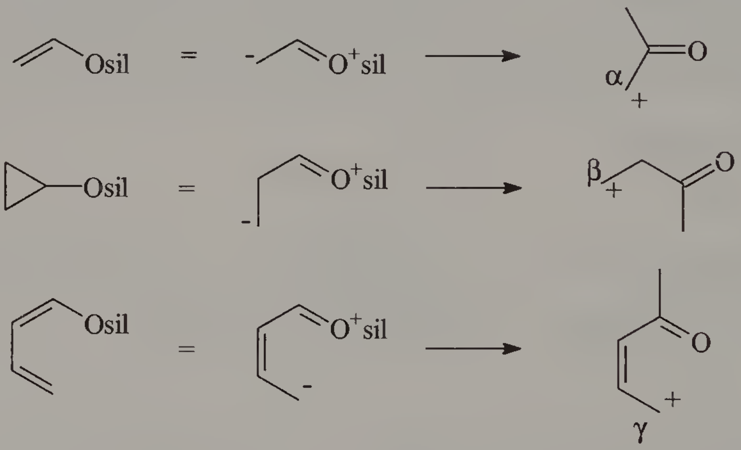
[a] References: for α-hydroxy ketones [26,27] ; for α-methoxy ketones [28] ; and for α-ketotriflates [29].

instead of ethanol. Also, 2-(trimethylsilyloxy)benzofuran, on treatment with IOB and these acids, followed by boron trifluoride etherate, afforded 3-acetoxy-(and 3-tosyloxy)-2-coumaranone. 1-Trimethylsilyloxy-2-oxa-bicyclo[3.1.0]hexane although not an enol ether, upon treatment with IOB and tetrabutylammonium fluoride afforded its ring homologated α,*β*-unsaturated lactone [22]:



Similar behaviour was shown by some analogues which instead of the 5-membered ring had a 6-, 7- or 14-membered ring. The unsaturated lactones were obtained in good yield, in reactions involving *β*-functionalization and concomitant elimination.

Overall, α-, *β*- and *γ*-functionalization is possible with the various silyl substrates reported in this section. In a formal sense, the relevant reactions discussed correspond to an umpolung of reactivity of the enolic or cyclopropyl systems, as depicted schematically below [22]:

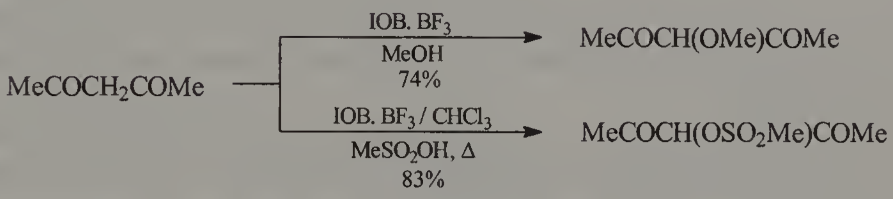


These synthetic equivalents of α-, *β*- and *γ*-carbonyl cations might also be useful in other reactions.

5.2.3 Ketones

α-Hydroxylation of ketones can be accomplished not only through their silyl enol ethers (previous Section) but also directly upon treatment with IOB in strongly basic methanol; their dimethyl acetals are formed, which are hydrolysed by acid to the α-hydroxyketones (acyloins, ketals) [33]. 2-Acetylpyridine, 2,6-diacetylpyridine and several more ketones (including the acetyl moiety of pregnenolone) were converted efficiently in this way into acyloins; equally effective for this transformation are DIB (Section 3.2.2) or [bis(trifluoroacetoxy)iodo]benzene (Section 4.2). Acetophenones and propiophenones were also converted into methyl esters of arylacetic or arylpropionic acids in strongly acidic conditions [34], in the same way as with DIB (Section 3.2.1).

The α-functionalization of *β*-diketones and *β*-ketoesters has been effected through IOB.BF_3. At room temperature methanol with 2,4-pentanedione gave its α-methoxy derivative, whereas methanesulphonic acid in refluxing chloroform afforded the α-mesylate [35]:



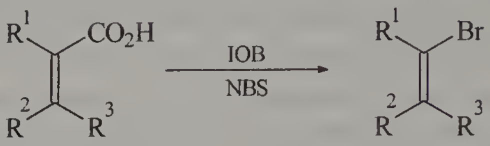
When 2 equivalents of substrate were treated with 1.2 equivalents of IOB.BF_3, self-coupling occurred, for example $PhCOCH_2CO_2Et$ was converted into $[PhCO(CO_2Et)CH]_2$ (68%). The introduction of the azido group was also successful in these substrates under similar conditions (Section 3.5.2).

α-Metalloketones containing thallium, lead or mercury were converted by IOB.BF_3 in methanol into α-methoxyketones, in high yield [36]. Dehydrogenation accompanied by aryl migration occurred in flavanones which were converted into isoflavones [37].

5.2.4 Acids

Acids of low molecular weight form readily with IOB [bis(acyloxy)iodo]benzenes, $PhI(OOCR)_2$, in solution. However, α-ketoacids did not afford the corresponding compounds, because they were readily decarboxylated, in dioxane, at room temperature. Decarboxylation also occurred with *α*,*β*-unsaturated acids, especially those having an aryl group at the *β*-position. The reaction started with the acid and IOB; the intermediate formed reacted further with *N*-chloro-, *N*-bromo-, or *N*-iodosuccinimide to afford the decarboxylated products, i.e. haloalkenes; the stereochemistry of the double bond was largely retained and best results were obtained with *N*-bromosuccinimide (NBS).

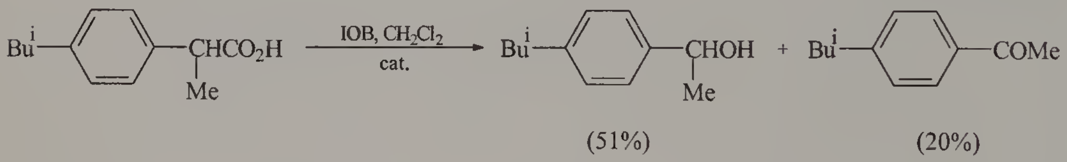
Oxidative decarboxylation of α,β-unsaturated acids [38]



The substrate (1 mmol) and IOB (110 mg, 5 mmol) were dissolved in acetonitrile–water (10 ml, 2:1) at 60°C. The mixture was stirred for 10 min and then NBS (218 mg, 1 mmol) was added. After stirring for 30 min at 60°C, the solvents were evaporated. The aqueous phase was washed with ether (3 × 10 ml), dried and concentrated. The residue was separated using flash chromatography with petroleum ether as the eluent.

The best yields (51–89%) were for substrates with $R^1 = H$ and phenyl rings (R^2 and/or R^3), especially when containing an electron-donating group. This modified Hunsdiecker reaction was equally successful with DIB; conventional methods for this transformation of α,β-unsaturated acids gave poor results. DIB has also been used for the photochemical halodecarboxylation of acids (Section 4.8.1).

α-Aryl carboxylic acids underwent decarboxylation when treated with IOB and a porphyrin catalyst (*meso*-tetrakis(pentafluorophenyl)porphyrin iron(III) chloride). The main products were alcohols accompanied usually by the corresponding ketones and sometimes by esters. In this way ibuprofen was converted into the following mixture [39]:

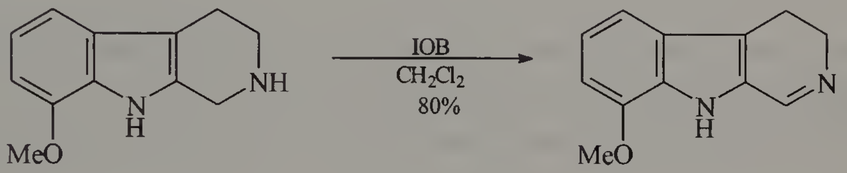


5.3 REACTIONS WITH NITROGEN COMPOUNDS

5.3.1 Amines

Primary aliphatic amines, on oxidation with IOB in dichloromethane or water, were converted into nitriles in moderate yield, e.g. hexylamine was dehydrogenated to hexanenitrile (57%), after 3 days stirring at room temperature with 2 equivalents of IOB. Similarly benzylamine gave benzonitrile; with one equivalent of IOB, the main product was the Schif's base $PhCH{=}NCH_2Ph$. Primary cycloamines with IOB in water afforded ketones, e.g. cyclohexylamine was oxidized to cyclohexanone (49%). The oxidation of secondary amines such as pyrrolidine and piperidine, and also tertiary cyclic amines, with two equivalents of IOB resulted in the formation of the corresponding lactams. Piperidine in the presence of trimethylsilyl cyanide afforded 2-cyano-piperidine (79%) [40].

Generally, dehydrogenation prevailed in secondary amines when treated with one equivalent of IOB in dichloromethane; in this way *N*-t-butylbenzylamine gave its imine ($PhCH = NBu^t$, 88%), whereas pyrrolidine was converted into a mixture of 1-pyrroline and its trimer. Hydrogen elimination followed Hofmann's rule, for example in the following transformation [41]:



The use of catalysts improved considerably the efficiency in some of these reactions, for example $PhCH = CHCH_2NHPh$ with IOB alone gave $PhCH{=}CH{-}CH{=}NPh$ (40%); the yield increased to 86% in the presence of $RuCl_2(PPh_3)_3$ and molecular sieves [42]. Another catalyst was the salicylidene complex Mn(III)(salen)Cl; however, further oxidation was noted in some cases, with formation of by-products such as aldehydes, acids or nitrones [43].

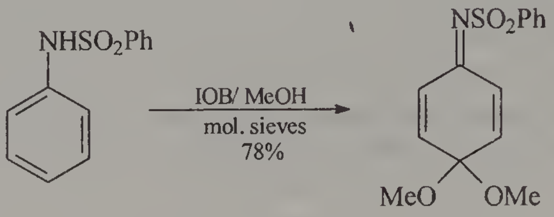
5.3.2 Amides

A reaction of considerable interest is the Hofmann type degradation of primary carboxamides to amines. Several examples have been reported of such efficient conversions, notably with the system IOB in formic acid (in water of acetonitrile), which forms *in situ* $PhI(OOCH)_2$ [44]. Other hypervalent iodine reagents have also been used extensively for these transformations (Sections 4.4.1 and 7.4.1). Yields may vary widely as illustrated for three similar amines obtained from the corresponding carboxamides with IOB-formic acid and with [hydroxy-(tosyloxy)iodo]benzene [45]:

Amine	IOB	PhI(OH)OTs
$(HO)_2P(O)CH_2NH_2$	73%	91%
$(HO)_2P(O)CH_2CH(Me)NH_2$	82%	30%
$(HO)_2P(O)CH(Me)CH_2NH_2$	65%	62%

It is worth mentioning that historically the first use of IOB as a reagent was reported in 1903: it converted in aqueous potassium hydroxide phthalimide into anthranilic acid (83%) [46].

IOB in methanol was the best reagent for the conversion of sulphonamides into quinone-imide monoketals, e.g [47]:



Previously, only electrochemical methods were suitable for this type of phenolic oxidation.

5.3.3 Amino acids

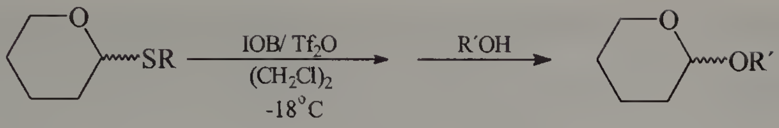
Decarboxylation with concomitant dehydrogenation occurred in some cyclic amino acids. For example, (*L*)-proline was converted into a mixture of 1-pyrroline and its trimer. The methyl ester of (*L*)-proline was simply dehydrogenated to its *β*-imine (69%). With two equivalents of IOB in chloroform (*L*)-proline was converted directly into 2-pyrrolidinone (70%). This transformation was less efficient for pipecolinic acid and (*L*)-pyrrolidinone-5-carboxylic acid [48].

5.4 REACTIONS WITH SULPHUR AND OTHER COMPOUNDS

5.4.1 Sulphur compounds

Sulphides are oxidized readily by most hypervalent iodine reagents. IOB alone is not suitable, since mixtures of sulphoxides and sulphones are formed under drastic conditions. However, in the presence of catalytic amounts of *p*-toluenesulphonic acid [49] or benzeneseleninic acid [50] various sulphides were cleanly oxidized to sulphoxides in excellent yields. Using a chiral catalyst asymmetric oxidation was highly successful [51].

IOB activated by triflic anhydride has been used to convert thioglycosides into *O*-glycosides (disaccharides). The reaction probably proceeds via a glycosyl triflate intermediate [52]:

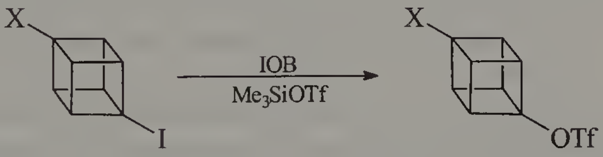


The substrates R′OH were partially protected (benzylated and benzoylated) glycosides or thioglycosides. Some glycosidations were greatly promoted by using silica gel. A substantial improvement involved the use of various acid catalysts such as tin (II) triflate or mixtures of antimony (III) and silver perchlorate [53]. Similar reactions were performed with BTI (Section 4.5). The conversion of the thiocarbonyl into carbonyl group using IOB in acetone has been reported in some 2-thiouracils [54].

5.4.2 Cubyl iodides

The conversion of cubyl iodides into cubyl triflates has considerable interest since it permits further functionalization of these otherwise unreactive substrates. The use of IOB and trimethylsilyl triflate was a good approach to this problem (see also Section 7.4.4).

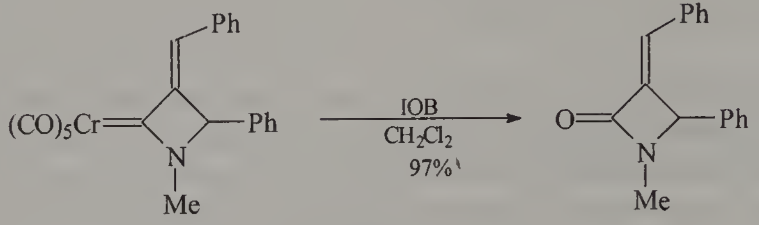
Cubyl triflates [55]



A mixture of cubyl iodide (1 mmol), IOB (3 mmol) and trimethylsilyl triflate (666 mg, 3 mmol) in dry dichloromethane was stirred at room temperature for 1 h to several days, depending on the substituent X; the following order was noted, concerning reaction time: $H < Me < CO_2Me < Br,I,Cl$. After the usual work up, the residues were purified by flash chromatography (with pentane) or microdistillation to give the pure products in 50–60% yield.

5.4.3 Organometallics

As already discussed (Section 5.2.3), α-metallated ketones were converted by IOB into α-methoxyketones, in presence of methanol. Generally, various organometallic compounds react readily with hypervalent iodine reagents undergoing an umpolung of reactivity; the intermediates formed need not be isolated, since they may react *in situ* with a variety of nucleophiles. A simple example illustrating the point is the transformation of benzyltributylstannane to methyl benzylether [21]. IOB transfers its oxygen to the organic moiety of metal–carbenoid complexes, as in the following example [56]:



Oxygen transfer to the metal site of several organometallics is also possible; in some instances this occurred under ultrasonic conditions. In this way its polymeric oxide was obtained from triphenylbismuthine, whereas triphenylstibine afforded its crystalline dimeric oxide [57]. Several metalloporphyrins are also oxygenated at the metal site by IOB. Some of the oxo species formed have been isolated but normally they are non-isolable. These systems have been used in some catalytic oxidations.

5.4.4 Catalytic oxidations with metalloporphyrins

Metalloporphyrins and some related metal complexes are effective catalysts in IOB oxidations, as already discussed for alkenes, and acids (Sections 5.1.1.1 and 5.2.4). Also, sulphides have been oxidized to sulphoxides [58]. Some other substrates of various types underwent such catalysed oxidations, because these systems mimic the natural oxidant cytochrome *P*-450 [2]. From a synthetic point of view, only a few reactions are of importance; alkanes were mainly used which underwent regio- and stereo-specific hydroxylation, for instance the methyl group of a pyrrole derivative was converted into hydroxymethyl, leading to one-pot preparation of dipyrromethanes [59]. The preparation of elaborated catalysts is, however, very demanding and precludes a wider use.

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–6–

(Difluoroiodo)- and (dichloroiodo)arenes

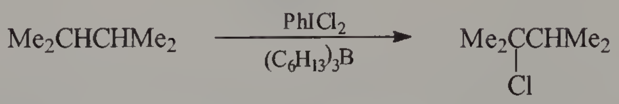
(Difluoroiodo)- and (dichloroiodo)arenes have been used not only in diverse halogenations but also in oxidations. In several instances they served as tamed molecular analogues of fluorine and chlorine. Both (difluoroiodo)- and (dichloroiodo)arenes possess high reactivity but they often react in a complicated way. A general comment concerning such cases is that the neutralization of acids released may be beneficial to the outcome of the reaction.

6.1 CHLORINATION

6.1.1 Chlorination at sp^3 carbon

(Dichloroiodo)benzene and certain ring-substituted analogues have been used for the chlorination of hydrocarbons and some other substrates at an sp^3 carbon. These reagents have a practical advantage over elemental chlorine, due to their easy handling. Further, they show a pronounced selectivity for a tertiary carbon, so that they effect useful chlorinations. For example, in the reaction of (dichloroiodo)benzene with the pair butane and 2,3-dimethylbutane, the ratios for chlorination at 1°, 2° and 3° carbon were, per hydrogen, 1:21:368; under similar conditions the ratios for chlorination with chlorine or t-butyl hypochlorite were 1:4:5 and 1:8:44, respectively. The high selectivity of (dichloroiodo)benzene is attributed to the abstraction of hydrogen by the bulky PhI·Cl group, in which chlorine is deactivated in comparison to atomic chlorine. This species is produced mostly photochemically, with light provided either by a high pressure mercury or by an incandescent lamp. The photochemical conditions were circumvented by using catalytic amounts of trihexylborane; the selectivity, when compared to the photochemical route, was essentially identical, with yields substantially improved.

2-Chloro-2,3-dimethylbutane [1]



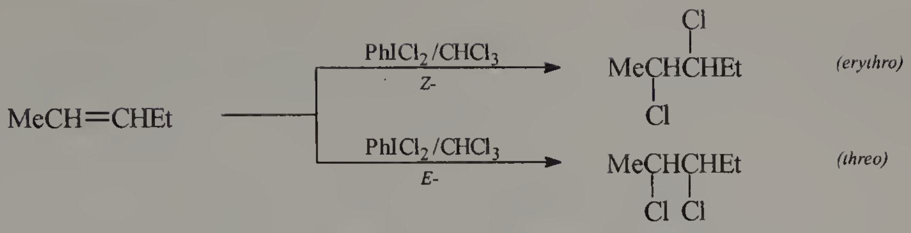
$$\mathrm{Me_2CHCHMe_2} \xrightarrow[(C_6H_{13})_3B]{PhICl_2} \mathrm{Me_2}\underset{\displaystyle \mathrm{Cl}}{\mathrm{C}}\mathrm{CHMe_2}$$

In a 250 ml three-necked flask was placed (dichloroiodo)benzene (7.25 g, 30 mmol) with light protection, under nitrogen. Then 2,3-dimethylbutane (30.25 g, 350 mmol) and trihexylborane (400 mg, 1.5 mmol) were introduced by syringes through a scptum inlet. The mixture was stirred at room temperature for about 2 h; during the reaction hydrogen chloride evolved was carried into an aqueous sodium hydroxide solution by a weak stream of nitrogen. The reaction mixture was neutralized with dilute sodium hydroxide, washed with water several times and dried. Fractional distillation afforded 2-chloro-2,3-dimethylbutane (3.22 g, 89%), b.p. 109–110°C.

Successful chlorination at a 3° carbon was reported for the acetate esters of cedryl and patchoulyl alcohols [2]. Several ethers were photochemically monochlorinated at the α-position, for example THF afforded its 2-chloroderivative (51%); because of their lability, the products were isolated as esters [3]. Ketones underwent α-chlorination by (dichloroiodo)benzene not only photochemically but also thermally in warm acetic acid in high yield. Under these conditions 2-butanone gave a mixture of 3-chloro- and 3,3-dichlorobutanone (80:20), whereas under photochemical conditions, in benzene, the selectivity was considerably improved (98:2). Diketones, both β- and δ-, were similarly monochlorinated [4,5].

6.1.2 Chlorination of alkenes

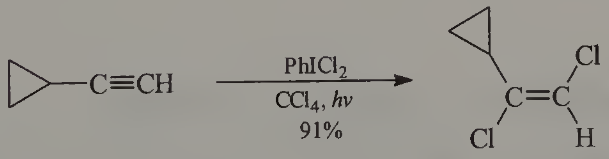
A large number of alkenes reacted successfully with (dichloroiodo)benzene adding chlorine to their double bonds; such chlorinations sometimes present interesting stereochemical features. Most of them proceeded thermally, in an inert atmosphere and in solvents of low polarity. Under these homolytic conditions *trans* addition of chlorine prevails, with high selectivity. When the conditions changed to ionic, then *cis* addition became important: small quantities of DMSO or THF were enough to bring about significant alterations; for example, 2-pentenes in chloroform gave exclusively *trans* products, the *erythro* dichloride from the (E)-isomer and the *threo* isomer from the (Z). The (Z)-isomer in chloroform-DMSO gave predominantly the *threo* adduct [6]:



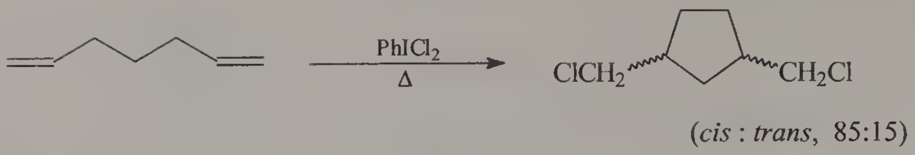
In cyclic alkenes such as cyclohexene and cycloheptene *trans* addition was also highly stereoselective [7]. However, *cis* cyclooctene afforded both *cis* and *trans* adducts in the ratio 1:3; in the presence of oxygen 1,4-dichlorides were also formed [8]. In cyclodecenes, both *cis* and *trans*, the main product was the allylic chloride, with some formation of transannular dichlorides [9]. In some substrates with an exocyclic double bond, such as methylene cyclobutane, only (dichloroiodo)benzene was suitable for a clean addition [10].

6.1.3 Chlorination of alkynes and dienes

Alkynes reacted with (dichloroiodo)benzene under free radical conditions to give *trans*-1,2-dichloro adducts. The stereoselectivity of the reaction was much better than with elemental chlorine; yields were also improved. An example is provided by the chlorination of cyclopropylacetylene under photochemical conditions [11]:



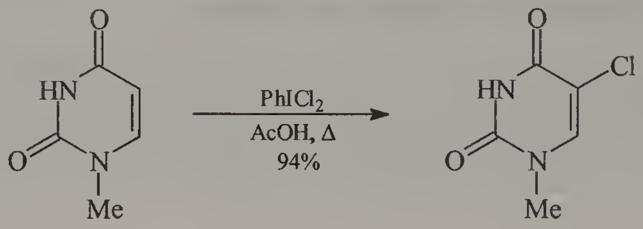
Allenic hydrocarbons, including cyclic ones, underwent chlorine addition under radical conditions; only one double bond reacted [12]. A number of conjugated dienes added chlorine in their reaction with (dichloroiodo)benzene under radical conditions. Both 1,2- and 1,4-addition occurred; their ratios varied, depending on the substitution of the non-cyclic substrate and the size of the cyclic ones; *trans* products were normally favoured [13]. 1,6-Dienes were cyclized to 1,2-bis chloromethyl cyclopentanes [14]:



Other substrates with the 1,6-diene skeleton reacted similarly [14,15].

6.1.4 Chlorination of aromatics and heterocycles

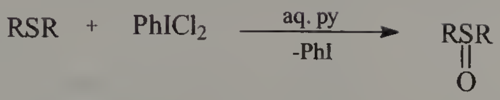
Activated aromatic compounds are chlorinated readily by (dichloroiodo)benzene. Generally, negligible amounts of *ortho*-chloro isomers are produced from diverse aromatic compounds, e.g. salicylic acid gave its 5-chloroderivative (89%) [16]. Exceptions were noted in the chlorination of the triphenyl phosphinimine of aniline which afforded *o*- and *p*-products in the ratio 7:3 [17], and of 2-naphthol which gave its 1-chloroderivative (84%) [16]. (Dichloroiodo)benzene was superior for the chlorination of uracil bases and protected nucleosides, e.g. [18]:



6.1.5 Chlorination and oxidation of sulphides

The reaction of sulphides with (dichloroiodo)benzene can lead to several kinds of products depending on the substrate and the reaction conditions [19]. Sulphides of great structural diversity (aliphatic, aromatic, heterocyclic) were oxidized efficiently by (dichloroiodo)benzene (one equivalent) in aqueous pyridine. The reaction was almost instantaneous and not noticeably sensitive to steric or electronic effects. Ethylenic double bonds were not attacked under these conditions; however, in vinylic sulphides containing an electron-withdrawing group (COOH or RSO) β- to the sulphur atom the oxidation was accompanied by nucleophilic attack to the double bond resulting in a mixture of products. The method is suitable for the preparation of ^{18}O-labelled sulphoxides using small quantities of $H_2{}^{18}O$.

Oxidation of sulphides to sulphoxides [20]

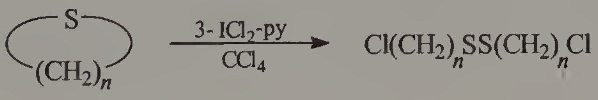


$$\mathrm{RSR} + \mathrm{PhICl_2} \xrightarrow[\text{-PhI}]{\text{aq. py}} \underset{\underset{\displaystyle \mathrm{O}}{\|}}{\mathrm{RSR}}$$

A solution of (dichloroiodo)benzene (2.75 g, 10 mmol) in anhydrous pyridine (5 ml) was added dropwise to a stirred solution of the sulphide (10 mmol) in 20% (v/v) aqueous pyridine (6–10 ml); for some reactive sulphides cooling was necessary, otherwise the temperature was maintained at 20°C. During the reaction direct sunlight was avoided. The reaction mixture was diluted with chloroform (50 ml) and pyridine was removed by washing with aqueous sulphuric acid. The chloroformic solution was washed with water, dried and the solvent evaporated to give the product. Many sulphoxides were prepared in this way in high yield, including 1,3-dithietanes [21] and α-phosphoryl sulphides [22]; some selenides behaved similarly [23]. With an excess of reagent sulphoxides were oxidized to sulphones in very good yields [24].

Chlorination not accompanied by oxidation occurred on treatment of aliphatic sulphides and phenylated dimethyl sulphide with 3-(dichloroiodo)pyridine in chloroform; for example, methyl ethyl sulphide afforded a mixture of the two monochlorinated sulphides ($CH_2ClSCH_2CH_3$ and $CH_3SCHClCH_3$) in a ratio of 1:3 [25].

Chlorinolysis is another reaction mode observed in some sulphides, in which sulphur retains its oxidation state. For example, phenyl trityl sulphide and benzyl trityl sulphide were converted into trityl chloride and sulphenyl chlorides [26]. Thiirane and thietane reacted similarly with 3-(dichloroiodo)pyridine to afford chlorinated disulphides [25]:

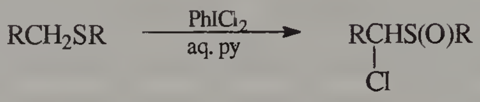


($n = 2$, 50%
$n = 3$, 64%)

It should be noted that 3-(dichloroiodo)pyridine has the advantage of making the separation procedure easy: after reaction, 3-iodopyridine is extracted with dilute acid and can be recycled.

By far, the most extensive studies and applications of (dichloroiodo)benzene involved the direct conversion of aliphatic sulphides into α-chlorosulphoxides. Related results were reported for the chlorination of sulphoxides to α-chlorosulphoxides, especially from the stereochemical point of view. Generally, the transformation of sulphides to α-chlorosulphoxides proceeds with (dichloroiodo)benzene dissolved in anhydrous pyridine which enhances the electrophilic character of iodine by formation of $PhIClpy^+Cl^-$; such bis pyridinium salts have actually been isolated as triflates (Section 12.2.2).

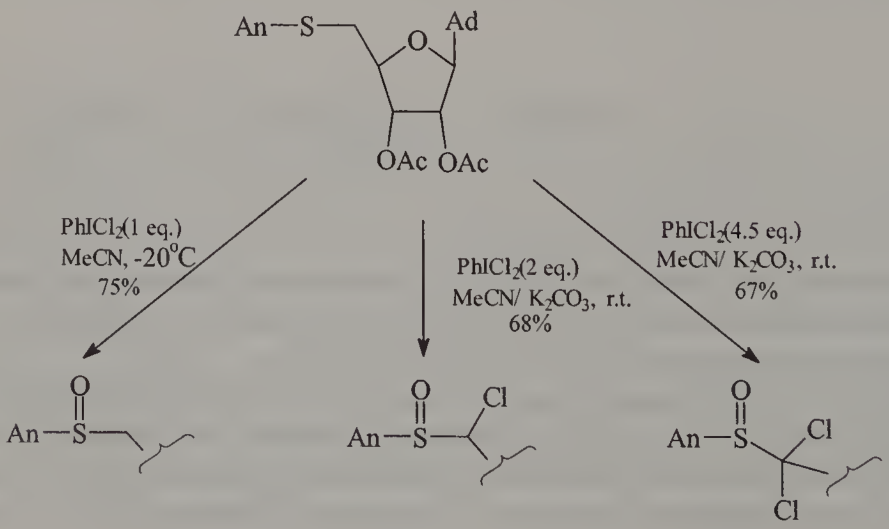
Oxidation of sulphides to α-chlorosulphoxides [27]



$$\mathrm{RCH_2SR} \xrightarrow[\text{aq. py}]{\mathrm{PhICl_2}} \mathrm{R\underset{\displaystyle \mathrm{Cl}}{C}HS(O)R}$$

A solution of (dichloroiodo)benzene (5.5 g, 20 mmol) in anhydrous pyridine (10 ml) was added dropwise at −40°C to a stirred solution of the sulphide (10 mmol) in 20% (v/v) aqueous pyridine (15 ml). The mixture was kept at −40°C for 1 h, away from direct sunlight and then at room temperature overnight. Chloroform (50 ml) was added and pyridine was removed with aqueous sulphuric acid; the organic solution was washed with water, dried and concentrated to give the crude product, which was purified by column chromatography on silica gel (ether–light petroleum). Several α-chlorosulphoxides were prepared in this way in 40–70% yield.

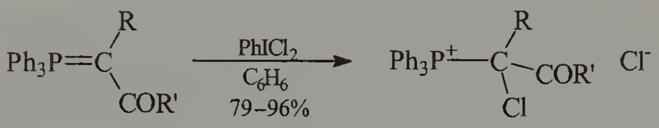
Interesting results were obtained with bis acetylated 5-*S*-(4-methoxyphenyl)-5-thioadenosine; as illustrated below, there are three different outcomes (An is anisyl, $4\text{-}MeOC_6H_4$, and Ad is the 9-adenine group) [28]:



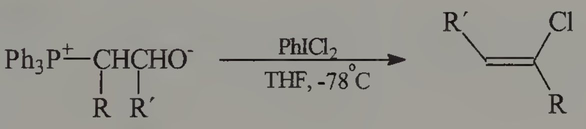
Among other oxidations mediated by (dichloroiodo)benzene, some unique transformations of β-lactams, penicillins and cephalosporins are of interest [19].

6.1.6 Chlorination of phosphonium ylides

The reaction of phosphonium ylides with (dichloroiodo)benzene under mild conditions permits the preparation of α-chlorinated phosphonium salts, e.g. [29]:



The ylide $Ph_3P{=}CHCOOMe$ similarly gave its chlorinated phosphonium salt in high yield which was converted into the chloroylide $Ph_3P{=}C(Cl)COOMe$; this underwent the Wittig reaction with several aldehydes [30]. Chloroalkenes may be formed stereoselectively by another approach which is a variation of the Wittig reaction: phosphonium salts prepared from ylides and aldehydes at low temperature were treated with butyl lithium to give β-oxido phosphonium ylides: these reacted *in situ* with(dichloroiodo)benzene to afford (*Z*)-chloroalkenes in moderate yield [31,32]:



$R' = Ph, R = Me$ (50%)
$R' = C_6H_{13}, R = Me$ (55%)

A mixture of (*E*)- and (*Z*)-chlorostyrenes was obtained from the above ylide, with $R = Ph$ and $R' = H$; once again, (dichloroiodo)benzene was differentiated from other chlorinating agents, since these ylides with *N*-chlorosuccinimide delivered the (*E*)-isomer with high selectivity.

6.2 REMOTE FUNCTIONALIZATION OF STEROIDS

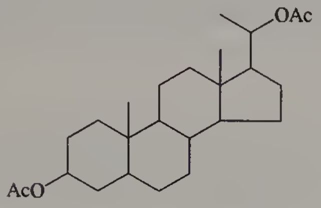
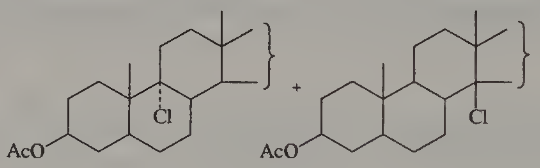
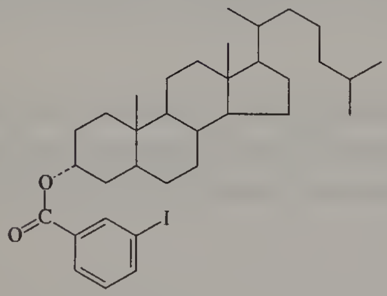
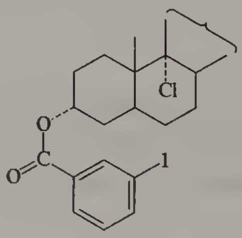
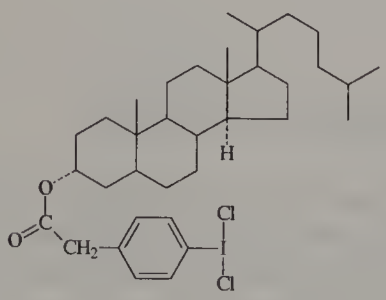
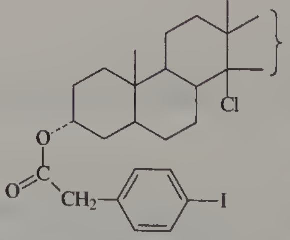
Non-activated carbon atoms of steroids can be chlorinated through (dichloroiodo)arenes or an iodophenyl fragment incorporated in the steroid molecule which is subsequently converted into ArI·Cl. This approach permits not only chlorination but also the introduction of some other groups. Detailed accounts of these biomimetic processes have been described [33] and some approaches are illustrated in Table 6.1.

Since these reactions are geometrically controlled, it was possible to change the selectivity with a different iodoaroyl moiety esterified with the hydroxy group of the sterol. Indeed, the substrate in the third example gave the C_{14} chlorinated product with a stereochemistry opposite to that of the hydrogen replaced. Chlorination at other positions was effected by using suitable iodophenylated esters. For example, the key step in a synthesis of androsterone acetate was chlorination at C_{17} [37]; also, 17-chlorosteroids of 9-fluoro-11-oxygenated cholestanols were produced and used for the degradation of steroidal side chains [38]. An ester from a 6-hydroxy-derivative of cholesterol effected chlorination at C_{20} [39].

Molecular mechanics calculations on transition states for hydrogen abstraction by chlorine atoms attached to iodine of various iodoaryl substrates help in designing effective systems for chlorination at the desired position [40]. The chloro-derivatives are normally further dehydrochlorinated in order to generate unsaturated products. This elimination, although sometimes spontaneous, was generally difficult to achieve. To overcome this problem, the substrates were brominated by adding an

TABLE 6.1

Photochemical remote chlorination of steroids through (dichloroiodo)arenes

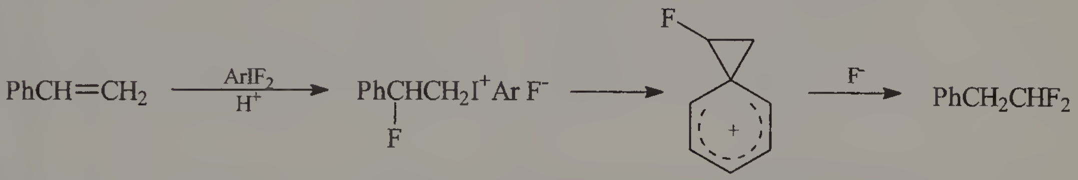
Substrate	Product(s)	Ref.
		[34]
		[35]
		[36]

excess of carbon tetrabromide in the reactants [41]. Similarly, the addition of thiocyanogen produced a steroidal thiocyanate (second example; in place of chlorine is bromine or the thiocyanato group).

6.3 FLUORINATION

6.3.1 Fluorination of unsaturated compounds

Simple alkenes do not give with (difluoroiodo)arenes clean reactions; phenylated alkenes under ionic conditions undergo addition of fluorine accompanied by rearrangement in presence of acid (HF, CF_3COOH). The reaction proceeds through an initial fluoroalkyl phenyliodonium adduct which is transformed to a phenonium cation and eventually to the rearranged product:



Substrates of this type which afforded *gem*-difluorides are shown in Table 6.2. The yields reported were substantially improved by using a polymer-supported reagent which had the added advantage that no separation from iodobenzene was needed; however, fluorination of the iodinated polystyrene requires the use of the expensive xenon difluoride [47, 48].

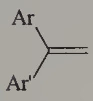
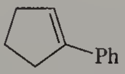
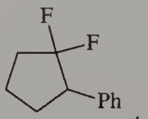
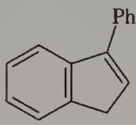
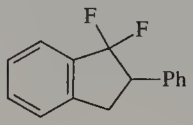
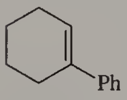
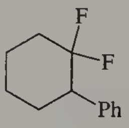
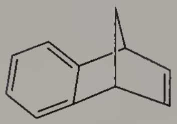
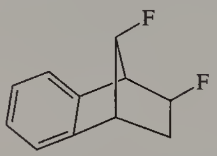
Conjugated dienes, i.e. 1,3-butadiene and 2,3-dimethyl-1,3-butadiene, added fluorine at 0°C ionically, without rearrangement, with formation of 1,2- and mainly 1,4-difluoro adducts; in contrast, xenon difluoride afforded exclusively 1,2-adducts. 1,3-Pentadienes, both *cis* and *trans*, gave mostly rearranged products [49]:

$$\mathrm{MeCH{=}CHCH{=}CH_2 \xrightarrow[H^+]{PhIF_2} MeCH{=}CHCH_2CHF_2}$$

Trimethylsilyl ethers of several steroidal ketones were α-fluorinated by 4-(difluoroiodo)toluene, in moderate yield because of concomitant elimination, accompanied by the formation of other by-products from nucleophilic substitution to a phenyliodonium intermediate. The analogous reaction with xenon difluoride resulted in much better yields but different stereochemistry [50].

TABLE 6.2

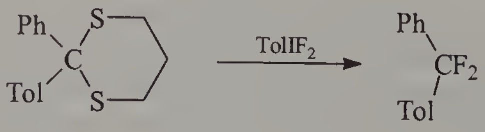
Fluorination of phenylated alkenes by 4-(difluoroiodo)arenes

Substrate	Product	Yield (%)	Ref.
$PhCH{=}CH_2$	$PhCH_2CHF_2$	37	[42]
$Ph_2C{=}CH_2$	$PhCF_2CH_2Ph$	60	[43]
$Ph_2C{=}CHMe$	$PhCF_2CH(Me)Ph$	65	[44]
	$ArCF_2CH_2Ar'$	~50	[45]
		60	[45]
		53	[45]
		63	[45]
		52	[46]

6.3.2 Fluorination of carbonyl compounds

Replacement of the oxygen of carbonyl compounds by two fluorine atoms may be achieved through several methods; one of the mildest involved the use of dithioacetals and 4-(difluoroiodo)toluene.

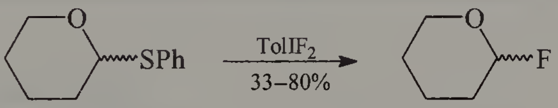
4-Tolyl-phenyl-difluoromethane [51]



A solution (Section 2.2) of 4-(difluoroiodo)toluene (538 mg, 2.1 mmol) in dichloromethane (2 ml) was added dropwise to a cooled (at 0°C) and stirred solution of the dithianic acetal of 4-methylbenzophenone (287 mg, 1 mmol) in dichloromethane (10 ml). The reaction was performed in a PTFE conical flask under an inert atmosphere. On completion, solvent removal and chromatography (silica gel) afforded the 4-tolyl-phenyl-difluoromethane (186 mg, 85%), m.p. not given.

An electrochemical methodology using an *in situ* prepared difluoride from *p*-iodoanisol is an alternative approach for indirect anodic *gem*-difluorination of dithioacetals [52].

Several protected (acetylated or benzylated) 1-fluoroglycosides were obtained in satisfactory yield under mild conditions from the corresponding phenyl-thioglycoside derivatives by reaction with 4-(difluoroiodo)toluene, according to the generalized scheme [53]:

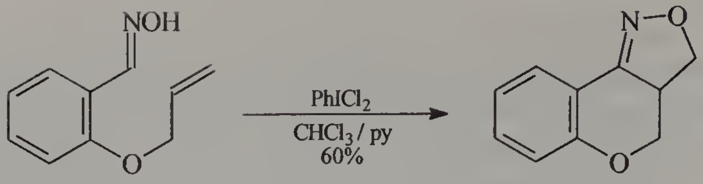


The stereochemistry of the reaction depended on the substrate: in some favourable cases a single stereoisomer was formed, whereas in others mixtures of α,β-isomers were obtained. An increase in yield was noted when the phenyl group of the thioglycoside was replaced by the 4-chlorophenyl group. Another useful fluorination involved xanthate esters, ROCSSMe, readily obtained from alcohols; these upon reaction with 4-(difluoroiodo)toluene were converted into alkyl fluorides in 48–75% yield [54].

6.4 FURTHER TRANSFORMATIONS

6.4.1 Dehydrogenations

Aldoximes from certain benzaldehydes were dehydrogenated to nitrile oxides by (dichloroiodo)benzene in hot chloroform with pyridine (or triethylamine). Since the products were not stable, they were isolated either in the form of dimers or as adducts with alkenes; from 2-allyloxy-benzaldoxime an intramolecular adduct was obtained [55]:



Ketoximes from some aromatic ketones (benzophenone and substituted acetophenones) underwent deoximation, at room temperature, in 65–80% yield [56].

6.4.2 Alkanes from lithium reagents

The reaction of (dichloroiodo)benzene with some organolithium reagents has demonstrated the possibility of carbon–carbon bond formation. The conditions for this condensation involved low temperature and a short reaction time [57]:

$$\mathrm{PhICl_2} + 2\,\mathrm{RLi} \xrightarrow[\text{Ar, 5 min}]{\text{THF, -80°C}} \mathrm{R{-}R}$$

Only the three isomeric butyl lithiums were tested, and hydrocarbon formation decreased in the order primary > secondary > tertiary.

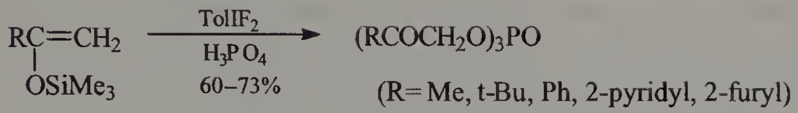
6.4.3 1,4-Diketones from silyl enol ethers

Another carbon–carbon bond forming reaction mediated by (difluoroiodo)benzene–boron trifluoride was reported using silyl enol ethers which underwent oxidative dimerization to 1,4-diketones [58] (see also Sections 5.2.2 and 12.2.2).

6.4.4 Oxyphosphorylation of silyl enol ethers

Mixtures of 4-(difluoroiodo)toluene and anhydrous phosphoric acid form a non-isolated hypervalent iodine species, probably $\mathrm{PhI(OH)(OPO_3H_2)}$, which reacts with silyl enol ethers producing tris-ketol phosphates. Interestingly, mono- or bis-ketol phosphates could not be obtained using the appropriate stoichiometry.

Tris-ketol phosphates [59]



$$\underset{\displaystyle\mathrm{OSiMe_3}}{\mathrm{RC}}{=}\mathrm{CH_2} \xrightarrow[\mathrm{H_3PO_4}\ 60\text{–}73\%]{\mathrm{TolIF_2}} \mathrm{(RCOCH_2O)_3PO}$$

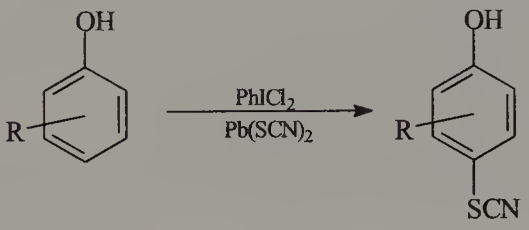
(R=Me, t-Bu, Ph, 2-pyridyl, 2-furyl)

To a mixture of crystalline anhydrous phosphoric acid (100 mg, 1.01 mmol) and 4-(difluoroiodo)toluene (775 mg, 3.05 mmol) in dry t-butanol (15 ml), under nitrogen, was added the silyl enol ether (6.05 mmol) at room temperature. After 6 h, the mixture was concentrated and the residue was recrystallized from acetone–hexanes to give the title compounds in 79–91% yield.

6.4.5 Thiocyanation of phenols

A variety of phenols and naphthols were converted efficiently into 4-thiocyanato derivatives by (dichloroiodo) benzene and lead thiocyanate.

Thiocyanation of phenols [60]



To an ice-cooled suspension of lead thiocyanate (485 mg, 1.5 mmol) in dry dichloromethane (10 ml) was added (dichloroiodo)benzene (330 mg, 1.2 mmol). The mixture was stirred for 20 min at 0°C and then the phenol (1 mmol) was added and the whole mixture was stirred for 1 h. The reaction mixture was filtered and silica (2 g) was added to the filtrate, which was concentrated. The product was adsorbed on silica and eluted with ethyl acetate–hexane to give the 4-thiocyanated phenol (61–95%) or naphthol (58–97%). In no case was any 2-isomer found. An alternative, more expensive, procedure for the thiocyanation of aromatics involved BTI (Section 4.5).

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–7–

[Hydroxy(tosyloxy)iodo]benzene and its Analogues

[Hydroxy(tosyloxy)iodo]benzene, PhI(OH)OTs (hereafter abbreviated HTI), is often called Koser's reagent. It is a readily available stable compound gaining popularity in diverse fields. Although in several reactions it behaves similarly to other hypervalent iodine reagents already discussed, there are many instances in which it shows a different reactivity or improved features. Its uses refer mostly to oxidations of various types and tosyloxylations (or oxysulphonylations with analogues bearing various RSO_3 groups). Some related compounds having an organosulphonyloxy group are also discussed in this chapter, including Zefirov's reagent, PhI(OTf)OI(OTf)Ph, and the product of its further transformation (Section 2.3). The chemistry of these reagents has been reviewed [1].

7.1 REACTIONS OF ALKENES AND ALLENES

7.1.1 Tosyloxylation and related additions

With HTI alkenes afforded stereoselectively *cis*-adducts, i.e. 1,2-bis tosylates of glycols, derived from the *syn* addition of two tosyloxy groups to the double bond, in moderate yield. Some representative examples are collected in Table 7.1, and a procedure follows.

erythro(DL)-2,3-*Bis(tosyloxy)pentane* [2]

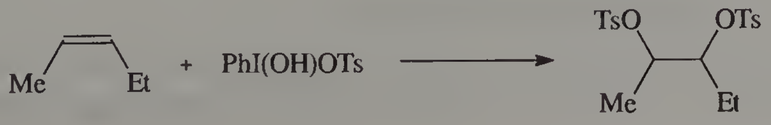
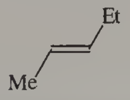
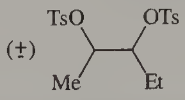
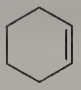
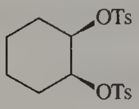
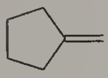
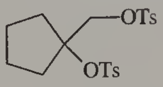
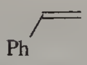
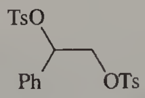
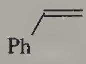
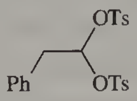
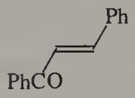
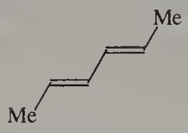


TABLE 7.1

Reactions of HTI with alkenes in dichloromethane [2]

Substrate	Product	Yield (%)
		48
		26–79[a]
		26
		62
 (neat)		63
	PhCOCH(OTs)CH(OTs)Ph[b]	57
	MeCH(OTs)CH=CH(OTs)Me[b]	35

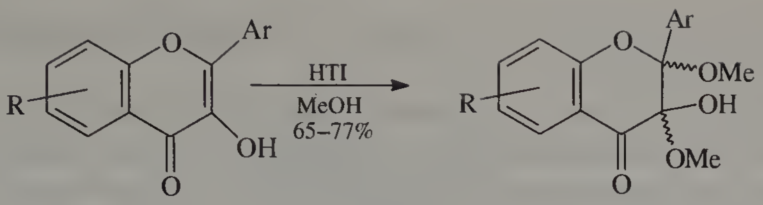
[a] The high yield was obtained using PhI(OMe)OTs.
[b] Uncertain geometry.

A mixture of HTI (3.92 g, 10 mmol) and *cis*-2-pentene (1.6 g, 23 mmol) in dichloromethane (20 ml) was allowed to stand at 3°C for 28 h. The reaction mixture was washed with water (2 × 20 ml), dried and concentrated to a yellow oil which was washed with pentane (15 ml) and crystallized from methanol–pentane (6 and 3 ml) at – 20°C to give *erythro*(DL)-2,3-bis(tosyloxy)pentane (827 mg, 40%), m.p. 82–83°C. An additional 10% was obtained on cooling the pentane wash.

Zefirov's reagent reacted similarly affording *cis*-bis triflates (see Section 12.2.2). The reaction of HTI and alkenes in the presence of salts with nucleofugal anions, such as lithium perchlorate, led to the addition of these anions to the double bond [3].

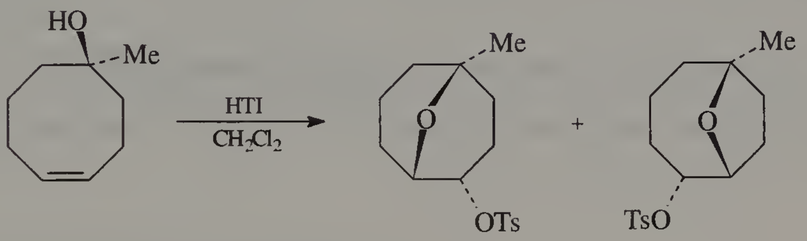
7.1.2 Bis methoxylation of flavonols

A number of flavonols were converted into hemiacetals by methanolic HTI at room temperature; the stereochemistry of the addition was not determined [4]:



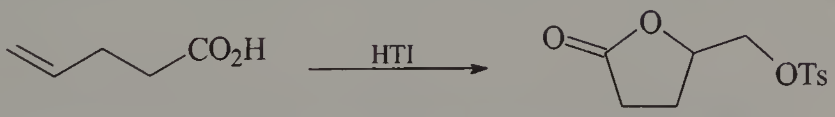
7.1.3 Intramolecular participation of nucleophilic functionalities in reactions of alkenes

Cyclooctene was unreactive towards HTI but 1-methyl-4-cycloocten-1-ol afforded an almost 1:1 mixture of two tosyloxy ethers (55%); the regioselectivity for the formation of the two skeletons was low, but the addition was highly *trans*-selective [5]:



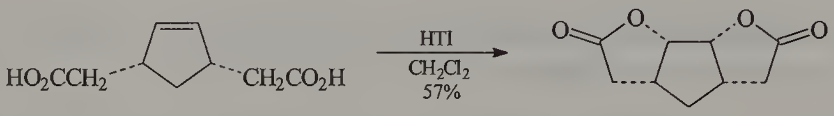
Several unsaturated acids were converted by HTI to 5- or 6-membered tosyloxy-lactones.

5-Tosyloxy-4-pentanolactone [6]



A solution of 4-pentenoic acid (1.1 g, 11 mmol) in dichloromethane (5 ml) was added dropwise at room temperature to a stirred suspension of HTI (3.92 g, 10 mmol) in dichloromethane (60 ml). Heat was evolved; after 6 h the reaction mixture was washed successively with water, saturated sodium bicarbonate and brine; then it was concentrated and dried. Treatment of the oily residue with ether removed iodobenzene and resulted in the isolation of 5-tosyloxy-4-pentanolactone (1.8 g, 60%) m.p. 80.5–81.5°C.

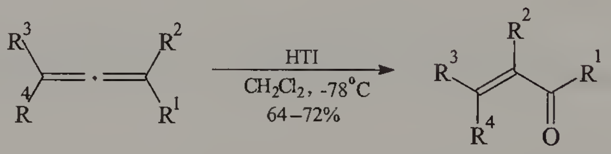
Elimination sometimes accompanied tosyloxylactonization; then, the crude reaction mixture was treated with 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) and unsaturated lactones were obtained directly. A series of suitably constructed unsaturated diacids were produced with HTI bis-lactones, as the result of stereoselective *cis*-addition of the carboxy groups to the double bond, for example [7]:



In some carbamates their nitrogen was found to participate in cyclizations similar to those reported with oxygen nucleophiles [8].

7.1.4 Conversion of allenes to carbonyl compounds

Phenylated allenes were converted readily by HTI into rearranged phenyl-substituted propenals or propen-1-ones [9]:



In an analogous way, 1-alkoxyallenes were transformed to 2-alkoxy-3-tosyloxypropanals. The same substrates with DIB afforded 3-acetoxy-3-alkoxy-propynes (Section 3.1).

7.2 REACTIONS OF ALKYNES AND ALCOHOLS

7.2.1 Conversion of alkynes into esters

Alkynes upon heating with HTI in methanol underwent an oxidative rearrangement to methyl carboxylates which were hydrolysed *in situ* to afford carboxylic acids; a typical procedure is given.

α-Methylphenylacetic acid [10]

$$PhC\equiv C-CH_3 \xrightarrow[\text{(ii) NaOH}]{\text{(i) PhI(OH)OTs/MeOH}} PhCH(CH_3)CO_2H$$

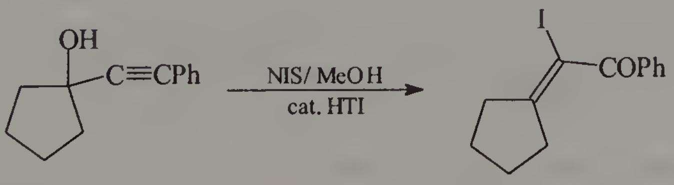
To a solution of HTI (5.16 g, 13 mmol) in methanol (60 ml) was added phenylpropyne (11.6 g, 10 mmol) and the solution was refluxed for 96 h. The reaction mixture was treated with a saturated solution of sodium bicarbonate, extracted with dichloromethane (3 × 50 ml), dried and concentrated to an oil; this was hydrolysed in 2*N* sodium hydroxide solution to give α-methylphenylacetic acid (9.9 g, 66%) b.p. 262°C.

The reaction was of general applicability; not only internal but also terminal alkynes reacted in the same way, e.g. 1-hexyne was converted into hexanoic acid (58%) and 2-ethynylthiophene to 2-thienylacetic acid (54%). By contrast, heating terminal alkynes in chloroform with HTI afforded alkynyl or alkenyl phenyliodonium salts; the former in refluxing methanol rearranged to methyl carboxylates [11].

7.2.2 Transformations of alkynols

Several alkynols reacted with elemental iodine (or NIS, or NBS) assisted by HTI – in either stoichiometric or catalytic amounts – to afford stereoselectively halogenated enones or enals. Examples of such transformations, some of which involved ring-expansion, are given in Table 7.2; a procedure follows.

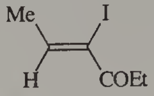
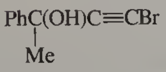
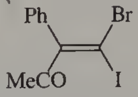
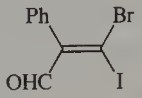
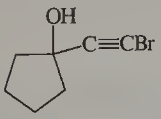
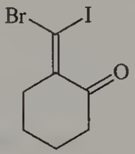
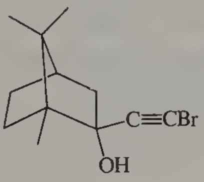
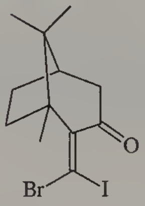
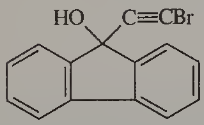
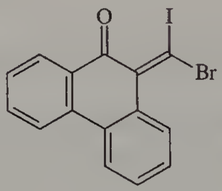
2-Cyclopentylidene-2-iodo-1-phenylethanone [15]



1-Phenylethynyl-1-cyclopentanol (352 mg, 1.89 mmol) in methanol (20 ml) was treated with *N*-iodosuccinimide (514 mg, 2.29 mmol) and HTI (96 mg, 0.24 mmol),

TABLE 7.2

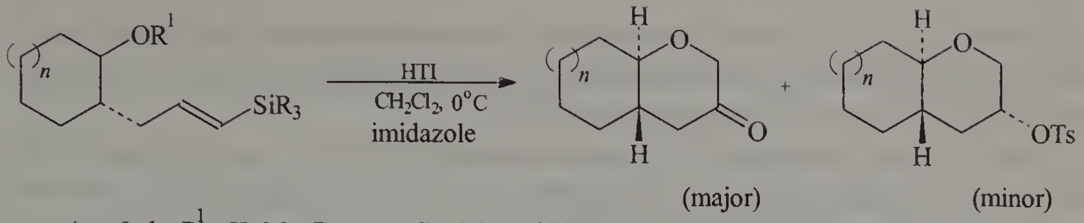
Conversion of alkynols into iodo-unsaturated carbonyl compounds using HTI and NIS or iodine

Substrate	Conditions	Product	Yield (%)	Ref.
$\mathrm{MeCH(OH)C{\equiv}CEt}$	NIS, MeOH, cat. HTI		85	[12]
$\underset{\mathrm{Me}}{\mathrm{PhC(OH)}}\mathrm{C{\equiv}CBr}$	NIS, MeCN, cat. HTI		72	[13]
$\mathrm{PhCH(OH)C{\equiv}CBr}$	I_2, MeCN, HTI		96	[14]
	I_2, MeCN, HTI		70	[15]
	I_2, MeCN, HTI		60	[16]
	I_2/ HTI		85	[17]

which were added in one portion to the stirred solution at room temperature with light protection. After 18 h, the reaction mixture was diluted with ether (75 ml) and washed with aqueous 5% sodium thiosulphate solution (25 ml), followed by water (3 × 25 ml). The organic layer was dried and concentrated to an oil which was purified by column chromatography on silica gel (hexanes; then ether) to give 2-cyclopentylidene-2-iodo-1-phenylethanone (429 mg, 73%) as an oil.

7.2.3 Synthesis of pyran-3-ones

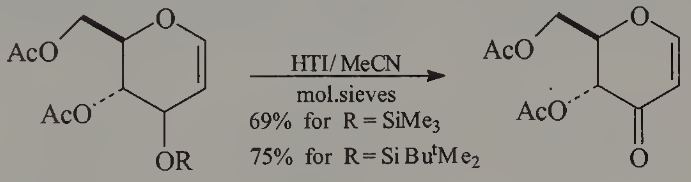
Silyl-substituted δ,ε-unsaturated alcohols and related ethers gave, with two equivalents of HTI at 0°C, a mixture of bicychic pyran-3-ones and tosyloxytetrahydropyrans [18]:


OR1
n
SiR3
HTI
CH2Cl2, 0°C
imidazole
H
O
n
O
H
+
H
O
n
OTs
H
(major)
(minor)

($n = 0, 1$; R^1= H, Me, Bu, etc. ; R= Me and Ph)

7.2.4 Oxidative deprotection of glycals

Variously protected glycals, at O-3, were deprotected by HTI, being converted oxidatively into 3-uloses. The group R was acetyl, benzoyl, etc. best results were obtained from silylated precursors. The double bond remained unaffected in these processes [19]:

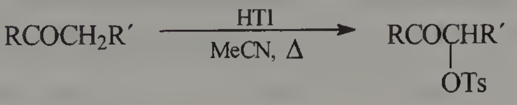

AcO
O
AcO
OR
HTI/ MeCN
mol.sieves
69% for R = SiMe3
75% for R = Si ButMe2
AcO
O
AcO
O

Another glycal, on treatment with HTI, afforded stereoselectively a 2-formyl tetrahydrofurfural as the major product [20].

7.3 REACTIONS OF KETO COMPOUNDS

7.3.1 Sulphonyloxylation

Enolizable ketones and related keto compounds are α-functionalized by HTI [21], e.g.:

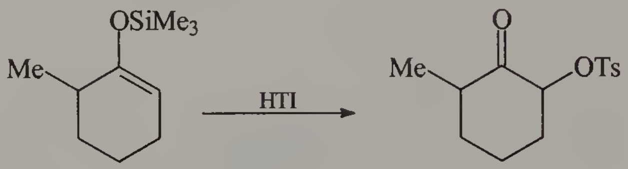


$$RCOCH_2R' \xrightarrow[\text{MeCN, }\Delta]{\text{HTI}} \underset{\substack{| \\ OTs}}{RCOCHR'}$$

Good yields were normally obtained, but some cyclic ketones failed to react. Then, sonication promoted significantly the efficacy of tosyloxylation [22]. The regioselectivity of tosyloxylation was low but the use of an analogue of HTI with a bulky RSO_2 group, [hydroxy(camphorosulphonyloxy)iodo]benzene, improved the situation in favour of the less hindered site [23].

The use of silyl enol ethers for sulphonyloxylations offers some advantages over ketones: conditions are milder and yields higher (85% for α-tosyloxy-cyclohexanone); also, it is possible to control the regiochemistry of the reaction. For example, 2-methyl-6-tosyloxy-cyclohexanone was prepared regioselectively from the corresponding silyl enol ether, without heating.

2-Methyl-6-tosyloxy-cyclohexanone [24]



To a solution of the silyl enol ether (2.21 g, 12 mmol) in dry dichloromethane (50 ml) was added HTI (3.92 g, 10 mmol), at room temperature. After 2 h stirring the reaction mixture was washed with aqueous sodium bicarbonate solution (3 × 50 ml), then the organic phase was dried and concentrated to give an oil. Addition of hexane followed by decantation of the hexane phase removed iodobenzene and some ketone; pure 2-methyl-6-tosyloxy-cyclohexanone was obtained by crystallization from ether (2.25 g, 80%), m.p. 112–114°C.

The use of silyl enol ethers permitted the preparation of α-tosyloxy ketones with acid-sensitive or oxidizable ring systems, such as furan and pyridine.

Another analogue of HTI which was used with either ketones or silyl enol ethers was [hydroxy(mesyloxy)iodo]benzene, $PhI(OH)OSO_2Me$ [25]. A related reagent formed *in situ* from iodosylbenzene and trimethylsilyl triflate, probably $PhI(OSiMe_3)OTf$, reacted similarly with silyl enol ethers to afford α-ketotriflates (see Table 5.3). *β*-Diketones and *β*-ketoesters underwent tosyloxylation by HTI; the reaction was very effective in substrates with a perfluoroalkyl moiety and gave their hydrates [26]:

$$\mathrm{RfCOCH_2COR} \xrightarrow[\substack{\mathrm{MeCN} \\ 79\text{–}97\%}]{\mathrm{HTI}} \mathrm{RfC(OH)_2CH(OTs)COR}$$

Simple esters, and also ε-caprolactone, in the form of their silyl enol derivatives afforded α-sulphonyloxylated derivatives [24], e.g.:

$$\mathrm{PhCH{=}C(OSiMe_3)OEt} \xrightarrow[\mathrm{CH_2Cl_2}\\ 85\%]{\mathrm{PhI(OH)OMs}} \mathrm{PhCH(OMs)COOEt}$$

7.3.2 Functionalization of acetophenones

α-Tosyloxyketones are mostly crystalline compounds, easy to isolate and handle; they are readily converted by nucleophiles into diverse derivatives, replacing the lachrymatory α-chloro- or α-bromoketones. For example, reaction of several acetophenones with HTI followed by addition of aniline or potassium thiocyanate afforded α-anilino- and α-thiocyanatoacetophenones, respectively [27,28]:

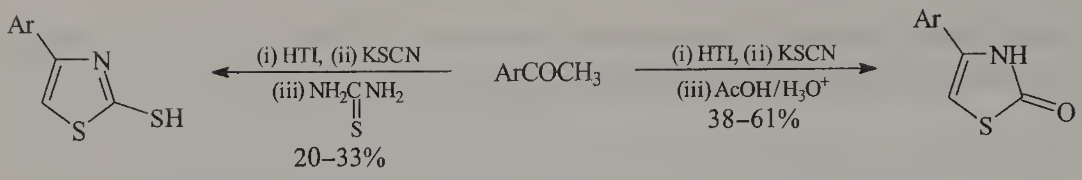
$$\mathrm{ArCOCH_3} \xrightarrow[\text{(ii) 2eq. PhNH}_2\\ 52\text{–}70\%]{\text{(i) HTI/ MeCN, }\Delta} \mathrm{ArCOCH_2NHPh}$$

$$\mathrm{ArCOCH_3} \xrightarrow[\text{(ii) KSCN}\\ 52\text{–}78\%]{\text{(i) HTI/ MeCN, }\Delta} \mathrm{ArCOCH_2SCN}$$

Another sulphur nucleophile, 2-mercaptobenzimidazole, gave similarly 2-phenacylthio-benzimidazole [29]. Acetophenones on treatment with methanolic HTI underwent rearrangement affording methyl arylacetates, $\mathrm{ArCH_2CO_2Me}$; the same compounds were obtained with iodosylbenzene in acidic methanol (Section 5.2.3).

7.3.3 Synthesis of heterocycles from keto compounds

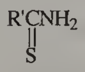
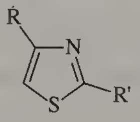
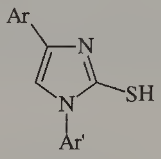
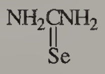
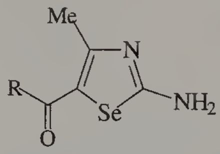
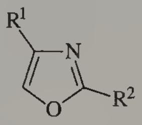
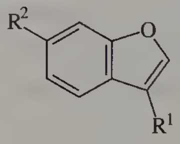
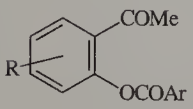
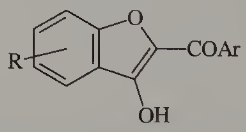
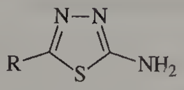
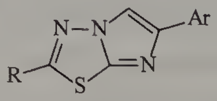
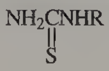
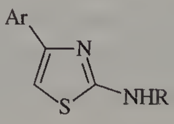
Following the same methodology of the previous Section, the synthesis of several heterocyclic systems in one-pot reactions has been achieved [30,31]. For example, thiocyanation combined with *in situ* addition of thiourea resulted in the formation of 2-sulphhydryl-1,3-thiazoles; alternatively, treatment of the reaction mixture with aqueous acid led to 1,3-thiazol-2-ones [28]:



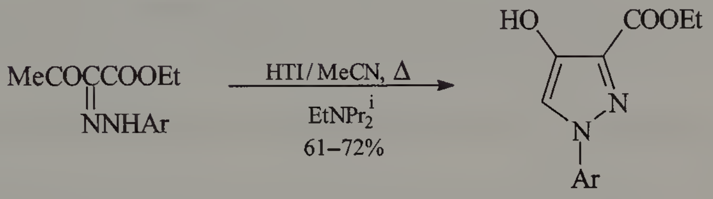
Further examples of heterocycles obtained by this approach are given in Table 7.3.

TABLE 7.3

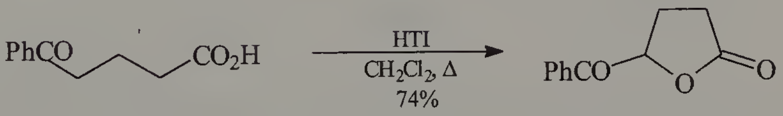
Synthesis of heterocycles from HTI-treated acetophenones and related keto compounds

Starting materials	Products	Yield (%)	Ref.
RCOMe +  $R'\underset{\overset{\|}{S}}{C}NH_2$		—	[32]
ArCOR + Ar'NH₂ + KSCN		—	[33]
RCOCH₂COMe +  $NH_2\underset{\overset{\|}{Se}}{C}NH_2$		74–79	[34]
R^1COMe R^2COOH/Et_3N ; $NH_4OAc/AcOH$ (through $ArCOCH_2OAr$)		—	[31]
R^1COMe p-$R^2C_6H_4OH$, K_2CO_3 ; PPA (through $ArCOCH_2OOCR$)		—	[31]
 KOH		70–80	[35]
ArCOMe 		51–68	[36]
ArCOMe  $NH_2\underset{\overset{\|}{S}}{C}NHR$		65–71	[34]

The functionality needed for cyclization may be incorporated in the ketone, as exemplified in one entry of Table 7.3. Intramolecular participation was also provided by arylhydrazones derived from ethyl acetoacetate, with aryls having electron-withdrawing substituents; when heated with HTI and a tertiary amine, they were transformed to ethyl 1-aryl-4-hydroxy-pyrazole-3-carboxylates [37]:



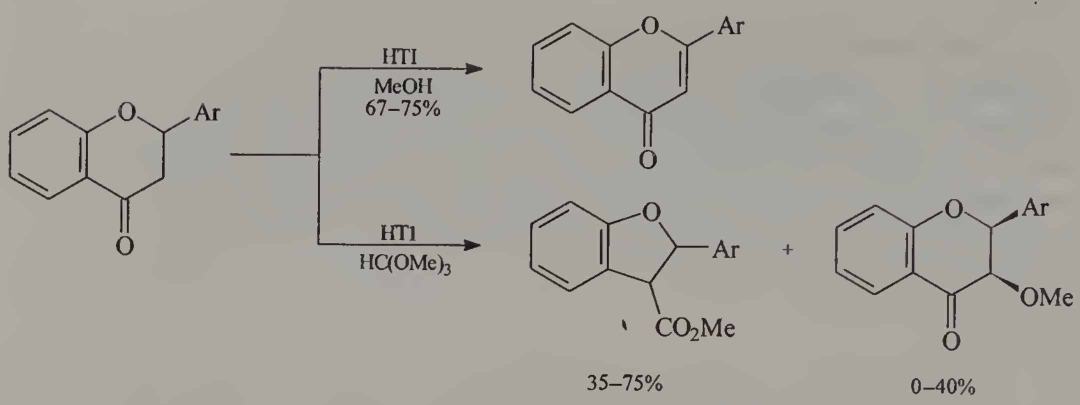
5-Ketoacids were cyclized by HTI to acyl- or keto-γ-lactones, for example [38]:



4,6-Diketoacids reacted with HTI in the same manner, at room temperature, affording diketo-δ-lactones. A different cyclization involved decarboxylative ring-closure of some enamine carboxylic acids to oxazoles [39].

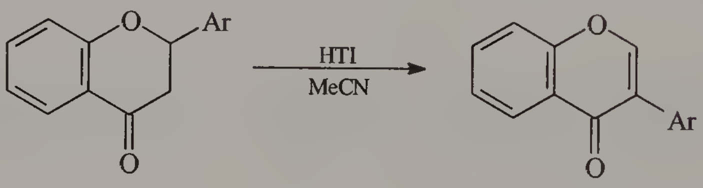
7.3.4 Transformations of flavanones

Flavanones undergo a variety of transformations by HTI or other hypervalent iodine reagents. In methanol, at room temperature, they were dehydrogenated to the corresponding flavones [40]. A similar dehydrogenation occurred in chromanones [41]. Dramatic solvent effects occurred when methanol was replaced by other solvents. Thus, in trimethyl orthoformate ring-contraction was the main pathway and methyl 2-aryl-2,3-dihydrobenzofuran-3-carboxylates the major products, accompanied by substantial amounts of 3-methoxyflavones [42]:



In boiling acetonitrile an aryl shift also took place, the only products being isoflavones.

Isoflavones from flavanones [43]

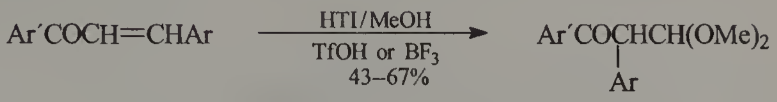


To a solution of flavanone (5 mmol) in acetonitrile (15–20 ml) was added HTI (1.97 g, 5 mmol) and the mixture was refluxed for about 12 h. The solvent was then removed and water (50–70 ml) was added; the resulting mixture was extracted with dichloromethane (3 × 50 ml), dried and concentrated to an oil. Pure products were obtained by crystallization, using either petroleum ether or ethanol, in 72–80% yield.

An almost exactly similar procedure, with methanol at room temperature, led to the preparation of flavones; for this, as well as for the reaction with trimethyl orthoformate, chromatographic separation was required.

7.3.5 Transformations of chalcones

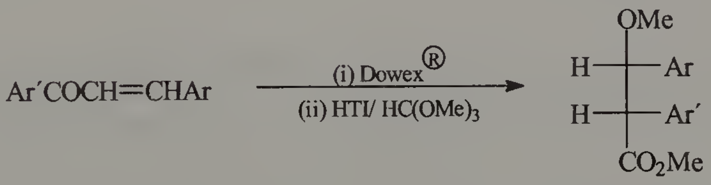
In addition to products obtained on treatment with iodosylbenzene in methanolic alkali (Section 5.1.1), chalcones underwent three different transformations by HTI. The first, in methanol, involved tosyloxylation of the double bond (Table 7.1). In the second, with methanolic HTI and acid catalysis, an oxidative 1,2-migration of the aryl group attached to the alkene moiety occurred, with formation of rearranged acetals [44]:



$$\mathrm{Ar'COCH{=}CHAr} \xrightarrow[\text{TfOH or BF}_3\ \ 43\text{–}67\%]{\text{HTI/MeOH}} \mathrm{Ar'CO\underset{Ar}{C}HCH(OMe)_2}$$

The third type of reactivity, using HTI in trimethyl orthoformate, involved migration of the aryl groups attached to the carbonyl moiety, resulting in a diastereoselective synthesis of methyl 2,3-diaryl-3-methoxypropanoates in their *erythro* form exclusively.

Methyl 2,3-diaryl-3-methoxypropanoates from chalcones [45]



To a stirred solution of chalcone (5 mmol) in trimethyl orthoformate (20 ml) was added Dowex® 50 × 4 cation exchange resin (3 g). After stirring at room temperature for 20 h, the mixture was filtered into a solution of HTI (2.37 g, 6 mmol) in trimethyl orthoformate (10 ml) and kept for 12 h. It was then quenched with 10% aqueous sodium bicarbonate (25 ml) and extracted with dichloromethane. The combined organic layers were washed with water, dried and concentrated; the residue was purified by column chromatography on silica gel (benzene), to afford methyl 2,3-diaryl-3-methoxypropanoates in 80–94% yield. This method was better than that reported with thallium (III) nitrate not only because this toxic reagent is avoided but also because yields were considerably higher.

7.4 REACTIONS OF NITROGEN, SULPHUR AND OTHER COMPOUNDS

7.4.1 Hofmann-type preparation of amines

Although BTI (Section 4.4.1) is the reagent of choice for the conversion of primary carboxamides into amines, other hypervalent iodine reagents are also of importance

(Sections 3.4.2 and 5.3.2). HTI was suitable for long-chain aliphatic amides which are unreactive under normal Hofmann conditions.

Alkylammonium tosylates from aliphatic carboxamides [46]

$$\mathrm{RCONH_2} \xrightarrow[\mathrm{MeCN},\ \Delta]{\mathrm{HTI}} \mathrm{RNH_3^+\ TsO^-}$$

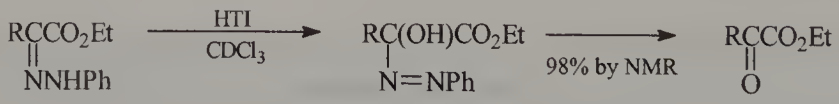
$$(\mathrm{R{=}Me\ to\ C_{20}H_{41}},\ \text{etc.})$$

A hot solution of the amide (10 mmol) in acetonitrile (30 ml) was added to a stirred mixture of HTI (3.92 g, 10 mmol) and acetonitrile (20 ml). After refluxing for a suitable period of time (15 min–15 h), on cooling the alkylammonium tosylate crystallized out in high yield.

Some bridgehead amines such as 4-iodo-1-cubylamine (58%) and 1-adamantylamine (85%) were also obtained in this way [47]. The direct formation of alkylammonium tosylates is advantageous because of the instability of some amines of this type. No special precautions, as with BTI, were needed with HTI which, however, did not work with some cyclic carboxamides; also, malonamide did not undergo degradation but tosyloxylation, affording α-tosyloxymalonamide (81%) [48]. The reaction involved the intermediacy of *N*-phenyliodonium salts ($\mathrm{RCONHI^+Ph\ TsO^-}$), which were actually isolated from carboxamides and [methoxy(tosyloxy)iodo]benzene [49].

7.4.2 Oxidation of phenylhydrazones

HTI was effective in converting phenylhydrazones and phenylhydrazones of α-keto esters into the parent ketones. The reaction proceeded through an azo intermediate, stable enough to be observable by ^{1}H-NMR, and was essentially quantitative [50]:



$$\underset{\mathrm{NNHPh}}{\overset{}{\mathrm{RC(=}}}\!\mathrm{)CO_2Et} \xrightarrow[\mathrm{CDCl_3}]{\mathrm{HTI}} \mathrm{RC(OH)(N{=}NPh)CO_2Et} \xrightarrow[\text{98\% by NMR}]{} \mathrm{RC(=O)CO_2Et}$$

Similar results were obtained by using BTI in acetonitrile at 0°C; the yields of isolated products were in the range of 80% (see also Section 7.3.3 for a synthesis of pyrazoles).

7.4.3 Oxidation of sulphur compounds

Sulphides reacted readily with [methoxy(tosyloxy)iodo]benzene to afford methoxysulphonium tosylates [51]:

$$R_2S \xrightarrow[\substack{CH_2Cl_2 \\ \sim 99\%}]{PhI(OMe)OTs} R_2S^+OMe\ TsO^-$$

The analogues [menthyloxy(tosyloxy)iodo]benzenes, with both (+) and (−) forms of menthol, in their reactions with non-symmetric sulphides caused considerable asymmetric induction; hydrolysis of their salts afforded sulphoxides of high optical purity [52]. By using *N*-phenyliodonio tosylates of benzamide (and some other similar derivatives from different amides, Section 7.4.1) dimethyl sulphide was converted into amidosulphonium tosylates which can serve as the precursors of sulphilimines [51]:

$$Me_2S + RCONHI^+Ph\ TsO^- \xrightarrow[69\text{–}90\%]{CH_2Cl_2} Me_2S^+NHCOR\ TsO^-$$

7.4.4 Oxidative substitution in iodoalkanes

As already mentioned, hypervalent iodine reagents are useful for the oxidatively assisted nucleophilic substitution of iodine in iodoalkanes (Section 5.4.2). In this way HTI was used for the preparation of some tosylates. A rearrangement occurred with neopentyl iodide, Me_3CCH_2I, which was converted into the ester $Me_2C(OTs)CH_2Me$ (85%) [53]. The most successful application of such reactions for preparative purposes was the functionalization of some iodocubanes and iodohomocubanes, and especially the preparation of their triflates and mesylates from iodosylbenzene-trimethylsilyl triflate and [hydroxy(mesyloxy)iodo]benzene, respectively [54,55].

7.4.5 Miscellaneous

Phenylacetylene on heating with NIS in methanol and catalytic amounts of HTI was transformed to the diiodo acetal $PhC(OMe)_2CHI_2$ (95%); under similar conditions, iodo-phenylacetylene afforded $PhC(OMe)_2COOMe$ (86%) [56]. Other reactions using NBS or NIS and catalytic HTI resulted in bromination and iodination of, respectively, polyalkylbenzenes [57] and *N*-acyl-2,3-dihydro-4-pyridones [58].

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–8–

Diaryl Iodonium Salts

This chapter includes diaryl iodonium salts and some related heteroaromatic and heterocyclic analogues; other categories are discussed separately in Chapter 9. Arylation is the dominating reaction of diaryl iodonium salts. From the applied point of view, they are useful in photopolymerizations and for the chemical amplification in imaging systems. Also, they show interesting biological activity [1,2].

8.1 PREPARATIVE METHODS

A large number of methods are available for the preparation of diaryl iodonium salts (hereafter simply iodonium salts). Among them, there are some of general applicability or improved efficiency. Examples from each major category are given.

8.1.1 Symmetrical diaryl iodonium salts

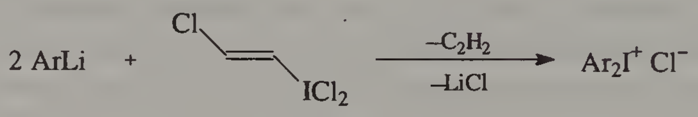
These iodonium salts are usually obtained directly from arenes or organometallics and an inorganic compound of iodine (III) or (V). Once formed, iodonium salts can exchange their anion with almost any other anion; exceptions are hydrosulphide, sulphide and cyanide. For large-scale preparations one of the early methods is always useful and can be applied to arenes of various kinds, including those bearing electron-withdrawing substituents.

Diphenyliodonium chloride [3]

$$C_6H_6 + I_2 + KIO_3 \xrightarrow{H_2SO_4} (C_6H_5)_2I^+ \, HOSO_3^-$$

To a stirred mixture of potassium iodate (107 g, 0.5 mol), benzene (90 ml, 1 mol) and acetic anhydride (200 ml), kept below 10°C, there was added a cold solution of acetic anhydride (100 ml) and concentrated sulphuric acid (225 ml). After being stirred overnight, the reaction mixture was poured into 400 g of ice, extracted with ether (2 × 100 ml) and treated twice with 20 g of charcoal. The filtered solution was mixed with ammonium chloride (100 g) in 350 ml of water and cooled in an ice bath. After removal of the precipitate, a second crop was obtained by a new treatment with aqueous ammonium chloride, and saturation of the mother liquid with ammonia gave a third crop. Recrystallization of the combined yield from methanol gave diphenyliodonium chloride (81.1 g, 52%), m.p. 228–229°C.

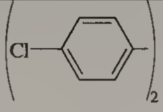
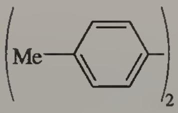
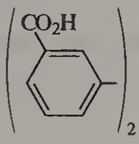
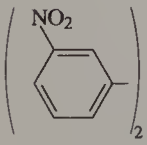
Apart from variations of this method [3–6], a different approach was preferable for certain iodonium salts, involving the use of organolithium compounds and *trans*-(dichloroiodo)vinyl chloride (CAUTION: EXPLOSIVE) [7]:



Some examples of iodonium salts prepared by these methods are given in Table 8.1.

TABLE 8.1

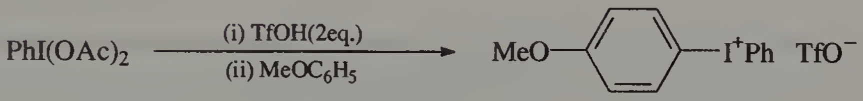
Preparation of symmetrical diaryl iodonium salts

Diaryl iodonium salt	Yield (%)	Method	Ref.
 $I^+ HOSO_3^-$	60	$(IO)_2SO_4$	[4]
 $I^+ I^-$	91	$IO_2^+ HOSO_3^-$	[4]
 $I^+ I^-$	53	$(IO)_2SO_4$	[3]
 $I^+ HOSO_3^-$	60	$IO(OSO_2F)$	[5]
$Ph_2I^+ TfO^-$	93	$PhSiMe_3 + IO(OTf)$	[6]
$(2\text{-Naphthyl})_2I^+ Cl^-$	55	2-Naphthyl Li + $ClCH{=}CHICl_2$	[7]
$(C_6F_5)_2I^+ TfO^-$	80	$I(O_2CCF_3)_3$	[8]

8.1.2 Unsymmetrical diaryl iodonium salts

Most known iodonium salts of this category have one phenyl and one aryl group. Various hypervalent iodine precursors can be used as effective electrophiles, notably the combination of (diacetoxyiodo)benzene with triflic acid. The reagent is formed *in situ* and is suitable for a range of activated to weakly deactivated arenes. The reactions proceed at room temperature and in some cases, e.g. with anisole, only the *p*-isomer was produced. Strongly deactivated arenes such as nitrobenzene did not react.

Phenyl 4-methoxyphenyl iodonium triflate [9]



To a stirred suspension of (diacetoxyiodo)benzene (660 mg, 2.05 mmol) in dichloromethane (10 ml), was added triflic acid (0.36 ml, 4.07 mmol) at 0°C with a syringe. The mixture was stirred for 1 h at room temperature, becoming a clear yellow solution. This was cooled to 0°C and anisole (238 mg, 2.2 mmol) was added dropwise with a syringe. The reaction mixture was stirred at room temperature for 1 h, concentrated and ether was added to induce crystallization. The solid formed was filtered, washed with ether and dried to give the title compound (771 mg, 82%), m.p. 110–111°C.

Iodoarenes may be oxidized *in situ* to an iodine(III) species which is subsequently coupled with the appropriate arene. Potassium persulphate [10] and chromium trioxide [11] were most suitable oxidants, notably for iodoarenes bearing electron-withdrawing substituents.

Another approach for the preparation of either symmetrical or unsymmetrical iodonium salts used organolithium or organomercury compounds and (dichloroiodo)arenes [12]. The problem of the formation of unwanted isomers during reactions involving aromatic electrophilic substitution may also be overcome by the condensation of iodosylarenes with iodylarenes [12]. Several iodonium triflates were prepared in high yield from activated or mildly deactivated arenes with iodosylbenzene and triflic anhydride or triflic acid [13,14] or sulphur trioxide [15]. Some of these compounds are shown in Table 8.2.

8.1.3 Iodonium salts with heteroaromatic groups

These iodonium salts may also be symmetrical or unsymmetrical. The methods for their preparation are essentially the same to those already discussed, with some

TABLE 8.2

Preparation of non-symmetrical iodonium salts

Iodonium salt	Method	Yield (%)	Ref.
PhI^+(5-indanyl) TfO^-	$PhI(OAc)_2$-TfOH	86	[9]
PhI^+(4-Cl phenyl) TfO^-	$PhI(OAc)_2$-TfOH	74 (*o*:*p* ; 4:96)	[9]
PhI^+(2-NO_2 phenyl) Br^-	$2\text{-}NO_2C_6H_4IO + H_2SO_4$	75	[3]
$(4\text{-}ClC_6H_4)I^+$(1-naphthyl) Br^-	$4\text{-}ClC_6H_4ICl_2$ + 1-naphthyl Li	61	[16]
$PhI^+C_6F_5\ Cl^-$	$PhCl_2 + C_6F_5Li$	23	[17]

variations. Particularly effective was the reaction of *trans*-(dichloroiodo)vinyl chloride with lithium heterocycles for difuryl, dithienyl and nitrogen-containing hetaryl iodonium salts [18–20]. Another good method, useful for furyl and thienyl iodonium salts, was the reaction of [hydroxy(tosyloxy)iodo]benzene with silylated heterocycles [21]. Dicyanoiodonium triflate, generated *in situ* from iodosyl triflate and trimethylsilyl cyanide, was the best reagent for the preparation of several bis hetaryl iodonium salts from the corresponding tributyltin substituted heterocycles.

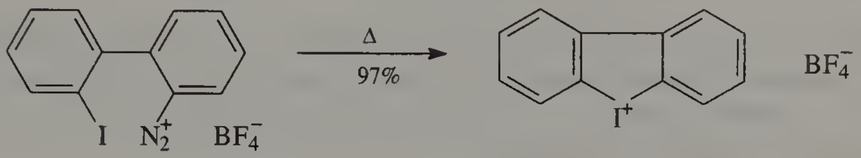
Bis hetaryl iodonium triflates [22]

$$O{=}IOTf \ + \ 2\ Me_3SiCN \longrightarrow (CN)_2I^+\ TfO^- \xrightarrow{2\ HetS\ nBu_3} Het_2I^+\ TfO^-$$

Trimethylsilyl cyanide (0.54 ml, 4 mmol) was added to a stirred suspension of iodosyl triflate (0.58 g, 2 mmol) in dichloromethane (15 ml) at −78°C under nitrogen. The mixture was allowed to warm to −20°C and stirred at this temperature for 15 min until the formation of a clear solution. The solution was cooled to −78°C and transferred to a cold stirred solution of the appropriate tributyltin heterocycle (4 mmol) in dichloromethane (15 ml). The mixture was brought to room temperature and crystallized by the addition of dry hexane (20–30 ml). The precipitated iodonium salt was filtered under nitrogen, washed with dry ether (30 ml) and dried *in vacuo*. Mono or bis hetaryl iodonium salts prepared by these and related methods also involved groups coming from selenophene [23], pyrazoles [24], benzothiophene [21], etc.

8.1.4 Heterocyclic iodonium salts

Many heterocycles in which the iodonium cationic centre is part of a ring are known; even an iodiranium salt has been isolated from adamantylideneadamantane and iodine-silver triflate [25]. Dibenziodolium salts are the commonest representatives of this class of compounds.They can be obtained from suitable precursors by methods analogous to those previously described, for example through oxidation of *o*-iodobiphenyl for the unsubstituted heterocycle. Thermolysis of iododiazonium salts coming from 2-amino-2-iodobiphenyls is another alternative [26]:



8.1.5 Interconversions of iodonium salts

Most iodonium salts are exceptionally stable and unreactive towards electrophiles and weak nucleophiles. These properties permit their transformation to other iodonium salts, by nitration, oxidation, etc. Exchange reactions between iodonium salts and lithiated arenes proceed through tris- and tetrakis-coordinated iodine(III) species and can lead to the formation of either symmetrical or unsymmetrical new iodonium salts. The counteranion of iodonium salts is of great importance in determining their reactivity; therefore, it is useful to convert iodonium salts into other salts with the desired anion. This procedure also has the advantage that it permits a better purification. The usual way to effect such an anion metathesis is to dissolve a given iodonium salt in a suitable solvent (water, ethanol or 90% formic acid); on addition of the appropriate inorganic salt the new iodonium salt precipitates [1,2]. Another way is to treat the iodonium salt with a base or an anion exchange resin; the iodonium hydroxide formed *in situ* on addition of the appropriate acid gives the corresponding iodonium salt. A non-ionic method described in a patent for the preparation of diphenyliodonium triflate involved treatment of diphenyliodonium chloride with trimethylsilyl triflate [27].

8.2 CARBON–CARBON BOND-FORMING REACTIONS

Diaryliodonium salts, with few exceptions, are stable compounds towards heat, oxygen and humidity; they are mildly light-sensitive and should be stored in the dark, without refrigeration. Generally, their reactivity is less pronounced than that of other hypervalent iodine compounds. Indeed, in several of their reactions relatively drastic conditions may be necessary, especially for the least reactive heterocyclic iodonium salts. The search for optimum conditions is often desirable even for well-established reactions, by applying new findings concerning the use of specific solvents, catalysts or radical traps. Most synthetically important reactions involve arylation of inorganic or organic nucleophiles.

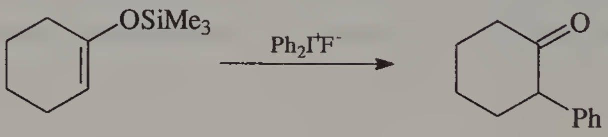
8.2.1 Arylation of keto compounds and esters

Iodonium salts are excellent reagents for *C*-arylation of a variety of keto compounds. These reactions proceed homolytically through radical-chain or radical non-chain processes, starting either by one-electron transfer to form radical pairs or by formation of iodanes as illustrated in a simplified way:

$$\begin{tikzcd}
Ar_2I{-}Nu \arrow[dr] & Ar_2I^+ \; + \; Nu^- \arrow[l] \arrow[r] & Ar_2\dot{I} \;\; \dot{Nu} \arrow[dl] \\
& ArI \; + \; ArNu &
\end{tikzcd}$$

Variable experimental conditions are suitable for these arylations, from low to reflux temperatures in t-butanol or DMF; the substrate is first converted into a carbanionic form *in situ* by a strong base. Several ordinary ketones were phenylated under conditions favouring the formation of potassium or lithium enolates and also through their silyl enol ethers. A general method has been developed for the synthesis of α-phenylketones and α,α-diphenylketones from their silyl enol ethers and diphenyliodonium fluoride, as shown in Table 8.3.

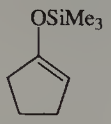
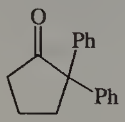
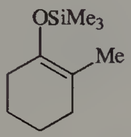
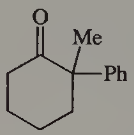
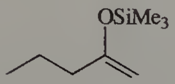
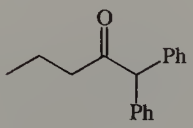
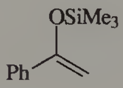
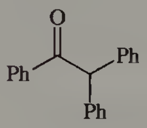
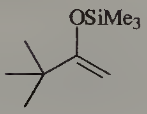
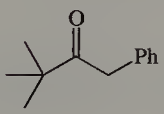
2-Phenylcyclohexanone [28]



A solution of the substrate (1.71 g, 10.06 mmol) in THF (5 ml) was added dropwise, under nitrogen, to a stirred mixture of diphenyliodonium fluoride (1.51 g, 5.03 mmol) in THF (15 ml) at −40°C. After 3 h at this temperature, the reaction mixture was allowed to warm to 10°C and was kept at room temperature for 30 min. Then it was treated with water (3 ml), and concentrated; the residue was dissolved in dichloromethane (100 ml) and the solution was washed with water (2 × 20 ml) and saturated aqueous sodium chloride (15 ml). After drying and concentration, the oil obtained was purified by flash column chromatography on silica gel (hexanes–dichloromethane) to give 2-phenylcyclohexanone (1.48 g, 88%), m.p. 55–57°C.

TABLE 8.3

Selected phenylation of silyl enol ethers by diphenyliodonium fluoride [28]

Substrate	Product	Yield (%)
		51
		77
		24
		47
		37

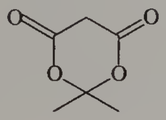
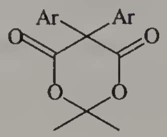
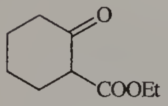
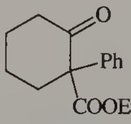
Phenylation and arylation have also been performed in bifunctional compounds such as malonates, *β*-diketones and *β*-ketoesters (Table 8.4). Diethyl malonate was arylated at room temperature affording mixtures of mono- and bis-arylated products, whereas isopropylidene malonate (Meldrum's acid) underwent bis arylation directly. Dimedone, the all carbon analogue of Meldrum's acid, was also mono- and bis-phenylated, with some concomitant *O*-phenylation [33]. Generally, *β*-diketones show often ambident reactivity but the O-arylated product is normally the minor one; an exception was noted in the triketone $(PhCO)_2CHCOPh$ which underwent mainly *O*-phenylation (68%) [33]. Several dianions from *β*-diketones have been arylated in high yields at the α-position, in a procedure superior to other methods [35].

8.2.2 Reactions with organometallics

Grignard reagents react in a complex manner with iodonium salts affording minimal amounts of alkylarenes or biphenyls. However, the reaction of methylmagnesium iodide in the presence of nickel chloride led to the formation of biaryls.

TABLE 8.4

Selected arylation of diketo compounds by iodonium sults

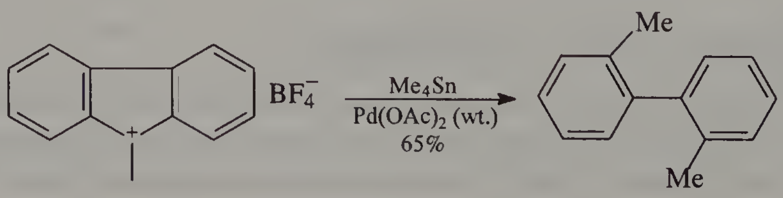
Substrate	Product	Yield (%)	Ref.
$CH_2(COOEt)_2$	$ArCH(COOEt)_2$ $Ar_2C(COOEt)_2$	23–68	[29]
$RCH(COOEt)_2$	$R(Ph)C(COOEt)_2$	34–67	[30]
		59–95	[31]
		80	[32]
PhCOCH$_2$COPh	PhCOCH(Ph)COPh	31	[33]
RCOCH$_2$COMe	RCOCH$_2$COCH$_2$Ar	40–98	[34]

Biaryls from diaryl iodonium salts [35]

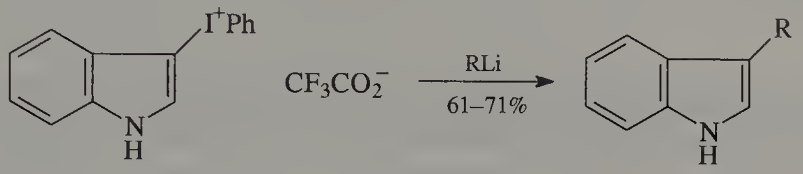
$$Ar_2I^+Br^- \xrightarrow[NiCl_2\text{ (cat.)}]{MeMgI} Ar{-}Ar$$

To a stirred solution of methyl magnesium iodide (748 mg, 4.5 mmol) in ether (15 ml), diphenyliodonium bromide (722 mg, 2 mmol) and anhydrous nickel chloride (15 mg) were added all at once at room temperature, under nitrogen. The mixture was stirred for 20 min, unreacted methyl magnesium iodide was decomposed by addition of water, the reaction mixture was neutralized with 10% hydrochloric acid, washed with water, and the ether layer dried and concentrated. The residue was chromatographed (silica, petroleum ether) to give the pure biaryls.

3,3$'$-Dinitrobiphenyl was prepared by another approach from (3,3$'$-dinitrodiphenyl)-iodonium bisulphate and (3-nitrophenyl)trimethylstannane (85%) with palladium catalysis; the same salt with tetramethyltin afforded 3-nitrotoluene (77%), whereas dibenziodolium tetrafluoroborate was converted into 2,2$'$-dimethylbiphenyl [37]:



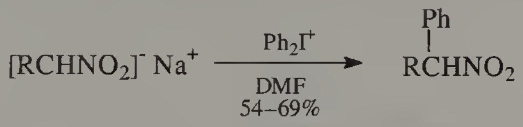
Reductive coupling of iodonium salts catalysed by a palladium–zinc system also produced biaryls in good yield [38]. Also very effective was the palladium-catalysed cross-coupling of iodonium salts with sodium tetraphenylborate in water [39]. The reaction of 3-indolyl phenyliodonium trifluoroacetate with several alkyl and aryl lithium reagents gave 3-substituted indoles [40]:



Alkyl (or phenyl) lithium formed with iron pentacarbonyl *in situ* lithium acyltetracarbonyl ferrates, Li[RCOFe(CO)$_4$], which with iodonium salts afforded aryl ketones (48–85%) [41].

8.2.3 Phenylation of nitro compounds

The sodium salts of aliphatic nitro compounds with diphenyliodonium tosylate afforded phenylated products exclusively from carbon [42]:



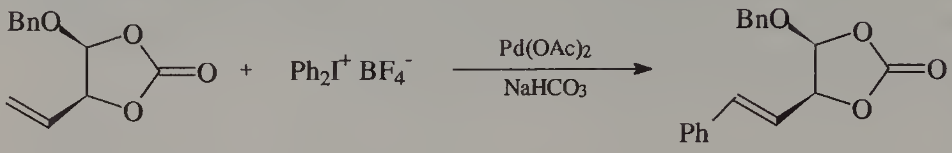
$$[RCHNO_2]^- Na^+ \xrightarrow[\text{DMF}\atop 54\text{–}69\%]{Ph_2I^+} \overset{\displaystyle Ph}{\overset{|}{R C}}HNO_2$$

Among the substrates were 1-nitropropane, 2-nitrobutane and nitrocyclohexane; the less reactive ethyl α-nitrocaproate was also phenylated, at 55°C. 1,1-Dinitroethane and 1,1-dinitropropane in the form of their potassium salts were phenylated in boiling t-butanol (67%) [43].

8.2.4 Arylation of ethylenic compounds

Ethylene reacted with iodonium salts in the presence of a palladium catalyst and a base to afford directly 1,2-bis arylated products (stilbenes). Styrene underwent arylation under similar conditions [44]. Allylic cyclic carbonates were efficiently phenylated by diphenyliodonium tetrafluoroborate; because of the mild conditions, no ring opening occurred, as was the case when iodobenzene was used.

4-Phenylvinyl-5-benzyloxymethyl-1,3-dioxol-2-one [45]



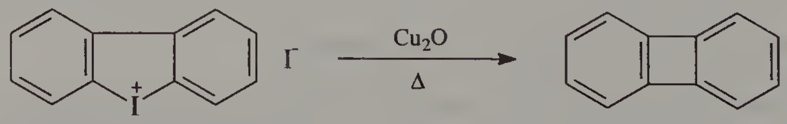
To a mixture of the iodonium salt (172 mg, 0.46 mmol) and palladium acetate (4 mg, 5 mol%) was added sodium bicarbonate (77 mg, 0.92 mmol) followed by the cyclic carbonate (110 mg, 0.46 mmol) in DMF (5 ml), under nitrogen, at room temperature. After stirring for 2 h, the reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with ether (2 × 20 ml). The extract was dried, the solvent removed and the residue chromatographed on silica (ethyl acetate–hexanes 1:4) to afford 4-phenylvinyl-5-benzyloxymethyl-1,3-dioxol-2-one (140 mg, 97%), m.p. not given.

Other unsaturated substrates arylated by various diaryliodonium salts included butenone, acrylic acid, methyl acrylate and acrylonitrile [46]. Allyl alcohols with diaryliodonium bromides and palladium catalysis were arylated with concomitant oxidation; for example, from α-methylallyl alcohol, aldehydes of the general formula $ArCH_2CH(Me)CHO$ were formed [47]. Copper acetylide [48] and phenylacetylene [49] were also arylated, with palladium catalysis.

8.2.5 Synthesis of biphenylenes

Biphenylene is commercially available but expensive. It is obtained by several methods; one of the best, in spite of the low yield, involved pyrolysis of dibenziodolium iodide in the presence of cuprous oxide.

Biphenylene [50]

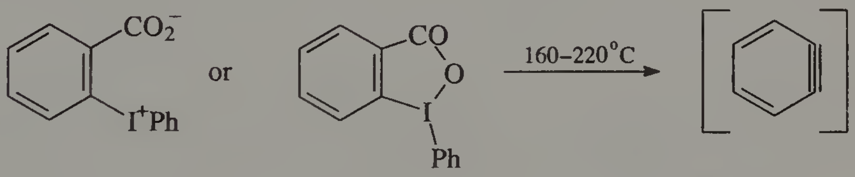


A 150 ml short-necked flask was fitted with an air-condenser having a pear-shaped bulb close to the ground joint attaching it to the flask. The apparatus was inclined at ca. 25° to the horizontal and rotated (ca. 100 rev/min) by a motor attached co-axially to the top of the condenser. The flask dipped into a fusible metal-bath fitted with a lid, and the metal surface was covered with a thick layer of charcoal. The iodonium salt (10 g) was powdered with cuprous oxide (80 g), the mixture heated for a few minutes at 100°C/1 mm Hg in the reaction flask, which was then attached to the condenser and rotated in the metal-bath (pre-heated to 350–360°C) for 4 min. The sublimed biphenylene was extracted into methanol (50 ml) and steam-distilled to afford pure biphenylene (1.05 g, 28%), m.p. 113–114°C.

Several substituted biphenylenes were prepared in this way. The reaction proceeds through 2,2′-diiodobiphenyl which on pyrolysis, however, gave biphenylene in lower yield.

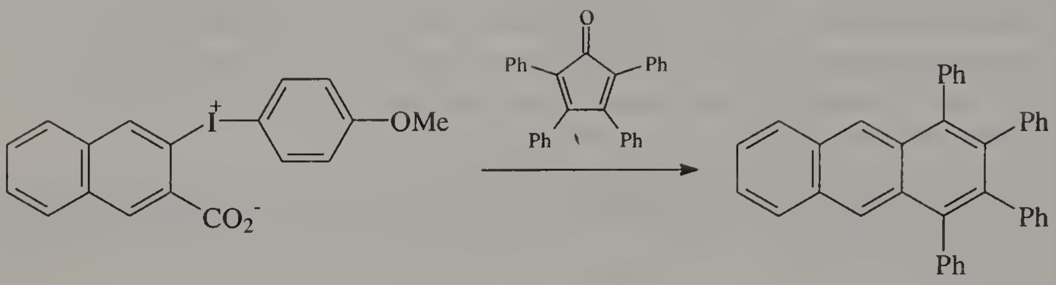
8.2.6 Benzyne generation and its reactions

Iodonium salts with a hydroxyl or a carboxyl group are readily converted into their inner salts, i.e. zwitterionic compounds of various types. 2-(Phenyliodonio) benzoate, whose structure may be cyclic, belongs to this category; it is prepared from *o*-iodobenzoic acid upon oxidation and coupling with benzene (or arenes) [51]. On strong heating, iodobenzene and carbon dioxide are eliminated, with formation of benzyne:



When thermolysis was performed in the presence of dienophiles, Diels–Alder products were formed, some of which at the high temperature underwent further transformation; for example, tetraphenylcyclopentadienone gave directly 1,2,3,4-tetraphenylnaphthalene (90%) [52]. The use of 2-phenyliodonio benzoate as a source of benzyne was especially suitable with some zwitterionic and mesoionic compounds of low reactivity, which did not react with other benzyne precursors [53]. Another iodonium zwitterion was used for the generation of 2,3-dehydronaphthalene, which on reaction with tetraphenylcyclopentadienone afforded 1,2,3,4-tetraphenylanthracene.

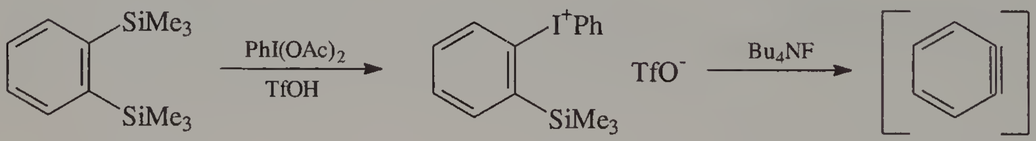
1,2,3,4-Tetraphenylanthracene [54]



(4-Methoxyphenyl)-2-naphthyliodonium carboxylate (obtained from 3-iodosyl-2-naphthoic acid by coupling with anisole) (1 g, 2.47 mmol) and tetraphenylcyclopentadienone (2.85 g, 7.4 mmol) were mixed and heated, under argon, in an oil bath at 240–250°C for 20 min. The reaction mixture was extracted with dichloromethane and ether and the combined solutions were concentrated; the residue was chromatographed on silica to give (after 4-iodoanisole) tetraphenylanthracene (0.66 g, 55%), m.p. 293–294°C.

Elimination of iodobenzene alone from 2-phenyliodonio benzoate leads to generation of another transient 1,4-dipole which was trapped by phosphaalkynes [55].

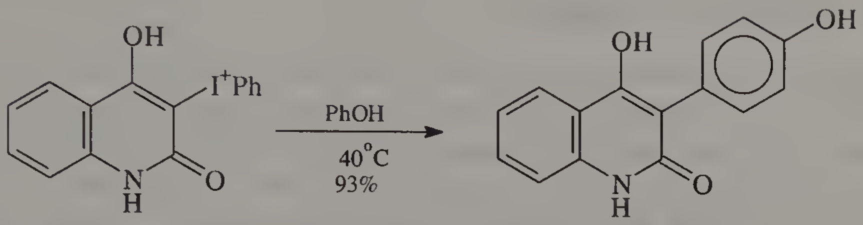
A new precursor, 2-trimethylsilyl-diphenyliodonium triflate, obtained from 1,2-bis-trimethylsilylbenzene, (diacetoxyiodo)benzene and triflic acid, permitted the generation of benzyne with tetrabutylammonium fluoride, at room temperature [56]:



This new benzyne precursor combines practical facility in its preparation with relative stability and safety in handling; in addition, its conversion into benzyne does not require a strong base or high temperature. Another useful feature of this methodology is that, as with substituted diphenyliodonium 2-carboxylates, only one aryne can be formed from substituted precursors. Indeed, two methyl analogues of 2-trimethylsilyl-diphenyliodonium triflate, in the presence of furan, afforded quantitatively the corresponding adducts; high yields of benzyne–diene adducts were also obtained with other 1,3-dienes.

8.2.7 Miscellaneous

The phenyliodonium salt of carbostyril on reaction with phenol, in the absence of solvent, was converted into a phenolic derivative [57]:



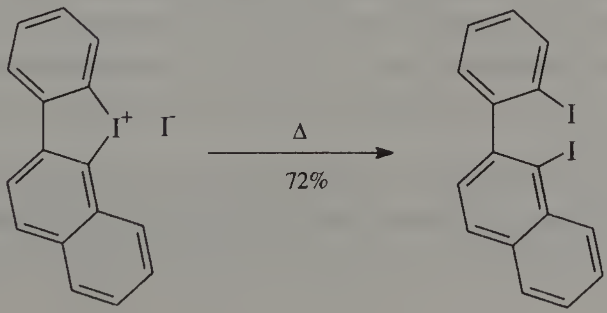
Other substrates arylated at a carbon atom included pyridine, carbon monoxide and sodium cyanide [1,2].

8.3 ARYLATION OF HETEROATOMS

Iodonium salts readily transfer one of their aryl groups to a heteroatom; substrates successfully arylated range from simple halide anions to complex natural products. The plethora of such reactions leaves no doubt that the use of iodonium salts is the best choice for arylations.

8.3.1 Arylation of halide anions

The thermolysis of iodonium salts in which their counteranion is a halide may be performed in the molten state or in solution; the products are an iodoarene and a haloarene. The reaction which is a nucleophilic aromatic substitution is, however, not preparatively useful; an exception was 3-indolyl phenyliodonium trifluoroacetate which on heating with various chlorides and bromides in DMSO afforded variable mixtures of 2- and 3-haloindoles. By contrast, the *N*-methyl and *N*-benzyl analogues gave only 2-chloro derivatives [58]. Sometimes useful products may be obtained from the thermolysis of dibenziodolium or other heterocyclic salts, as exemplified in the preparation of 1-iodo-2-(2′-iodophenyl)naphthalene [59]:

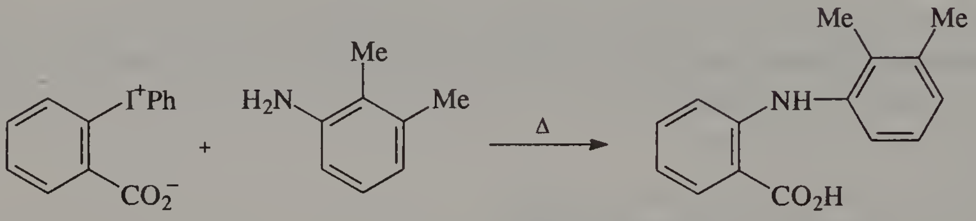


The thermolysis of some diaryliodonium tetrafluoroborates in the presence of potassium fluoride led to the formation of fluoroarenes (38–85%) [60].

8.3.2 Arylation at nitrogen

The arylation of nitrite and azide anions as well as some amines can be of synthetic interest in some instances; for example, difuryl, dithienyl and diselenophyl iodonium salts were useful substrates for the preparation of the corresponding nitro heterocycles [61]. Diphenyliodonium 2-carboxylate transferred its carboxylate-bearing ring with high specificity to several anilines in a reaction especially suitable for the preparation of weakly basic and sterically hindered *N*-arylanthranilic acids.

N-*(2,3-dimethylphenyl)anthranilic acid* [62]



A solution of diphenyliodonium 2-carboxylate (2.0 g, 6.18 mmol), 2,3-dimethylaniline (0.90 g, 7.4 mmol) and cupric acetate (40 mg) in 2-propanol (8 ml) was heated under reflux for 15 h. The mixture was concentrated and taken up in dilute sodium hydroxide solution. After ether extraction and filtration of the aqueous phase, the filtrate was added slowly to acid to give *N*-(2,3-dimethylphenyl)anthranilic acid (1.45 g, 97%), m.p. 220–222°C.

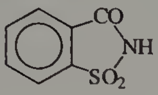
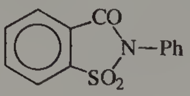
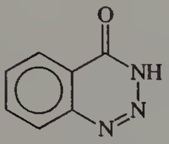
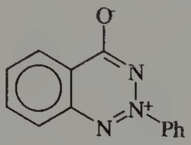
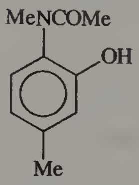
Several *N*-arylanthranilic acids were prepared in this way from anilines or related substrates, notably a series of methyl anthranilates [63]. Other nitrogen-containing compounds arylated by iodonium salts appear in Table 8.5.

Conditions may vary widely, according to the substrate. For example, sodium saccharinate was phenylated after 24 h reflux in aqueous ethanol, whereas the phenylation of t-butyl *N*-hydroxycarbamate was effected in DMSO at room temperature.

Pyridine was also phenylated at nitrogen by diphenyliodonium tetrafluoroborate, to *N*-phenylpyridinium tetrafluoroborate (88%) [68]. The less polar bromide did not react, whereas the chloride in aqueous pyridine led to the formation of *C*-phenylated pyridines [69].

TABLE 8.5

Arylation of nitrogen nucleophiles by iodonium salts

Substrate	Product	Yield (%)	Ref.
		75	[64]
		61	[65]
p-$MeC_6H_4SO_2NH_2$	p-$MeC_6H_4SO_2NPh_2$	45	[64]
$HN(OH)COOBu^t$	$PhN(OH)COOBu^t$	56	[66]
MeN(OH)COMe		59	[67]

8.3.3 Arylation at oxygen

A great deal of work involved *O*-arylation of phenols, because of the synthetic importance attached to tyrosine ethers related to thyroxine. Thus, mild conditions leading to high yields have been developed, notably the use of copper bronze and triethylamine at room temperature [70]. The analogous reactions of iodonium salts with alkoxides are less important synthetically, because of many by-products. Nevertheless, the use of radical traps such as 1,1-diphenylethylene improves the situation considerably. The dibenziodolium cation did not give any methoxy derivative with sodium methoxide, but with sodium acetate, 2-acetoxy-2′-iodobiphenyl was obtained quantitatively [71]. Another substrate, 3-indolyl phenyliodonium trifluoroacetate afforded with methanol-boron trifluoride 3-methoxyindole (60%) [40]. Some nitrogen-containing compounds arylated at oxygen are listed in Table 8.6. An important reaction not appearing in Table 8.6 is the phenylation of *N*-hydroxyphthalimide, since hydrazinolysis of the product is the best way for the preparation of *O*-phenylhydroxylamine.

N-*Phenyloxyphthalimide* [78]

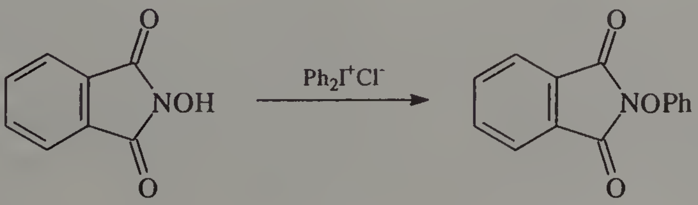
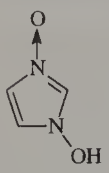
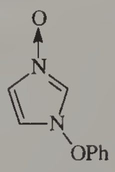
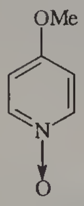
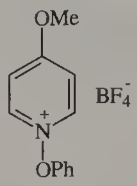
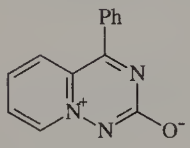
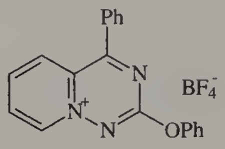
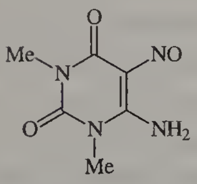
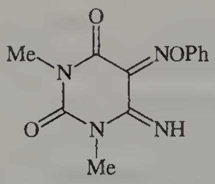


TABLE 8.6

Arylation at oxygen of nitrogen-containing nucleophiles by iodonium salts

Nucleophile	Product	Yield (%)	Ref.
PhCONHOH	PhCONHOPh	66	[72]
		70	[73]
		95	[74]
		72	[75]
		99	[76]
$R_2C{=}NOH$	$R_2C{=}NOAr + R_2C{=}N(O)Ar$	(variable)	[77]

To a stirred mixture of anhydrous potassium carbonate (7 g, 50.7 mmol) and *N*-hydroxyphthalimide (14 g, 95 mmol) in DMSO (250 ml) was added, over 5 min, diphenyliodonium chloride (38 g, 120 mmol). After 15 h of stirring at room temperature the reaction mixture was added to ice (600 g). Colourless crystals of *N*-phenyloxyphthalimide separated after 1 h. They were collected, washed with water and dried to give 20 g (90%) of crude product; upon recrystallization from ethanol pure *N*-phenyloxyphthalimide (13.5 g, 66%) was obtained, m.p. 143.5–145°C.

Ambident reactivity was shown by oximate anions; normally, *O*-arylation predominated over N-arylation, with ratios of oxime ethers to nitrones ranging from 9:1 (for the benzophenone oxime anion) to 1.7:1 (for the fluorenone oxime anion) [77]. The arylation of two heterocyclic oximes was performed under mild conditions and led mainly to the corresponding oxime ethers which served as good precursors for the generation of unstable aryl fulminates, ArONC [79,80].

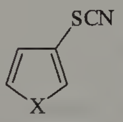
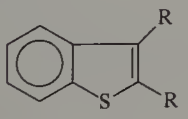
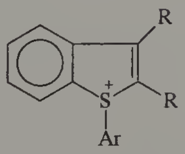
8.3.4 Arylation at a chalcogen

Compounds with a nucleophilic sulphur are readily arylated by iodonium salts in their anionic form, and less readily in other cases, notably in sulphides; triaryl sulphonium salts are useful photoinitiators in cationic polymerizations. A list of chalcogen compounds arylated by iodonium salts appears in Table 8.7.

Some comments should be added for a few cases. The reaction of diphenyliodonium tetrafluoroborate with sodium thiocyanate, and sodium phenylsulphinate, was also carried out in chloroform–water, at reflux, with very high yields; similar efficient phenylation occurred with other anions [84]. Although these reactions were not performed on a preparative scale, it is likely that similar conditions may be applicable to other iodonium salts as well, for example in the thiocyanation of di-(3-thienyl)iodonium ion which gave 3-thiocyanatothiophene (43%), the best yield compared with other methods [18]. Concerning the preparation of triarylsulphonium

TABLE 8.7

Arylation of sulphur, selenium and tellurium nucleophiles by iodonium salts

Nucleophile	Product	Yield (%)	Ref.
Na_2SO_3	$PhSO_3Na$	95	[64]
NaSCN	 (X=S, Se)	43–48	[18]
PhSR	Ph_2S^+R	81–98	[81]
ArSH	Ph_2S^+Ar	48–87	[82]
Ph_2S	Ph_2S^+Ar	65–99	[83]
		81–97	[84]
$ArSO_2Na$	$ArSO_2Ar'$	22–95	[85]
$R_2NC(S)SNa$	$R_2NC(S)SAr$	56–86	[86]
RCOSK	RCOSAr	42–76	[87]
ArCSSNa	ArCSSAr′	65–88	[88]
Ph_2Se	Ph_2Se^+Ar	49–90	[83]
ArSeNa	ArSeAr′	58–75	[89]
$(EtO)_2P(O)SeNa$	ArSeSeAr	62–82	[90]
Na_2Te	Ar_2Te	76–92	[91]
ArTeNa	ArTeAr′	46–81	[92]

salts, both thiophenols and sulphides are suitable starting materials; the use of copper (I) or (II) compounds as catalysts is essential.

Triarylsulphonium salts [82]

$$2\,Ar_2I^+ + Ar'SH \xrightarrow[Cu(PhCOO)_2]{Bu_3N} Ar_2S^+Ar'$$

A 50 ml flask equipped with a reflux condenser and a thermometer was charged with thiophenol (10 mmol), the iodonium salt (20 mmol), tributylamine (2.22 g, 10 mmol) and cupric benzoate (0.2 g). The mixture was stirred and heated at 120–125°C for 3 h under nitrogen. On cooling, the reaction mixture was washed with anhydrous ether (3 × 50 ml) to remove the iodoarenes. The residue was recrystallized from ethanol to give triarylsulphonium salts (48–87%). Similar conditions with slight variations were used when sulphides were the starting material.

8.3.5 Arylation at other elements

The arylation of phosphite anions using several iodonium salts is the most important reaction of this Section. Although aryl phosphonates have been prepared by numerous methods, this approach has the advantages of easy availability of starting materials, mild reaction conditions, simple workup, and better yields.

Dialkyl aryl phosphonates [93]

$$Ar_2I^+Cl + Na^+\,{}^-PO(OR)_2 \longrightarrow ArPO(OR)_2$$

To a stirred solution of dialkylphosphite (3 mmol) in DMF (15 ml) sodium hydride (0.072 g, 3 mmol) was added under nitrogen. After completion of the reaction, the iodonium salt (1.5 mmol) was added. The mixture was heated at 70–80°C with stirring for 4–7 h. After cooling, the reaction mixture was diluted with water (80 ml) and the product was extracted with dichloromethane (3 × 50 ml). The extract was washed with water (2 × 80 ml) and dried, the solvent was removed and the residue chromatographed (silica column, cyclohexane, then chloroform) to give the title compounds (81–93%).

Arylation at phosphorus has also been reported in triphenylphosphine; best yields of phosphonium salts were obtained under photochemical conditions [94]. Metals were also arylated, either in their elemental form, such as bismuth, or in organometallics containing iron, iridium, etc. [1,2].

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–9–

Phenyliodonium Salts With an Aliphatic Moiety

There are three major categories of this type of compound, in which the aliphatic part may be a perfluoroalkyl, an alkenyl or an alkynyl group; two recent additions – with a cyano or a diazoacetate group – are promising reagents for future applications.

9.1 PREPARATIVE METHODS

9.1.1 Perfluoroalkyl phenyliodonium salts

Compounds of this family are numerous, since the phenyl ring may be substituted, whereas perfluoroalkyl (Rf) groups of great diversity have been used. Actually, the preparation that follows is for compounds containing the group $RfCH_2$; the same procedure was essentially used for other ArI^+Rf salts.

*1*H,*1*H-*Perfluoroalkyl phenyliodonium triflates* [1]

$$RfCH_2I \xrightarrow{CF_3CO_3H} RfCH_2I(O_2CCF_3)_2 \xrightarrow[TfOH]{PhH} PhI^+CH_2Rf\ TfO^-$$

A mixture of trifluoroacetic anhydride (82 ml) and trifluoroacetic acid (0.7 ml) was treated dropwise with 60% hydrogen peroxide (6.45 ml) with stirring at 0°C. After 10 min, the substrate (143 mmol of polyfluoroiodoalkane) was added into the mixture and stirring was continued for 1 day at 0°C to room temperature. Evaporation to dryness gave almost quantitatively 1-[bis(trifluoroacetoxy) iodo]polyfluoroalkane as a white solid. Benzene (189 mmol) and triflic acid (122 mmol) were added into a mixture of this trifluoroacetate in 1,1,2-trichloro-1,2,2-

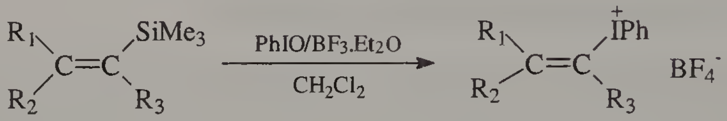
trifluoroethane at 0°C and this was stirred at 0°C for 1 day. The reaction mixture was evaporated to dryness and the resulting solid mass was washed with chloroform to give the iodonium triflate. Further purification was effected by recrystallization from acetonitrile or acetonitrile–ether at room temperature. The yields ranged between 72 and 88%. These iodonium salts are stable and some of them are commercially available.

In a related method the stable triflates or tosylates, $RfI^{+}OH\ RSO_3^{-}$, were coupled with trimethylsilylbenzene [2].

9.1.2 Alkenyl phenyliodonium salts

The best procedure for the preparation of these compounds involves alkenylsilanes and iodosylbenzene activated by either triethyloxonium tetrafluoroborate or boron trifluoride etherate. The reaction proceeds stereospecifically with retention of configuration.

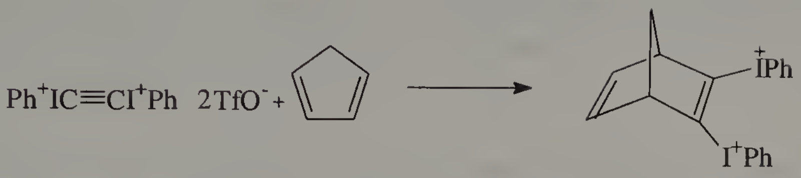
Alkenyl phenyliodonium tetrafluoroborates [3]



Boron trifluoride etherate (2.5 equiv. with respect to the alkenylsilane) was added dropwise to a stirred suspension of the appropriate alkenylsilane and iodosylbenzene (2.5 equivalent with respect to the alkenylsilane), in dichloromethane, under nitrogen. A yellow colour developed, while the mixture was stirred for 15 min to 7 h, at 0°C or room temperature, according to the substrate. A saturated aqueous sodium tetrafluoroborate solution was added and the mixture was stirred vigorously for 0.5 h. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was concentrated to give an oil which was washed several times with hexane and/or ether by decantation. Further purification was accomplished by repeated dissolution of the salt in dichloromethane or ethyl acetate followed by slow precipitation with hexane or ether.

Instead of silyl-, stannylalkenes are also suitable precursors [4]; cyano phenyliodonium triflate (Section 9.1.4) was here the reagent of choice. This variation enabled the preparation of the parent ethenyl and several trisubstituted alkenyl phenyliodonium triflates [5]. More elaborate members were obtained through additions to the triple bond of alkynyl iodonium salts, notably Diels–Alder adducts.

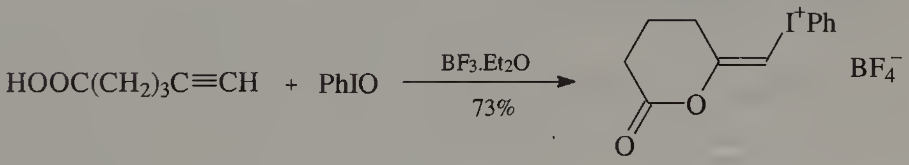
2,3-Bis(phenyliodonio)norbornadiene triflate [6]



A solution of cyclopentadiene (136 mg, 2 mmol) in acetonitrile (20 ml) was added to a stirred suspension of the bisphenyliodonium triflate of acetylene (730 mg, 1 mmol) in acetonitrile (20 ml) at – 35°C under nitrogen. The mixture was warmed to room temperature and stirred for 1 h; then it was concentrated to a volume of about 1 ml and crystallized by addition of dichloromethane (20 ml) and ether (10 ml). Recrystallization from acetonitrile–dichloromethane gave the pure salt (0.55 g, 69%) m.p. 177–179°C.

The same salt from acetylene afforded similarly adducts with furan and 1,3-diphenylisobenzofuran. A number of alkynyl iodonium salts underwent also [2 + 3] cycloaddition with dipolarophiles such as α-diazocarbonyl compounds, nitrile oxides, etc., allowing the preparation of iodonium salts with an alkenyl or a heterocyclic moiety [7].

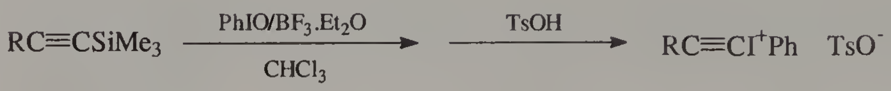
An interesting lactonization of 4- or 5-alkynoic acids with concomitant formation of alkenyl iodonium salts occurred on treatment of the acids with iodosylbenzene-boron trifluoride [8]:



9.1.3 Alkynyl phenyliodonium salts

Alkynes, alkynylsilanes and alkynylstannanes constitute the usual precursors for these compounds. A simplified procedure has been developed involving readily available starting materials and resulting in very good yields.

Alkynyl phenyliodonium tosylates [9]



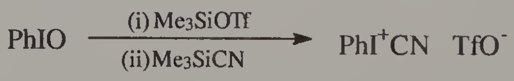
$$RC{\equiv}CSiMe_3 \xrightarrow[CHCl_3]{PhIO/BF_3.Et_2O} \xrightarrow{TsOH} RC{\equiv}CI^+Ph \quad TsO^-$$

To a suspension of iodosylbenzene (1.1 g, 5 mmol) and the appropriate 1-trimethylsilyl-1-alkyne (5 mmol, prepared from 1-alkyne and trimethylchlorosilane in nearly quantitative yield, or obtained commercially) in chloroform (10 ml) was slowly added boron trifluoride etherate (710 mg, 5 mmol) at 0°C. The mixture was stirred at room temperature for 3–4 h, then recooled at 0°C and a solution of *p*-toluenesulphonic acid hydrate (3.8 g, 20 mmol) in water (20 ml) was added; the resulting mixture was stirred vigorously for a few minutes. The organic phase was separated and the aqueous phase was washed with additional chloroform. The combined organic phase was washed with water, dried and concentrated. The residual oil solidified upon addition of ether. The solid was filtered, washed with ether and air-dried to give alkynyl phenyliodonium tosylates (62–89%).

Variations of this method permit the preparation of diverse salts, most of which are stable crystalline compounds. The group R in the alkynyl moiety can be of virtually any kind, for example aryl, aroyl, alkenyl, alkynyl, cyano, trimethylsilyl, etc. For some of these compounds only alkynylstannanes were suitable precursors, in combination with cyano phenyliodonium triflate; double salts were also obtained in this way [10,11].

9.1.4 Other iodonium salts

Cyano phenyliodonium triflate [12]



$$PhIO \xrightarrow[(ii)Me_3SiCN]{(i)Me_3SiOTf} PhI^+CN \quad TfO^-$$

Trimethylsilyl triflate (2.22 g, 1.93 ml, 10 mmol) was added to a stirred suspension of iodosylbenzene (2.2 g, 10 mmol) in dichloromethane (30 ml) at −30°C under nitrogen. The mixture was allowed to warm to −5°C and stirred until formation of a yellow solution. This was recooled to −30°C and trimethylsilyl cyanide (1.08 g, 1.45 ml, 11 mmol) was added via a syringe; the mixture was allowed to warm to −5°C and stirred for 1 h. The precipitate was filtered under nitrogen, washed with cold ether and dried *in vacuo* to give cyano phenyliodonium triflate (3.37 g, 89%), m.p. 118°C (from acetonitrile–ether).

A related salt, *o*-COOH-$C_6H_4I^+CN$ $MeSO_3^-$, was obtained from a cyclic precursor and trimethylsilyl cyanide [13]. Another potentially useful compound, ethyl diazoacetato phenyliodonium triflate, was prepared from DIB, ethyl diazoacetate and trimethylsilyl triflate [14]:

$$PhI(OAc)_2 + N_2CHCO_2Et \xrightarrow{Me_3SiOTf} PhI^+C(N_2)CO_2Et \quad TfO^-$$

9.2 REACTIVITY OF PERFLUOROALKYL PHENYLIODONIUM SALTS

These salts are valuable reagents for the transfer of perfluoroalkyl groups to nucleophiles, charged and non-charged. The reactions are performed under mild conditions in a regiospecific way, and products come almost exclusively from the Rf moiety:

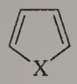
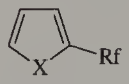
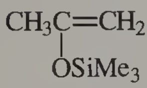
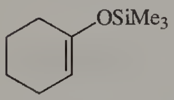
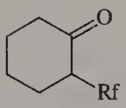
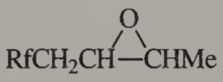
$$PhI^+Rf + Nu^- \longrightarrow Rf{-}Nu + PhI$$

9.2.1 Perfluoroalkylation of carbon nucleophiles

Many carbon nucleophiles were perfluoroalkylated by several perfluoroalkyl iodonium salts. Detailed procedures were often not disclosed,but it appears that reactions are fairly simple to perform. An example is cited for the reaction with Grignard reagents and an idea about the potential of such perfluoroalkylations can be formed from selected substrates appearing in Table 9.1. Although the yields were sometimes moderate, this methodology constitutes one of the best approaches for the introduction of Rf groups to organic and inorganic compounds.

TABLE 9.1

Perfluoroalkylation of carbon nucleophiles using perfluoroalkyl phenyliodonium salts

Substrate	Product	Yield (%)	Ref.
C_6H_6	C_6H_5Rf	89–97	[15,16,17]
C_6H_5OH	RfC_6H_4OH (*o*, *m*, *p*)	55	[15]
$C_6H_5NMe_2$	$RfC_6H_4NMe_2$ (*o*, *p*)	37	[15]
	 (X= O,S, NH)	73–92	[15,17]
 $CH_3\underset{OSiMe_3}{C}=CH_2$	CH_3COCH_2Rf	88	[18]
		71	[18]
$CH_2=CHCH=CHOSiMe_3$	$RfCH_2CH=CHCHO$	70	[18]
$PhC\equiv CH$ /MeOH	$PhC\equiv CRf$	100	[19]
$PhC\equiv CH$ /HCOOH	$PhCOCH_2Rf$	86	[19]
$C_6H_{13}C\equiv CH$	$C_6H_{13}CH=CHRf$	41	[19]
$C_3H_7C\equiv CC_3H_7$	$C_3H_7C(Rf)=CHC_3H_7$	44	[19]
$PhCH=CH_2$	E-$PhCH=CHRf$	83	[20]
$CH_2=CH_2$ /H_2O	$RfCH_2CH_2OH$	42	[20]
$CH_2=CHCH=CH_2$ /H_2O	$RfCH_2CH=CHCH_2OH$	59	[20]
$CH_2=CHCH(Me)OH$ }	 $RfCH_2\overset{O}{CH-CHMe}$ $RfCH_2CH_2COMe$	81 (1:1)	[20]
$CH_2=CHCH=CH_2$ /O_2	$RfCH_2CH=CHCHO$	47	[21]
$[Me_2CNO_2]Li$	$Me_2C(Rf)NO_2$	51	[22]
$PhCH=C(OSiMe_3)OMe$	$PhCH(CH_2CF_3)CO_2Me$	92	[23]

Perfluoroalkylation of Grignard compounds [24]

$$\mathrm{PhI^{+}Rf\ \ TfO^{-}\ +\ RMgX \longrightarrow R{-}Rf}$$

The iodonium salt (Rf = C_2F_5, C_3F_7, C_4F_9, C_6F_{13} and C_8F_{17}) (1.3 mmol) was added in several portions to a stirred solution of the Grignard reagent (1.4 mmol, 0.4–0.8 mmol ml^{-1} of THF or ether) in THF (13 ml) at −78°C. After stirring for 2 h at −78°C the reaction mixture was quenched with aqueous ammonium chloride and extracted with pentane. The extract was dried and concentrated, and the residue was subjected to column chromatography on silica gel (pentane); finally, the pure product was obtained by distillation. The yields ranged between 10 and 82%. Lithium acetylides reacted similarly.

All reactions of Table 9.1 were performed in pyridine, usually at room temperature; by addition of water, methanol, acetic acid, etc. it was possible to prepare several functionalized compounds from alkenes and alkadienes.

9.2.2 Perfluoroalkylation at heteroatoms

Alkyl and aryl thiols afforded with perfluoroalkyl iodonium salts in the presence of pyridine the corresponding sulphides in good to excellent yields [25]. Several sulphides and sulphoxides upon reaction with trifluoroethyl phenyliodonium triflate were converted into 2,2,2-trifluoroethyl sulphonium salts [26].

Several amines such as anilines, pyridine, etc., were perfluoroalkylated affording the corresponding ammonium or pyridinium salts [26–28]. Other substrates which underwent perfluoroalkylation included triphenylphosphine [26], sodium nitrite [29], potassium thiocyanate [29] and potassium selenocyanate [29].

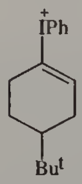
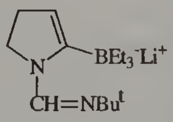
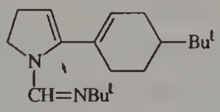
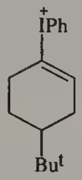
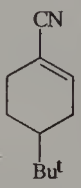
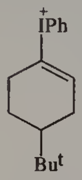
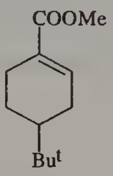
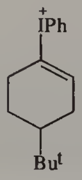
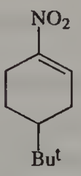
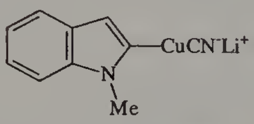
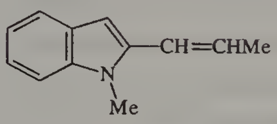
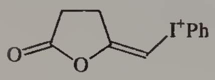
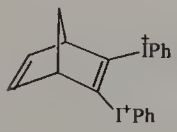
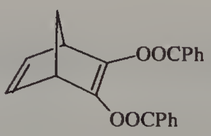
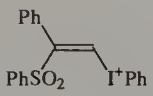
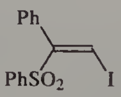
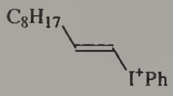
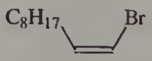
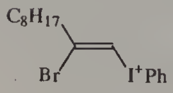
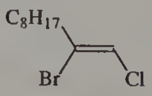
9.3 REACTIVITY OF ALKENYL PHENYLIODONIUM SALTS

The exceptional nucleofugality of the phenyliodonio group has been determined in an alkenyl salt and it is about 10^6 times greater than that of triflate [30]. This remarkable property makes alkenyl iodonium salts excellent vinyl cation equivalents in nucleophilic substitutions. The chemistry of alkenyl iodonium salts is dominated by the transfer of their aliphatic moiety to a variety of nucleophiles; other important reactions involve Michael-type addition and alkylidenecarbene generation, along with elimination to alkynes which is actually an undesirable side-reaction.

Examples of preparative (and mechanistic) interest are listed in Table 9.2.

TABLE 9.2

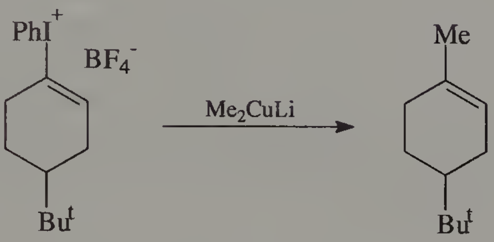
Selected alkenylations with phenyl alkenyl iodonium salts

Reagents		Products	Yield (%)	Ref.
Iodonium salt	Nucleophile			
			61	[31]
	$KCu(CN)_2$		92	[3]
	CO/MeOH/Pd		84	[3]
	$NaNO_2/CuSO_4$		55	[3]
$MeCH{=}CHI^+Ph$			70	[32]
	Et_2NH	$Et_2NCO(CH_2)_2COCH_2NEt_2$	67	[8]
$PhI^+CH{=}CH_2$	TfO^-	$CH_2{=}CHOTf$	15	[5]
	PhCOONa		25	[33]
	Bu_4NI		93	[34]
	Bu_4NBr		95	[35]
	Bu_4NCl		91	[36]

9.3.1 Alkenylation of organometallics

Simple and phenylated alkynes were prepared from alkenyl iodonium salts and lithium organocuprates.

1-Methyl-4-t-butylcyclohexene [3]



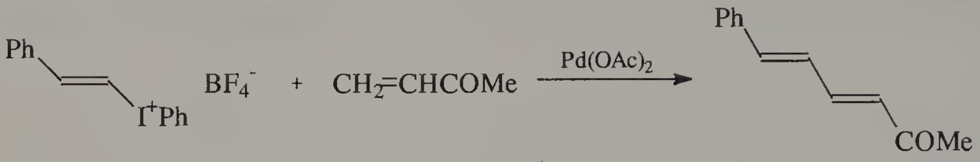
A solution of dimethyl lithium cuprate was prepared by adding methyl lithium (0.94 ml, 1.4 mmol of 1.5 M) in ether to a stirred slurry of cuprous iodide (133 mg, 0.7 mmol) in THF (5 ml) at −20°C, under nitrogen. The iodonium salt (40 mg, 0.093 mmol) in THF (1 ml) was added at −78°C and the reaction mixture was stirred for 4 h at −78°C. Then, it was quenched with water and analysed by GC which indicated a 73% yield of 1-methyl-4-t-butylcyclohexene.

Phenylation, by using diphenyl lithium cuprate, was stereospecific in both *E* and *Z* isomers of appropriate alkenyl iodonium salt, proceeding with complete retention of configuration.

9.3.2 Reactions producing dienes, enynes and enediynes

Synthetic methods for the preparation of dienes and enynes abound, yet the use of alkenyl iodonium salts offers distinct advantages. Their coupling reactions with electron-deficient alkenes and alkenyl- or alkynylstannanes constitute a valuable extension to the previously existing methodology, because of mild conditions, ease of operation, high stereoselectivity and good yields. The simplest reaction of this category is with unsaturated carbonyl compounds and requires palladium catalysis.

trans, trans-*6-Phenyl-hexa-3,5-diene-2-one* [37]

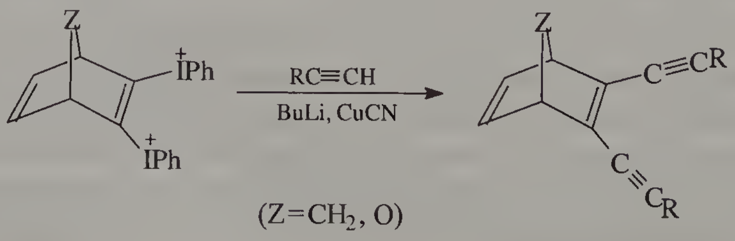


To a stirred mixture of the iodonium salt (197 mg, 0.5 mmol), palladium acetate (5.6 mg) and sodium bicarbonate (420 mg, 5 mmol) in DMF (2 ml) was added butenone (17.5 mg, 2.5 mmol), under argon, at room temperature. After 2 h, precipitation of palladium black was observed; then, saturated aqueous ammonium chloride was added to the reaction mixture, followed by extraction with ethyl acetate. The organic layer was dried, the solvent evaporated and the residue purified by flash chromatography (hexanes–ethyl acetate) to give *trans, trans*-6-phenyl-hexa-3,5-diene-2-one (63 mg, 73%), m.p. not given.

Other alkenyl iodonium salts which furnished functionalized dienes had a cyclohexenyl, a 2-(tosyloxy)hexenyl or a tosyloxyvinyl moiety; the unsaturated partners included propenal, methyl acrylate and styrene. The yields were consistently high (64–85%) and the stereoselectivity invariably *trans*. An alternative method for the synthesis of dienes involved alkenyl stannanes such as $CH_2{=}CHSnBu_3$, *E*-$PhCH{=}CHCH_2SnBu_3$ and $CH_2{=}CHCH_2SnBu_3$ [38]. Several alkynylstannanes afforded similarly enynes in good yield [39].

Bicyclic enediynes were obtained from the Diels–Alder adducts of cyclopentadiene or furan with bis phenyliodonium acetylene triflate and lithium alkynyl cuprates. In this case the reaction conditions were more demanding and yields less satisfactory.

Bicyclic enediynes [40]



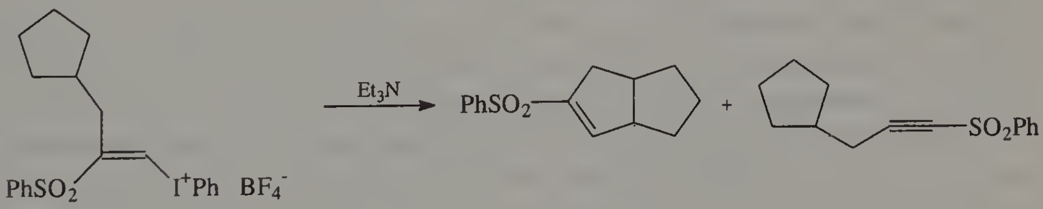
Great care should be exercised in these preparations, in order to exclude traces of moisture. To a stirred solution of the alkyne (6 mmol) in dichloromethane (50 ml) was added butyl lithium (2.4 ml of a 2.5 M solution in hexane) at – 70°C, under a positive pressure of nitrogen. After 10 min, cuprous cyanide (0.27 g, 3 mmol) was added and stirring continued for 2 h at – 40°C. The mixture was cooled to – 70°C and the iodonium salt (1 mmol) was added; this mixture was allowed to warm to room temperature slowly and stirred for another 10 h. Then it was poured into a saturated aqueous solution of ammonium chloride (100 ml), extracted with dichloromethane and the organic layer was dried and concentrated. The residue was purified by filtration through a short silica column (hexane, then dichloromethane); solvent evaporation afforded pure bicyclic enediynes, in 36–69% yield.

9.3.3 Carbocyclizations

Most reactions of this category involve the base-induced generation of alkylidenecarbenes ($R_2C{=}C$:) which undergo an intramolecular 1,5-carbon–hydrogen insertion providing a useful route for the construction of substituted cyclopentenes; a competing intramolecular pathway is rearrangement to alkynes.

A series of 2-β-phenylsulphonylalkenyl iodonium salts (prepared from alkynyl iodonium salts and phenylsulphinic acid) upon base treatment underwent predominantly cyclization, in contrast to the sulphenyl and sulphinyl bearing analogues, which gave alkynes.

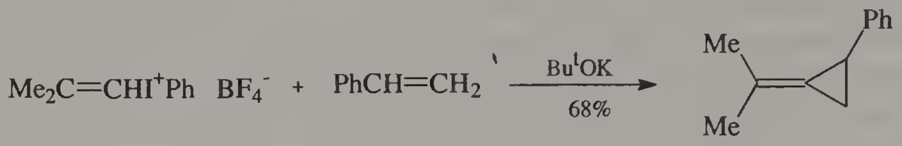
3-(Phenylsulphonyl)bicyclo[3.3.0]-2-octene [41]



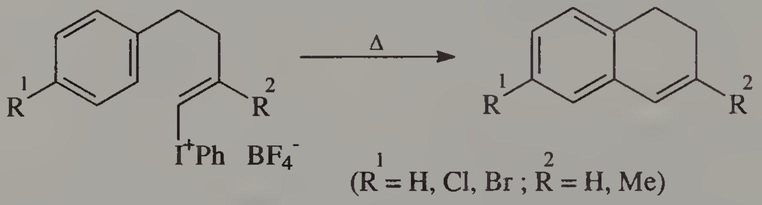
To a solution of the iodonium salt (103 mg, 0.19 mmol) in benzene (3 ml) was added triethylamine (22 mg, 0.23 mmol) at room temperature, under nitrogen, and the mixture was stirred for 30 min. The reaction mixture was poured into water and extracted with ether. Drying of the extract and concentration produced an oil which was purified by preparative TLC (hexane–chloroform) to give 3-(phenylsulphonyl)bicyclo[3.3.0]-2-octene (33 mg, 71%) and the accompanying alkyne (8 mg, 18%) as colourless oils.

Clean conversions to 1-bromoalkynes were recorded in base-induced reactions of *β*-bromoalkenyl iodonium salts, whereas the corresponding *β*-chloro-analogues afforded mixtures of 1-chloroalkynes and 1-chlorocyclopentenes [42].

Alkylidenecarbenes gave methylenecyclopropanes with alkenes, as exemplified in the reaction of a simple alkenyl iodonium salt with styrene [43]:



An addition–elimination sequence was proposed for the intramolecular aromatic cyclization of a series of 4-aryl-alkenyl iodonium salts which were converted into dihydronaphthalenes [44]:

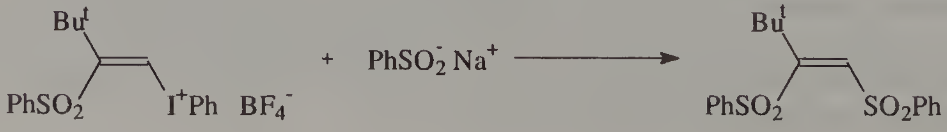


(R^1 = H, Cl, Br ; R^2 = H, Me)

Gentle heating in chloroform was enough to bring about this cyclization (52–71%).

9.3.4 Alkenylation at sulphur and halides

Whereas oxygen nucleophiles gave poor yields of alkenylated products with alkenyl iodonium salts, the reactions with sulphur nucleophiles proceeded more efficiently, leading to unsaturated sulphides and sulphones. Thus, 4-t-butylcyclohexenyl phenyliodonium salts afforded with sodium thiophenoxide 4-t-butylcyclohexenyl phenyl sulphide (81%) [3] and with sodium phenylsulphinate the corresponding sulphone (29%); in the presence of 18-crown-6, the yield of the latter rose to 80% [45]. *β*-Phenylsulphonylalkenyl iodonium salts with sodium phenylsulphinate at 0°C, without any catalyst, afforded *Z*-1,2-bis(phenylsulphonyl)alkenes, in high yield with retention of the stereochemistry [45]:

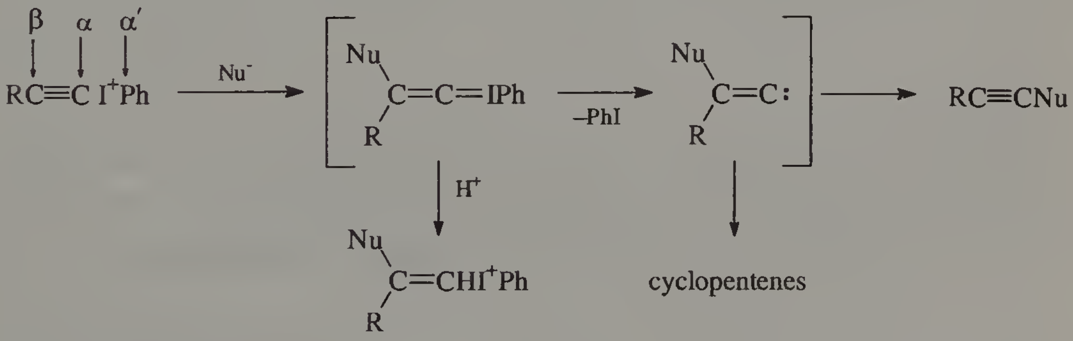


Several unsaturated *Z*-1,2-disulphones were also obtained in high yield from *β*-chloroalkenyl iodonium salts with 2 equivalents of sodium phenylsulphinate through *β*-phenylsulphonylalkenyl iodonium salts [46].

The substitution of alkenyl iodonium salts by halides, using tetrabutylammonium salts, has been studied (Table 9.2). Exclusive inversion of configuration occurred in acetonitrile, so that *E*-precursors gave solely *Z*-haloalkenes in high yield [35]. In marked contrast, complete retention occurred with cuprous and potassium halides in dichloromethane. Retention of configuration was also noted in reactions of *β*-substituted alkenyl iodonium salts; for example, from *β*-phenylsulphonyl decenyl phenyliodonium ion, *cis* products were formed exclusively in high yield [34].

9.4 REACTIVITY OF ALKYNYL PHENYLIODONIUM SALTS

These highly reactive yet stable species are strong electrophiles of tetraphilic character, since nucleophiles may attack three different carbon atoms (α,β,α') and iodine. In most reactions the first step is a Michael addition at *β-C* with formation of an alkenyl zwitterionic intermediate (ylide) which normally eliminates iodobenzene, generating an alkylidene carbene; then, a 1,2-shift of the nucleophile ensues. The final result is its combination with the alkynyl moiety which behaves formally as an alkynyl cation. The initial adduct may react with an electrophile, notably a proton, in which case alkenyl iodonium salts are obtained; also, cyclopentenes may be formed by intramolecular C-H 1,5-insertion from the alkylidenecarbenes:

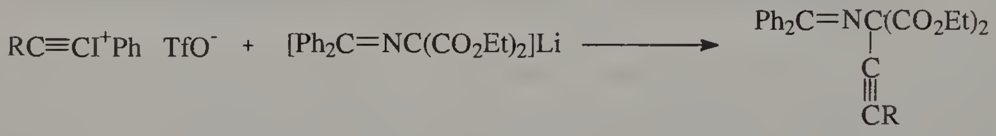


9.4.1 Reactions involving carbon–carbon bond formation

Enynes were prepared in good yield from alkynyl iodonium salts and alkenylcopper reagents, stereospecifically. This approach was suitable for the synthesis of conjugated enynes, using a trisubstituted alkene with complete retention of its geometry [47]. 1,3-Diynes were similarly obtained by coupling alkynyl iodonium salts with alkynyl copper reagents; some unwanted symmetrical diynes were formed here as by-products from self-coupling of the organocopper moiety [48]:

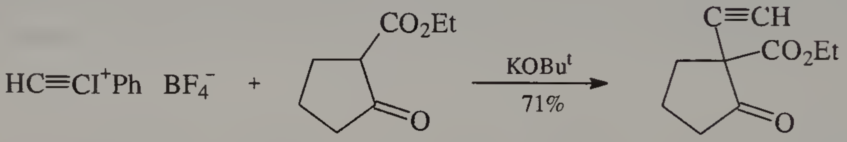
$$\mathrm{RC{\equiv}CI^{+}Ph\ \ TsO^{-}} + \mathrm{(R'C{\equiv}C)_2CuLi} \xrightarrow[-70^{\circ}\mathrm{C}]{\mathrm{THF}} \underset{60-75\%}{\mathrm{RC{\equiv}C{-}C{\equiv}CR'}} + \underset{4-23\%}{\mathrm{R'C{\equiv}C{-}C{\equiv}CR'}}$$

Using this method, several mesogen diacetylenes were obtained [49]. Palladium-catalysed coupling of an allylic cyclic carbonate with 1-pentynyl phenyliodonium tetrafluoroborate to give an enyne was highly successful [50]. Alkynyl iodonium triflates and lithium salts of diethyl 2-[(diphenylmethylene)amino]malonate were used for the preparation of alkynyl-α-amino acid derivatives, e.g. [51]:



$$\mathrm{RC{\equiv}CI^{+}Ph\ \ TfO^{-}} + \mathrm{[Ph_2C{=}NC(CO_2Et)_2]Li} \longrightarrow \mathrm{Ph_2C{=}N\underset{\underset{\displaystyle CR}{|||}}{\overset{|}{C}}(CO_2Et)_2}$$

Ethynyl phenyliodonium tetrafluoroborate was useful for the efficient α-ethynylation of *β*-carbonyl compounds and nitrocyclohexane, e.g. [52]:



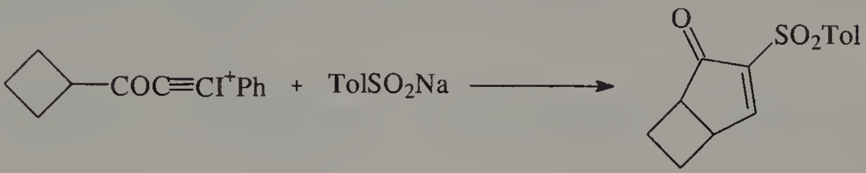
An interesting reaction between the bis phenyl iodonium triflate of acetylene and the silyl enol ether of acetophenone afforded an allene (PhCOCH=C=C=CHCOPh, 84%) [6]. Also, alkynyl iodonium tosylates and carbon monoxide in methanol or ethanol, with palladium catalysis, furnished alkyne carboxylates [53].

9.4.2 Cyclopentene annulation

Appropriately substitued alkynyl iodonium salts afforded with nucleophiles cyclopentene derivatives. This annulation can be either [5 + 0], when all carbon atoms come from the alkyl chain of the alkynyl moiety, or a [2 + 3] process, in which three carbon atoms come from the nucleophile. Competition between [5 + 0] and [2 + 3] annulation may occur in some cases.

Irrespective of mechanistic details, most reactions gave only one product in good to high yield. A wide variety not only of cyclopentenes or indenes, but also of heterocycles such as furans, benzo[b]furans and γ-lactams were prepared in this way. Selected examples are listed in Table 9.3.

3-Tosyl-bicyclo[3.2.0]-3-heptene-2-one [57]



The iodonium triflate (460 mg, 1 mmol) was added to a stirred slurry of anhydrous sodium *p*-toluene sulphinate (180 mg, 1.01 mmol) in dichloromethane (15 ml) at 20°C under nitrogen. After 15 min water (10 ml) was added and the phases were separated; the aqueous layer was extracted with additional dichloromethane (2 × 5 ml), and the combined organic extracts were dried. The filtered solution was treated with hexanes (30 ml) and concentrated. The solid residue was purified by radial chromatography (silica gel, 200–400 mesh, dichloromethane–hexanes) to afford 3-tosyl-bicyclo[3.2.0]-3-heptene-2-one (197 mg, 75%), m.p. 164–165°C. The method is general for the preparation of sulphones with a cyclopentenone moiety; other alkenyl iodonium salts gave alkynyl sulphones with sulphinates (Section 9.4.4).

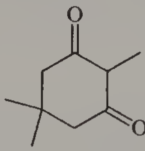
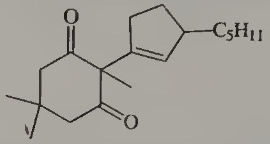
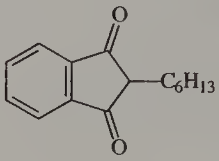
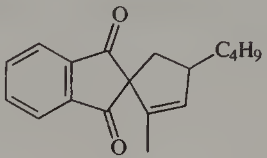
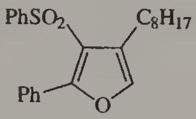
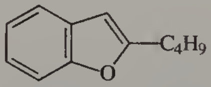
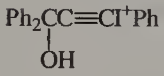
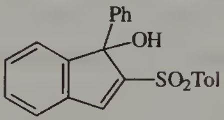
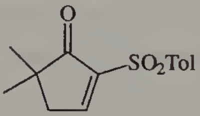
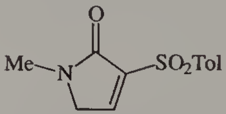
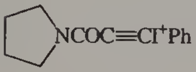
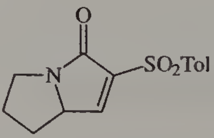
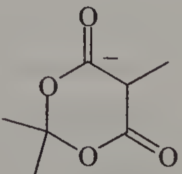
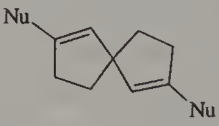
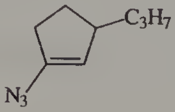
9.4.3 Reactions with oxygen nucleophiles

Stable esters coming formally from alkynols and carboxylic, sulphonic or dialkyl phosphoric acids were prepared for the first time *via* alkynyliodonium salts with the corresponding anion. Several alkynyl carboxylates were obtained by anion exchange of alkynyl iodonium tosylates; the initially formed salts, $PhI^+C\equiv CR\ RCO_2^-$, were converted spontaneously into the esters on elution through a chromatographic column packed with an anion-exchange resin ($Pol^+ArCO_2^-$):

$$RC\equiv CI^+Ph\ \ TsO^- \xrightarrow[\substack{CH_2Cl_2 \\ 10\text{–}40\%}]{Pol^+\ ArCO_2^-} RC\equiv CO_2CAr$$

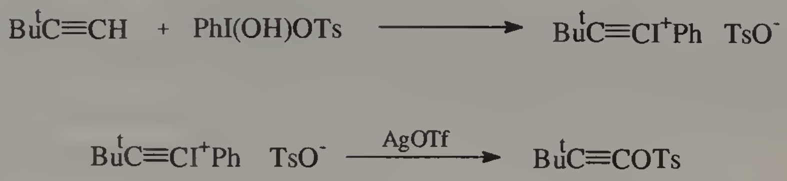
TABLE 9.3

Annulated products from alkynyl iodonium salts and nucleophiles

Iodonium salt	Nucleophile	Product	Yield (%)	Ref.
$C_8H_{17}C\equiv CI^+Ph$			50	[54]
$MeC\equiv CI^+Ph$			73	[54]
$C_8H_{17}C\equiv CI^+Ph$	$PhCOCH_2SO_2Ph$		67	[54]
$C_4H_9C\equiv CI^+Ar$ ($Ar=p\text{-}C_6H_4I(OTf)Ph$)	PhONa		62	[55]
 $Ph_2C(OH)C\equiv CI^+Ph$	$TolSO_2Na$		50	[56]
$^tBuCOC\equiv CI^+Ph$	$TolSO_2Na$		72	[57]
$Me_2NCOC\equiv CI^+Ph$	$TolSO_2Na$		63	[57]
	$TolSO_2Na$		63	[57]
$PhI^+C\equiv C(CH_2)_5C\equiv CI^+Ph$	 (Nu)		77	[11]
$C_6H_{13}C\equiv CI^+Ph$	NaN_3		58	[58]

An alternative approach for alkynyl carboxylates involved reaction between [bis(acyloxy)iodo]benzenes and lithium acetylides [59]. Alkynyl iodonium salts afforded with sodium carboxylates in the presence of water 1-acyloxyketones; heating in an excess of acetic acid gave similarly α-acetoxy ketones [60]. Alkynyl tosylates and mesylates were obtained from the thermal decomposition of isolable alkynyl iodonium sulphonates.

t-Butylethynyl phenyliodonium tosylate and t-Butylethynyl tosylate [61]



$$\overset{t}{\mathrm{Bu}}\mathrm{C{\equiv}CH} + \mathrm{PhI(OH)OTs} \longrightarrow \overset{t}{\mathrm{Bu}}\mathrm{C{\equiv}CI^{+}Ph\ \ TsO^{-}}$$

$$\overset{t}{\mathrm{Bu}}\mathrm{C{\equiv}CI^{+}Ph\ \ TsO^{-}} \xrightarrow{\mathrm{AgOTf}} \overset{t}{\mathrm{Bu}}\mathrm{C{\equiv}COTs}$$

t-Butylacetylene (6 g, 9 ml, 73 mmol) and [hydroxy (tosyloxy) iodo] benzene (8 g, 20 mmol) were refluxed in chloroform (50 ml) for 5 h. The resulting solution was concentrated and the residue was washed with ether to provide the iodonium tosylate (6.1 g, 67%) m.p. 129–133°C.

The tosylate (2 g, 4.4 mmol) was decomposed in a solution of acetonitrile (10 ml) which was stirred in the presence of silver triflate (100 mg, 0.39 mmol) for 20 h. After concentration, the residue was taken up in 1:1 dichloromethane–hexanes, filtered, concentrated and subjected to Kugelrohr distillation (130°C, 0.15 torr), to give 412 mg (37%) of pure ester.

Other alkynyl phenyliodonium arylsulphonates were prepared by modified procedures, notably from iodosylbenzene and alkynylsilanes, in good yields (62–89%). The decomposition stage proceeded also in satisfactory yields, up to 88% [61]. Bis alkynyl dibenzoates and ditosylates were prepared from the corresponding bis iodonium salts of the general formula $\mathrm{PhI^{+}C{\equiv}C(CH_2)_{\mathit{n}}C{\equiv}CI^{+}Ph}$, where $n = 5,6,8$ [62].

Alkynyl dialkyl phosphates of the general formula $\mathrm{RC{\equiv}COPO(OR')_2}$, were prepared by a similar spontaneous decomposition of the less stable salts $\mathrm{RC{\equiv}CI^{+}PhC^{-}OPO(OR)_2}$, some of which are isolable; alternatively, either alkynes and [hydroxy(dialkylphosphoryloxy)iodo]benzene or alkynysilanes and iodosylbenzene–boron trifluoride can be used [63].

Diphenyloxyacetylene was prepared from lithium phenyloxide and a bis iodonium salt of acetylene.

Diphenyloxyacetylene [6]

$$\mathrm{PhI^+C{\equiv}CI^+Ph\ \ 2TfO^- + 2PhOLi \longrightarrow PhOC{\equiv}COPh}$$

To a solution of phenol (235 mg, 2.5 mmol) in dichloromethane (25 ml) at − 30°C, under nitrogen, was added with stirring butyl lithium (1 ml of 2.5 M solution in hexane). The mixture was cooled to − 78°C and the iodonium salt (730 mg, 1 mmol) was added; after 15 min of stirring at − 78°C the reaction mixture was allowed to warm to room temperature. The dark solution was filtered through silica gel (5 g) and the solvent evaporated. Column chromatography (silica gel, hexane) gave diphenyloxyacetylene (120 mg, 57%) as a colourless oil.

Sodium phenyloxide and alkynyl (*p*-phenylene)bis iodonium triflates afforded 2-substituted benzo[b]furans (Table 9.3).

9.4.4 Reactions with sulphur nucleophiles

Sodium thiophenoxide and bis phenyliodonium acetylene triflate afforded cleanly 1,2-bis(phenylthio)acetylene [6]. Alkynyl iodonium salts have alkynylated several arene sulphonates which were converted into alkynyl aryl sulphones. The process is probably the best among other methods, as far as yield, availability of starting materials, non-toxicity and ease of handling are concerned.

t-Butylethynyl p-*chlorophenyl sulphone* [64]

$$\mathrm{B\overset{t}{u}C{\equiv}CI^+Ph\ \ TsO^- + \mathit{p}\text{-}ClC_6H_4SO_2Na \longrightarrow B\overset{t}{u}C{\equiv}CSO_2C_6H_4Cl}$$

A solution of the iodonium salt (912 mg, 2 mmol) in chloroform (10 ml) was added to a solution of sodium *p*-chlorobenzene sulphinate (496 mg, 2.5 mmol) and triethylbenzylammonium chloride (22.8 mg, 0.1 mmol) in water (10 ml). The mixture was stirred at room temperature for 5 h; then the organic layer was separated, the water layer extracted with chloroform (3 × 10 ml) and the combined organic layers washed with water (3 × 20 ml) and dried. After concentration, the residue was chromatographed on silica gel (hexane–chloroform) to give the pure sulphone (472 mg, 92%) m.p. 80–82°C.

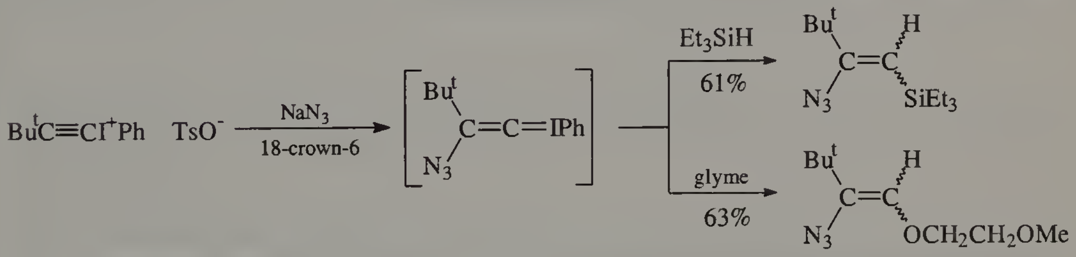
Equally good yields were also obtained from alkynyl iodonium triflates without phase transfer catalysis [65]. With arenesulphinic acids in methanol the reaction stopped at the stage of *Z*-*β*-sulphonylalkenyl iodonium salt [41].

Thiocyanation was very effective with several alkynyl iodonium salts, in a simple process avoiding the previously used cyanogen chloride or mercury compounds; best yields of alkynyl thiocyanates were obtained using potassium thiocyanate in DMF [66].

Another superior method using alkynyl iodonium salts involved the preparation of *S*-alkynyl *O,O*-dialkylphosphorodithioates; high yields were obtained under phase transfer catalysis [67]. Similarly, with potassium *p*-toluenethiosulphonate were obtained esters of the general formula *p*-Tol$SO_2SC{\equiv}CR$ [68].

9.4.5 Reactions with nitrogen nucleophiles

Sodium azide with alkynyl iodonium tosylates at – 70°C afforded an unstable ylide which in the presence of triethylsilane was transformed to different products, depending on the solvent [58]:



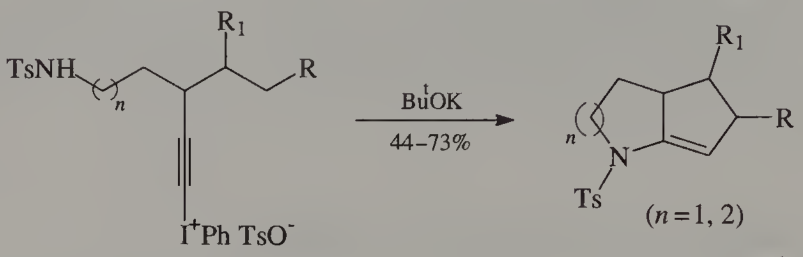
Other pathways, with trimethylsilyl azide and the appropriate iodonium salts, involved the formation of 3-alkyl-1-azido-cyclopentenes (Table 9.3.) or *Z*-*β*-azidoalkenyl iodonium salts [69]. Several types of alkynyl iodonium salts afforded with lithium diphenylamide push–pull ynamines overcoming some inherent limitations of other methods.

*Benzoyl(*N,N*-diphenylamino)acetylene* [70]

$$PhCOC{\equiv}CI^+Ph\ \ TfO^- + Ph_2NLi \longrightarrow PhCOC{\equiv}CNPh_2$$

To a stirred solution of diphenylamine (0.51 g, 3 mmol) in ether (40 ml) was added butyl lithium (1.2 ml, 2.5 M, 3 mmol) at – 78°C under nitrogen. The iodonium salt (1.44 g, 3 mmol) was added all at once and the solution was stirred for 1 h. The reaction mixture was eluted through silica gel with dichloromethane and concentrated. Silica gel radial chromatography (200–400 mesh, 2 mm plate, dichloromethane) and removal of the solvent gave benzoyl(*N,N*-diphenylamino) acetylene (160 mg, 66%) as a red oil.

Of special importance was the synthesis of bicyclic tosylenamides in tandem reactions of appropriate tosylamide-containing alkynyl iodonium salts [71]:



This method provided an efficient access to cyclopentylamine-containing alkaloid skeleta. Similarly, by using 1-propynyl phenyliodonium triflate and various tosylamide anions, the preparation of dihydropyrroles and indoles was reported [72].

9.4.6 Reactions with phosphorus and arsenic nucleophiles

Triphenylphosphine with alkynyl iodonium salts in sunlight gave quantitatively the corresponding phosphonium salts, some of which could not be obtained by other methods [73]. Trialkyl phosphites were also reactive towards alkynyl iodonium salts; several dialkyl alkynylphosphonates were prepared in good yield, e.g. [74]:

$$Me_2CHCH_2C\equiv CI^+Ph\ TsO^- + P(OMe)_3 \xrightarrow[63\%]{} Me_2CHCH_2C\equiv CPO(OMe)_2$$

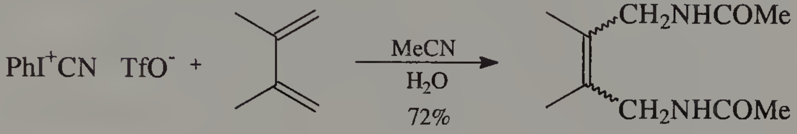
A general synthesis of 1-alkynyl triphenylarsonium salts has been elaborated from alkynyl iodonium salts and triphenylarsine under mild conditions [75]:

$$RC\equiv CI^+Ph\ BF_4^- + AsPh_3 \xrightarrow[\substack{N_2\\ 77\text{–}95\%}]{CH_2Cl_2} RC\equiv CAs^+Ph_3\ BF_4^-$$

Other approaches were not suitable for the preparation of these salts.

9.5 REACTIVITY OF OTHER IODONIUM SALTS

Cyano phenyliodonium triflate activated alkenes toward nucleophilic addition; in wet acetonitrile 1,2-bis acetamido alkanes were obtained, whereas a diene afforded the corresponding 1,4-adducts (both isomers) [76]:



The salt $PhI^+C(N_2)COOEt\ TfO^-$ reacted with several neutral nucleophiles, such as triethylamine, pyridine, dimethyl sulphide, etc. affording the triflates of α-onio-substituted diazoesters, in 53–95% yield [14].

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– 10 –

Phenyliodonium Zwitterions

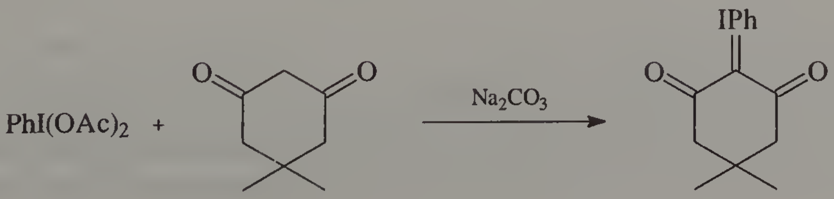
In numerous iodonium compounds the positive charge at iodine is internally compensated by a negative charge. Among them of special interest are those with this charge localized formally at an α-carbon or nitrogen atom, i.e. 1,2-dipoles. In several instances the charge may be dispersed on a system of neighbouring bonds giving rise to 1,4-zwitterionic structures, with an anionic oxygen or nitrogen atom. Generally, no clear distinction exists between these two types. The name phenyliodonium ylide will be used loosely for those zwitterions for which crystal and spectral data favour the 1,2-dipolic structure.

10.1 PREPARATION

10.1.1 Phenyliodonium ylides

Precursors of this class are compounds with an active methylene group and some sulphonamides; in them two hydrogen atoms have been replaced by the phenyliodonio (PhI^+) group. The standard method for the preparation of ylides is the reaction of DIB with the appropriate precursor in aqueous or alcoholic alkali (preferably potassium hydroxide for non-cyclic precursors and sodium carbonate for cyclic ones).

Phenyliodonium 4,4-dimethyl-2,6-dioxocyclohexylide [1] *(phenyliodonium ylide of dimedone)*



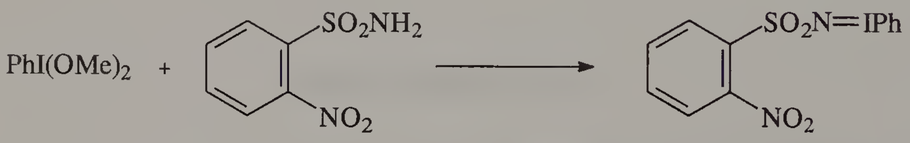
A solution of (diacetoxyiodo)benzene (32.2 g, 0.1 mol) in ethanol (100 ml) was added all at once to a stirred solution of the diketone (dimedone, 14 g, 0.1 mol) in aqueous 10% sodium carbonate (300 ml), at room temperature. After 30 min of stirring, the reaction mixture was poured onto ice water (300 ml) and the ylide was extracted with dichloromethane (3 × 100 ml); the organic layer was dried and concentrated to give phenyliodonium 4,4-dimethyl-2,6-dioxocyclohexylide (28.0 g, 82%) as a solid mass decomposing on heating.

Some ylides can be recrystallized from ordinary solvents; others are thermally labile and can be purified by dissolution in dichloromethane and precipitation by ether. In fairly acidic precursors, such as $CH_2(SO_2Rf)_2$, no alkali is necessary [2].

The rhodium catalysed decomposition of 2-diazo-1,3-diketones in iodobenzene produced phenyliodonium ylides in 37–71% yield [3]; similarly, *o*-iodophenyl precursors were converted intramolecularly into cyclic ylides [4,5].

Although ylides coming from sulphonamides can be obtained through the above general method, an alternative procedure has been developed using (dimethoxyiodo)benzene.

[(2-Nitrophenylsulphonylimino)iodo]benzene [6]

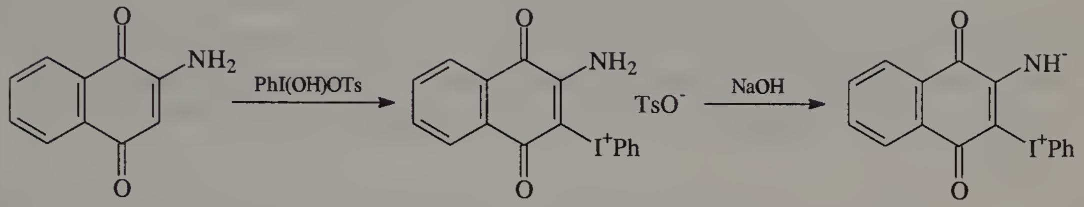


Iodosylbenzene (1.1 g, 5 mmol) was stirred for 15 min in methanol (40 ml), under nitrogen. About 3 g of powdered Linde 3A molecular sieves were added (heated previously at 400°C and 0.01 torr for 15 h) and the suspension was stirred in a capped Schlenk tube for 2 h. The molecular sieves were removed and the drying process was repeated with a fresh portion of molecular sieves. A small loss of iodosylbenzene (44 mg) was indicated by iodometric titration. To the filtrate, after removal of the solid phase, was added the sulphonamide (1 g, 4.95 mmol) portionwise; the solution turned yellow and a precipitate separated. After concentration to a small volume, dichloromethane (5 ml) was added and the solid mass was collected, washed with dichloromethane and dried affording [(2-nitrophenylsulphonylimino)iodo]benzene (1.8 g, 92%), as an amorphous powder, decomposing on heating.

10.1.2 Phenyliodonium 1,4 dipoles

These zwitterions come mainly from acidic phenols or some acidic heterocycles; their precursors include 2-hydroxy or 2-amino-1,4-quinones and related compounds of enolic or enamine character. Here, one sp^2 *C*-bound hydrogen atom is replaced by the phenyliodonio group and another one is removed from oxygen or nitrogen as a proton. Compounds of this type are also known in the form of isolable iodonium salts.

2-Phenyliodonio-1,4-naphthoquinone-3-imide [7]



To a stirred suspension of 2-amino-1,4-naphthoquinone (173 mg, 1 mmol) in dichloromethane (15 ml) was added [hydroxy(tosyloxy)iodo]benzene (411 mg, 1.05 mmol). After 20 min, the yellow iodonium salt which separated was collected, washed with dichloromethane and dried (520 mg, 95%). This salt (547 mg, 1 mmol) was added to a cold aqueous solution of 2% sodium hydroxide (2 mmol). The mixture was stirred until the yellow colour turned red, about 20 min; the precipitate was collected, washed with water and ether and dried to give 2-phenyliodonio-1,4-naphthoquinone-3-imide (263 mg, 70%), m.p. 115–117°C.

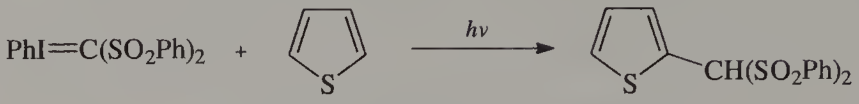
10.2 REACTIVITY OF IODINE–CARBON YLIDES

In most of their reactions these ylides behave formally as carbene precursors. Iodonium ylides in this capacity have a resemblance to diazo compounds with which they often compare favourably. Many of their reactions proceed better under photochemical conditions.

10.2.1 Carbene insertions

The group $C(SO_2R)_2$ from several ylides $PhI{=}C(SO_2R)_2$ was inserted to a carbon–hydrogen bond, for example in benzene and thiophene, thermally or photochemically.

2-Bis(phenylsulphonyl)methyl-thiophene [8]



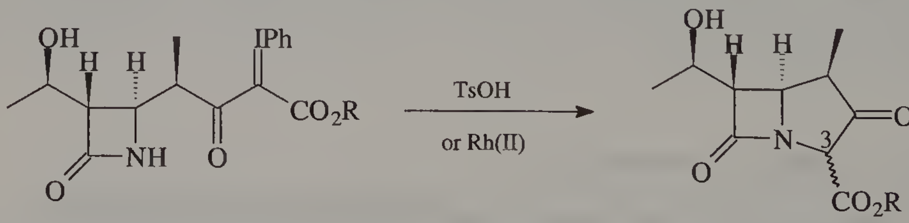
The ylide (500 mg, 1 mmol) in neat thiophene (15 ml) was irradiated in a Pyrex tube with a 400 W low pressure mercury lamp for 5 h. After removal of volatiles, the residue was purified by column chromatography on silica gel (dichloromethane–hexanes) to give 2-bis(phenylsulphonyl)methyl-thiophene (211 mg, 56%) m.p. 174–176°C.

Insertion of the fragment $C(COR)_2$ to a sp-carbon–hydrogen bond has also been reported with ylides coming from β-dicarbonyl compounds. In these reactions the initial product underwent an extensive rearrangement to 2-acyl-4-alkyl-1-naphthol [9]. With these ylides alcohols afforded ethers, e.g. [9]:

$$PhI{=}C(COPh)_2 + C_2H_5CMe_2OH \xrightarrow[65\%]{h\nu} C_2H_5CMe_2OCH(COPh)_2$$

The ylide $PhI{=}C(SO_2CF_3)_2$ was exceptionally stable, melting at 140°C without decomposition. On irradiation in methanol, it gave the ether $MeOCH(SO_2CF_3)_2$ [10]; however, this as well as some other photolytic reactions of such ylides with polyfluoroalkyl sulphonyl groups were not confirmed [2].

Intramolecular acid- or rhodium [II]-catalysed carbene nitrogen–hydrogen insertion from iodonium ylide intermediates was used in an efficient synthesis of 1-β-methylcarbapenems; the cyclization products had different stereoselectivity, depending on the catalyst [11]:



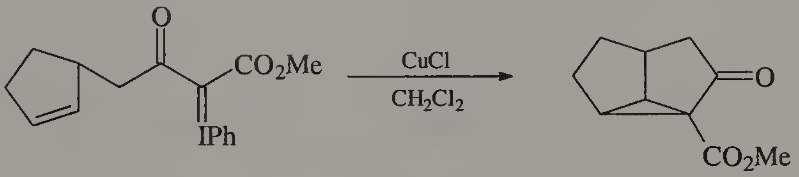
(R=benzhydryl)

(TsOH: 3*S*, 94%
Rh (II): 3*R*, 86%)

10.2.2 Cyclopropanation

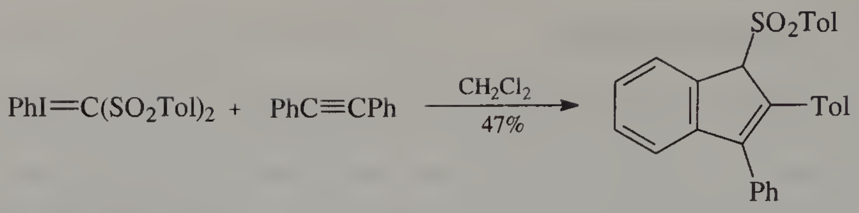
Several iodonium ylides, thermally or photochemically, transferred their carbene moiety to alkenes which were converted into cyclopropane derivatives. The thermal decomposition of ylides was usually catalysed by copper or rhodium salts and was most efficient in intramolecular cyclopropanation. Reactions of $PhI{=}C(CO_2Me)_2$ with styrenes, allylbenzene and phenylacetylene have established the intermediacy of carbenes; in the presence of a chiral catalyst, intramolecular cyclopropanation resulted in the preparation of a product in 67% enantiomeric excess [12].

1-Carbomethoxy-2-oxo-tricyclo[3.3.0.0^{2,8}]octane [13]



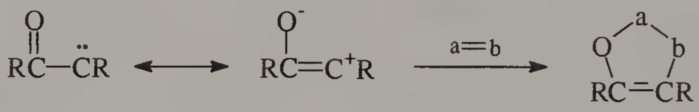
The ylide (3.7 g, 10 mmol, prepared by the general method) in dichloromethane (20 ml) was treated with cuprous chloride (15 mg) under nitrogen at 0°C. The reaction mixture was stirred for 10 min at 0°C and for 1 h at room temperature. After filtration and concentration, the residue was chromatographed on silica gel (hexanes–ethyl acetate, 9:1) to give 1-carbomethoxy-2-oxo-tricyclo[3.3.0.0^{2,8}]-octane (1.6 g, 90%) as an oil.

The yields were not always so high, as shown in Table 10.1, which gives some selected examples of cyclopropanation or further transformation. Nevertheless, several useful compounds were obtained by this methodology. The advantage of using iodonium ylides rather than their diazo analogues is that the hazards of the latter, i.e. explosive character, toxicity and carcinogenicity, are avoided. Further, diazo disulphones $(RSO_2)_2CN_2$ are generally stable and can not always serve as carbene precursors. By contrast, the analogous ylides $PhI{=}C(SO_2R)_2$ gave the cyclopropanation reaction with several alkenes [2,19]; sometimes the final products were indane derivatives resulting from SO_2 elimination. A similar behaviour was observed with alkynes: they reacted at room temperature, without catalyst, with various ylides from disulphones affording, through cyclopropenes, indene derivatives [19]:

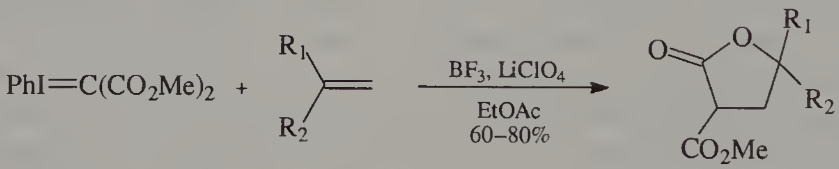


10.2.3 Cycloadditions

Iodonium ylides coming from precursors with one or two keto groups react thermally or photochemically with alkenes, alkynes, nitriles and some heterocumulenes. The products are 5-membered heterocycles with at least one oxygen atom, as illustrated in Table 10.2. Their formation can be described as the result of a formal [3 + 2] cycloaddition from the mesomeric 1,3-dipole structure of ketocarbenes, according to the general scheme (a = b mostly ethylenic double bonds):



Competition between C=O and C=C was observed in diphenylketene from which a lactone and a ketene acetal were obtained with the ylide of dimedone [23]. A different type of cycloaddition occurred with $PhI{=}C(CO_2Me)_2$; this reacted catalytically with several alkenes (1-hexene, styrene, methyl methacrylate, etc.) with formation of lactones [24]:



With cyclohexene and silyl enol ethers, under these conditions, there was no cyclization; the former gave a mixture of 3- and 4-bis(methoxycarbonyl)methylcyclohexenes, whereas the latter afforded $RCOCH_2CH(CO_2Me)_2$ (up to 60%) [24]. Lactones were formed from $PhI{=}C(C_4F_9)CO_2Et$ with catalysis by cupric triflate [25].

TABLE 10.1

Intra- and intermolecular cyclopropanation *via* iodonium ylides

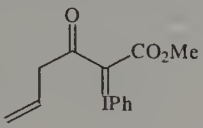
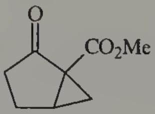
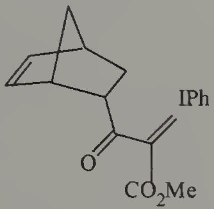
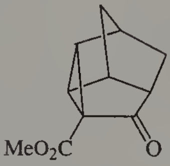
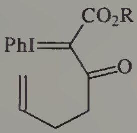
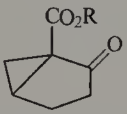
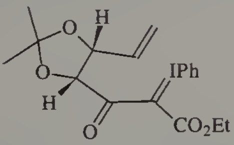
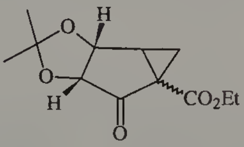
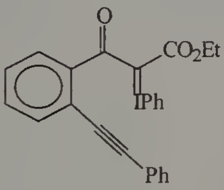
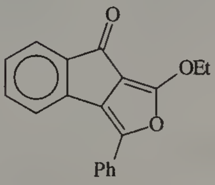
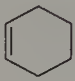
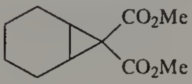
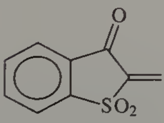
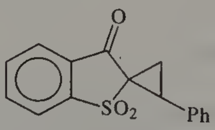
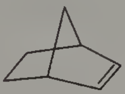
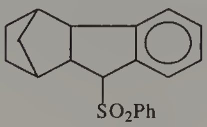
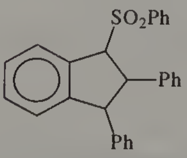
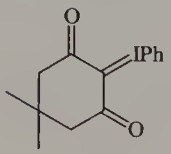
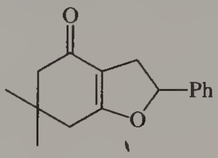
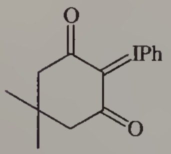
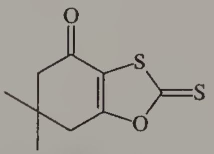
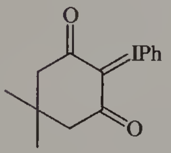
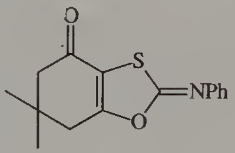
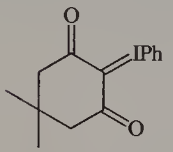
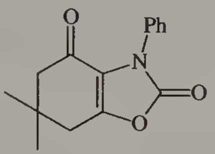
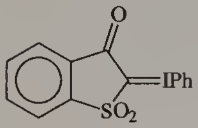
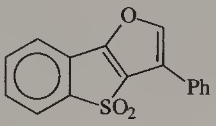
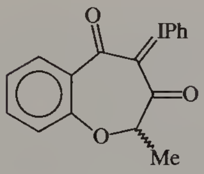
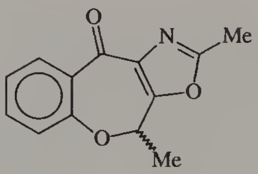
Precursors	Products	Yield (%)	Ref.
A. Intramolecular			
		76	[13]
		71	[13]
 (R= from chiral alcohol)	 (diastereomers)	80	[14]
		45	[15]
		58	[16]
B. Intermolecular			
PhI=C(CO$_2$Me)$_2$ + 		38	[17]
 + PhCH=CH$_2$		80	[18]
PhI=C(SO$_2$Ph)$_2$ + 		74	[19]
PhI=C(SO$_2$Ph)$_2$ + PhCH=CHPh		44	[19]

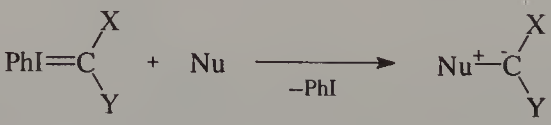
TABLE 10.2

Cycloadditions through iodonium ylides

Ylide	Partner	Product	Yield (%)	Ref.
	$PhCH{=}CH_2$		95	[20]
	$S{=}C{=}S$		85	[20]
	$PhNC{=}S$		74	[20]
	$PhN{=}CO$		44	[21]
	$PhC{\equiv}CH$		34	[18]
	$MeC{\equiv}N$		80	[22]

10.2.4 Transylidation

Several non-charged nucleophiles of nitrogen, phosphorus, arsenic, and sulphur displace the phenyliodonio group from iodonium ylides, with formation of new ylides, according to the generalized scheme:



$$PhI{=}C(X)(Y) + Nu \xrightarrow[-PhI]{} Nu^{+}{-}\bar{C}(X)(Y)$$

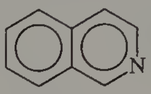
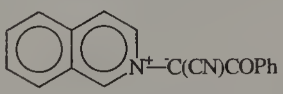
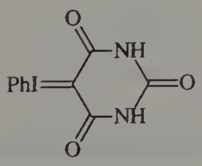
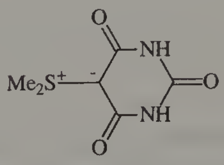
Pyridines, quinolines, triphenylphosphine, sulphides, selenides and thioureas are among such nucleophiles, which under the proper conditions, usually copper or light catalysis, react with almost any ylide. Iodine from *o*-iodophenylated *β*-diketones may also serve as the nucleophilic centre in intramolecular reactions of some ylides, with formation of cyclic iodonium ylides [4]. Table 10.3 lists some examples of general interest.

In some ylides photolytic conditions were necessary for their transylidation [30]. The conversion of iodonium ylides into α-halogeno derivatives of the parent carbonyl compound (or other precursor) with hydrogen halides is normally effected directly, without isolation of their iodonium salts. A similar reaction with halogens leads to the formation of α,α-bis halogenated products [31]. The reaction of pyridines with the non-isolable $PhI{=}C(CN)_2$ is of interest, since it permits the ready transfer of the $C(CN)_2$ functionality to the nitrogen of pyridine, quinoline, etc.; the yields here were generally moderate but in some cases the products could not be obtained using other dicyanocarbene precursors [32].

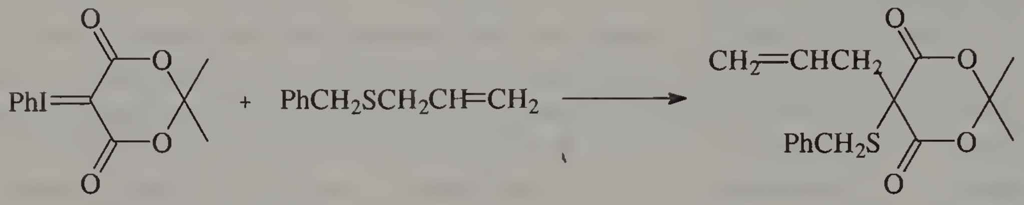
Sulphonium ylides are in certain cases unstable and they undergo further transformation affording useful final products. In this way allylic sulphides and selenides were used to transfer an alkylthio- or alkylseleno-group onto the α-carbon of *β*-dicarbonyl compounds in the form of their ylides; the sequence of reactions were a transylidation followed by [2,3]-sigmatropic rearrangement.

TABLE 10.3

Transylidation of iodonium ylides

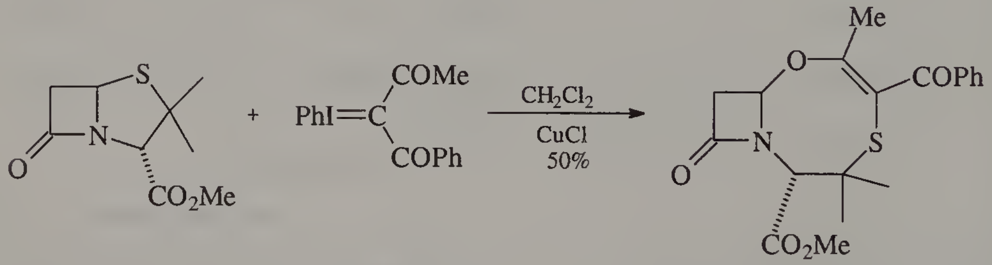
Ylide	Nucleophile	Product	Yield (%)	Ref.
$PhI{=}C(NO_2)_2$	$(H_2N)_2C{=}S$	$(H_2N)_2C{=}\overset{+}{S}{-}\overset{-}{C}(NO_2)_2$	85	[26]
$PhI{=}C(SO_2Me)_2$	Ph_3P	$Ph_3\overset{+}{P}{-}\overset{-}{C}(SO_2Me)_2$	81	[27]
$PhI{=}C(CO_2Me)_2$	Ph_3As	$Ph_3\overset{+}{As}{-}\overset{-}{C}(CO_2Me)_2$	69	[17]
$PhI{=}C(SO_2Ph)_2$	$(EtO)_3P$	$(EtO)_3\overset{+}{P}{-}\overset{-}{C}(SO_2Ph)_2$	87	[27]
PhI=C(CN)COPh			83	[28]
	Me_2S		80	[29]

5-Allyl-5-benzylthioisopropylidene malonate [33]



The ylide (668 mg, 2 mmol) was added to a stirred solution of the sulphide (328 mg, 2 mmol) in dichloromethane (15 ml) at room temperature. After 4 h, the reaction mixture was concentrated and the residue was purified by column chromatography on silica gel to give 5-allyl-5-benzylthioisopropylidene malonate (520 mg, 85%), m.p. 68–69°C.

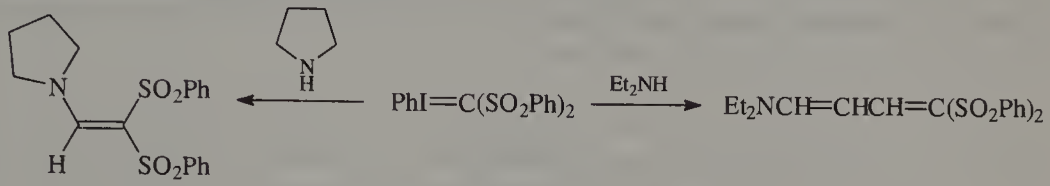
Analogous products were formed from the non-cyclic ylides $PhI{=}C(COPh)_2$, $PhI{=}C(COMe)_2$ and $PhI{=}C(COMe)CO_2Et$ with benzyl or alkyl allylic sulphides; several alkyl allyl selenides reacted similarly. Cyclic sulphides belonging to penams underwent ring expansion on treatment with several iodonium ylides bearing two keto groups, in the presence of catalytic amounts of cuprous chloride. The use of diazo analogues failed to give similar products. The reaction with ylides was regioselective, so that in $PhI{=}C(COMe)COPh$ or $PhI{=}C(COMe)CO_2Et$ it was the acetyl oxygen that participated in the ring expansion [34]:



The thermal reaction, catalysed by $Cu(acac)_2$, of thiobenzophenones with ylides coming from bis arylsulphonyl methane is also likely to proceed by an initial transylidation; the main products are here benzo[*c*]thiophenes [35;36]. The carbanionic carbon of iodonium ylides is devoid of nucleophilic character, yet $PhI{=}C(SO_2Ph)_2$ gave, with iodomethane, the methylated iododisulphone $MeC(I)(SO_2Ph)_2$ (68%). This reaction, performed at room temperature without any catalyst, is probably the result of a nucleophilic attack from iodine of iodomethane to iodine of the ylide [37].

10.2.5 Reactions with amines

Unexpected results came from the reactions of the ylide $PhI{=}C(SO_2Ph)_2$ with pyrrolidine and diethylamine; in the first case an enamine [38] and in the second a dienamine [39] were the main products:

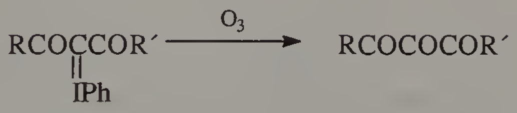


A more conventional reaction of ylides from β-dicarbonyl precursors with some aniline tosylates furnished *N*-arylated β-dicarbonyl compounds [40].

10.2.6 Miscellaneous reactions

Phenyliodonium β-diketonates underwent ozonolytic fragmentation, providing a useful synthesis of unsolvated *vic*-triketones in high yields.

1,2,3-Tricarbonyl compounds [1]



$$RCO\underset{\underset{IPh}{\|}}{C}COR' \xrightarrow{O_3} RCOCOCOR'$$

Carefully dried apparatus and solvent are a prerequisite of ozonation. A solution of the ylide (10 mmol) in dichloromethane (100–200 ml) was ozonized with an ozonizer (oxygen mixture) at −40 to −60°C, depending on the ylide. The most reactive ylides required only the equimolecular amount of ozone. When the peroxide test was negative the deep-coloured solution was concentrated and the residue purified by distillation, sublimation or recrystallization. More than 20 triketones were prepared in this way, in yields ranging between 65 and 92%.

Some ylides from cyclic precursors are thermally labile and isomerize to iodo-enol ethers; for example, the ylide of dimedone afforded 2-iodo-3-phenoxy-5,5-dimethyl-2-cyclohexanone [41]. A similar reaction involving cleavage of the I-C_{phenyl} bond occurred with triethylphosphite; 2-iodo-3-ethoxy-5,5-dimethyl-2-cyclohexen-1-one was the main product (65%) [42].

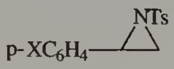
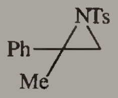
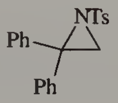
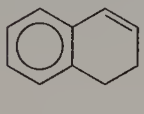
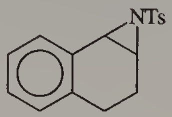
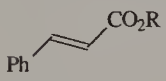
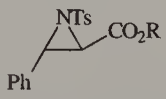
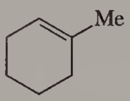
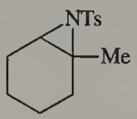
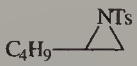
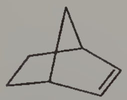
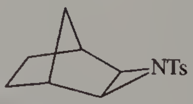
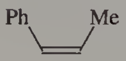
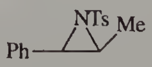
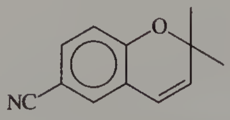
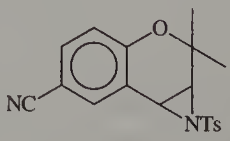
10.3 REACTIVITY OF IODINE–NITROGEN YLIDES

10.3.1 Aziridination of alkenes and dienes

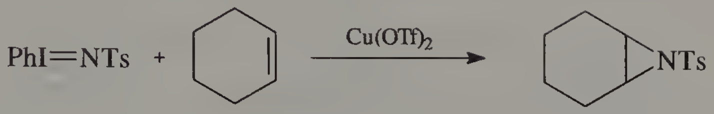
[(*N*-Tosylimino)iodo]benzene, PhI=NTs, is an excellent nitrene precursor for the aziridination of alkenes. A selection of aziridines prepared in this way are shown in Table 10.4. Copper catalysis was essential for these reactions; in some cases metal-porphyrin catalysts were also effective.

TABLE 10.4

Metal-catalysed aziridination of alkenes by [(*N*-tosylimino)iodo]benzene

Alkene	Aziridine	Yield (%)	Ref.
p-$XC_6H_4CH{=}CH_2$ (X= H, Me, Cl, OMe, NO_2)		73–90	[43]
$PhC(Me){=}CH_2$		78	[43]
$Ph_2C{=}CH_2$		90	[44]
		73	[43]
		62–69	[43]
		66	[43]
$C_4H_9CH{=}CH_2$		66	[43]
		95	[43]
		79,67%ee	[45]
		75,98%ee	[45]

N-*Tosyl-7-azabicyclo[4.1.0]heptane* [43]



To a suspension of cupric triflate (20 mg, 0.055 mmol) in a solution of cyclohexene (0.54 ml, 0.43 g, 5.33 mmol) in acetonitrile (5 ml) the ylide (400 mg, 1.07 mmol) was added under a flow of nitrogen. When all of it went into solution, at room temperature, the reaction mixture was filtered through a plug of silica with 50 ml of ethyl acetate as eluent. Concentration and purification by flash column chromatography on silica (hexane–ethyl acetate 4:1) provided the title compound (161 mg, 60%) m.p. 55.5°C.

Asymmetric aziridination was also successfully performed using benzylidene derivatives of 1,2-diaminocyclohexane in presence of cuprous triflate [45].

For the aziridination of 1,3-dienes, copper catalysis gave better yields of *N*-tosyl-2-alkenyl aziridines; with 1,3-cyclooctadiene, 1,4-addition occurred exclusively (50%) [46]. Good results were also obtained on rhodium catalysed decomposition of PhI=NNs (Ns = *p*-nitrophenylsulphonyl); with some alkenes the aziridination was stereospecific, whereas with chiral catalysts asymmetric induction (up to 73% ee) was achieved. However, cyclohexene gave predominantly (70%) a product derived from nitrene insertion into an allylic carbon–hydrogen bond [47].

10.3.2 Amination

By using PhI=NTs, effective carbon–hydrogen insertion of its tosylino group occurred to silyl enol ethers and silyl acetals. In this way *N*-tosylated α-aminoketones and α-amino ethers were prepared (Table 10.5), in better yield than when ethyl aziformate ($EtOCON_3$) served as the nitrene precursor. Trialkylboranes bearing primary alkyl groups afforded *N*-tosylamines, without catalysis, in good yield [48]:

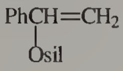
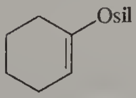
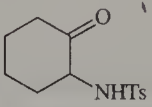
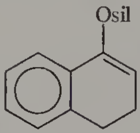
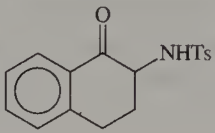
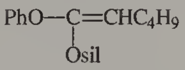
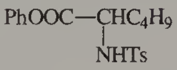
$$\mathrm{PhI{=}NTs} + \mathrm{R_3B} \xrightarrow[\text{(ii) H}_2\text{O}]{\text{(i) THF}} \mathrm{RNHTs}$$

60–99%

With 9-octyl-9-borabicyclo[3.3.1]nonane the initially formed amide was further oxidized to provide 5-tosylamino-cyclooctanol.

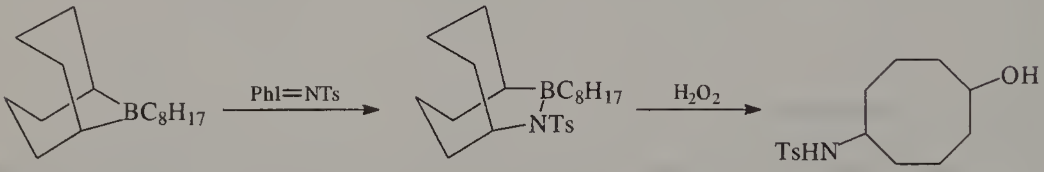
TABLE 10.5

Copper-catalysed amination of silyl enol ethers and silyl ketene acetals by [(*N*-tosylimino)iodo]benzene[a] [43]

Precursor	Product	Yield (%)
 $PhC(Osil)=CH_2$	$PhCOCH_2NHTs$	75
		64
		53
 $PhO—C(Osil)=CHC_4H_9$	 $PhOOC—CH(NHTs)C_4H_9$	50

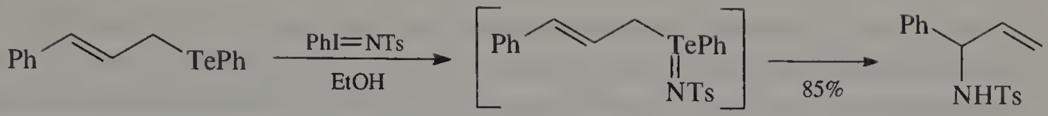
[a] The designation sil is for Me_3Si.

5-Tosylamino-cyclooctanol [48]



A solution of the borane (1 mmol) in THF (3 ml) was treated with the ylide (374 mg, 1 mmol) under argon, at room temperature. After stirring for 3 h, 3N aqueous sodium hydroxide (2 ml) and 30% hydrogen peroxide (1 ml) were added to the reaction mixture, which was allowed to stand overnight; it was then neutralized with 1 N HCl (7 ml), extracted with dichloromethane (3 × 15 ml) and dried. Concentration and purification by preparative TLC (petroleum ether–ether) yielded 5-tosylamino-cyclooctanol (266 mg, 91%) m.p. 88–89°C.

Allylic phenyl tellurides, prepared *in situ* from the corresponding halides and diphenyl ditelluride, were converted by PhI = NTs, through a [2,3] sigmatropic rearrangement of ylidic intermediates, into *N*-tosylated allylic amines, e.g. [49]:



Allylic amination was also effected in a chiral cinnamyl ferrocenyl selenide ($PhCH{=}CHCH_2Fc^*$), with formation of the chiral amine $PhCH(NHTs)CH{=}CH_2$ in up to 87% ee [50].

10.3.3 Further transfer of arylsulphonylimino groups

In several instances, transylidation through PhI=NTs leads to stable new ylides. For example, upon reaction with anisole, triphenylphosphine, and DMSO the corresponding sulphonium and phosphonium ylides were formed [51]. Further, the same ylide has been used for the preparation of iodine–carbon ylides by exchange with β-diketones. The mildness of the method makes it suitable for high purity ylides, especially when they are thermally labile [52].

In the presence of catalytic amounts of palladium complexes, carbon monoxide with ylides of the general formula $PhI{=}NSO_2Ar$ afforded arylsulphonyl isocyanates (isolated as *N*-aryl-*N*-2′-chlorophenylureas, on reaction with 2-chloroaniline) [53]:

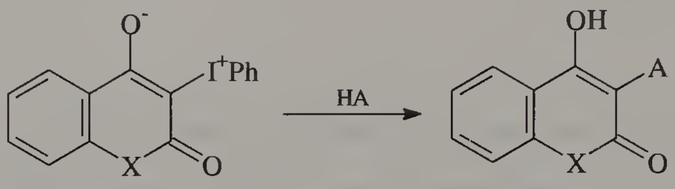
$$PhI{=}NSO_2Ar + CO \xrightarrow[\substack{CH_2Cl_2, 38\text{ bar, r.t.} \\ 52\text{–}80\%}]{PdCl_2(PhCN)_2} ArSO_2NCO$$

10.4 REACTIVITY OF 1,4-DIPOLES

Members of this family of zwitterions are iodine–oxygen or iodine–nitrogen 1,4-dipoles. Some of their reactions bear analogy to those of iodine–carbon ylides, whereas in some others there are differences.

10.4.1 Reactions with nucleophiles and electrophiles

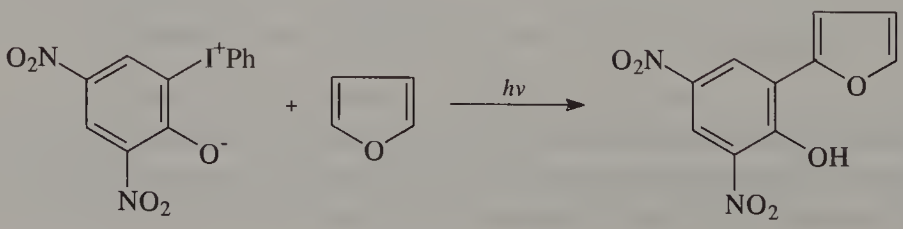
Whereas iodine–carbon ylides undergo the transylidation reaction normally with copper catalysis, 1,4-dipoles require acid catalysis; in this way they react with several nucleophiles through their protonated form, i.e. as iodonium salts, some of which are isolable. Pyridine, nicotinamide, isoquinoline, dimethylsulphide, thiolane are examples of neutral nucleophiles successfully used for such reactions [30]. In addition, aniline and phenol also reacted with the iodonium salt coming from 4-hydroxy-quinoline-2(*1H*)-one affording, respectively, *N*-phenylamino and 4-hydroxyphenyl derivatives. Similar dipoles on treatment with acids, thiophenol or acidic methanol afforded the corresponding 3-substituted derivatives, all in high yields, e.g. [54]:



(X= NH, NMe, O ; A= Br, AcO, PhS, MeO)

The 3-phenyliodonium dipole of 2-hydroxy-1,4-naphthoquinone gave analogous products with hydrogen halides, whereas with bromine it furnished 3,3-dibromo-1,2,4-trioxo-1,2,3,4-tetrahydronaphthalene, all in good yields. It is worth noting that 2-hydroxy-3-iodo-1,4-naphthoquinone was also obtained from the mechanistically interesting reaction of the dipole with iodomethane in methanol [55]. The phenyliodonio dipole from 2,4-dinitrophenol reacted directly with nucleophiles such as sodium methoxide and butylamine, affording, respectively, methoxy and butylamino derivatives [57]. The same compound showed photochemical reactivity with nucleophiles; in methanol it afforded 6-methoxy-2,4-dinitrophenol, whereas with pyridine it underwent transylidation; thioureas, by contrast, formed stable adducts in which iodine of the dipole became covalently linked to sulphur [56]. Aromatic compounds such as benzene, anisole and 1,4-dimethoxybenzene gave 6-aryl-2,4-dinitrophenols; an analogous reaction occurred with furan, 2-methylfuran and thiophene.

2,4-Dinitro-6-(2′-furyl)phenol [57]



A suspension of the dipole (386 mg, 1 mmol) in acetonitrile (10 ml) and furan (10 ml) was irradiated with a low pressure mercury lamp (400 W) in a Pyrex vessel under stirring for 4 h. The reaction mixture was concentrated and chromatographed on a silica gel column (dichloromethane–hexane 2:1) to give 2,4-dinitro-6-(2′-furyl)phenol (175 mg, 74%), m.p. 175–176°C.

10.4.2 Cycloadditions

Under photochemical conditions several 1,4-dipoles reacted with alkenes, alkynes, phenyl isothiocyanate and carbon disulphide to afford, after iodobenzene expulsion, cyclic adducts in moderate to low yields. This drawback is offset by the fact that it is difficult to obtain some of these compounds through alternative methods. Table 10.6 are listed selected examples of cyclic compounds formed by this methodology. Formally, these reactions can be considered as 1,3-dipolar cycloadditions, in which the 1,3-dipole comes from the iodonium precursor after elimination of iodobenzene; actually, they arise most probably through 6-membered intermediate iodanes.

10.4.3 Rearrangements

In common with cyclic ylides, several (but not all) iodine–oxygen dipoles on heating in methanol, acetonitrile or DMF undergo a 1,4-sigmatropic rearrangement, affording *O*-phenyl (or aryl) iodoethers (Table 10.7).

This rearrangement is important because some of the products have been used to prepare benzofurans or other compounds. An analogous rearrangement occurred with iodine–nitrogen dipoles coming from 2-amino and 2-phenylamino-1,4-naphthoquinones. The latter was unstable; it was formed from its tosylate which spontaneously rearranged, at 5°C [7]. Dipoles coming from 2-hydroxy-1,4-benzoquinones and 2-hydroxy-1,4-naphthoquinone on heating in moist acetonitrile did not undergo this rearrangement but were converted into 2-cyclopentene-1,4-diones.

2-Phenyl-2-cyclopentene-1,4-dione [60]

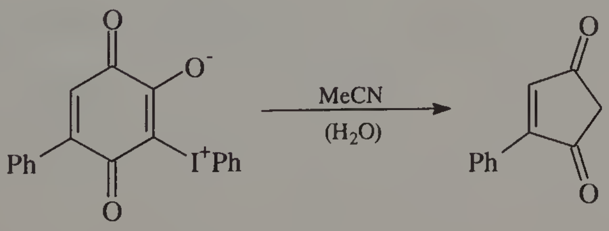


TABLE 10.6

Photochemical reactions of 1,4-phenyliodonium dipoles leading to the formation of cyclic compounds

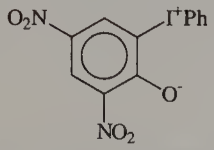
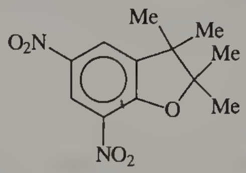
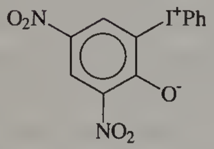
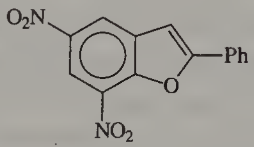
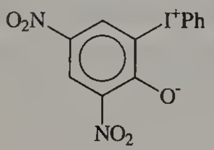
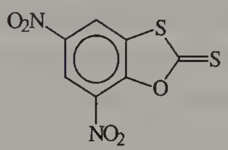
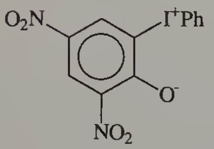
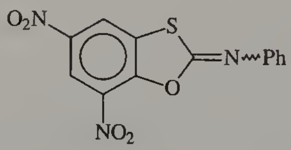
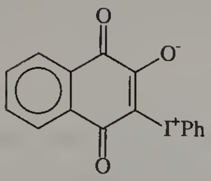
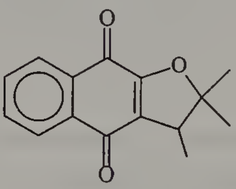
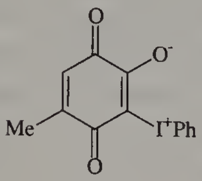
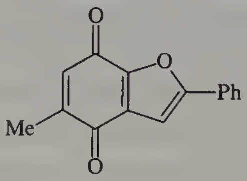
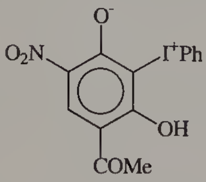
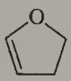
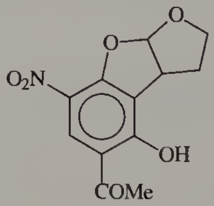
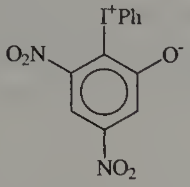
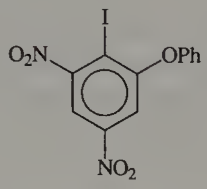
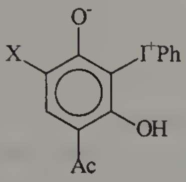
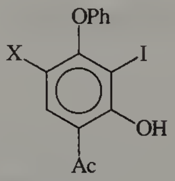
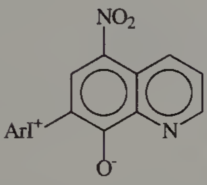
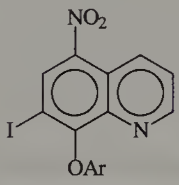
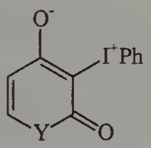
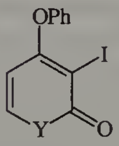
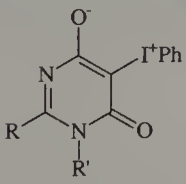
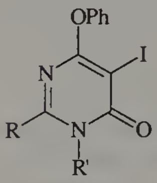
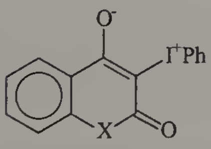
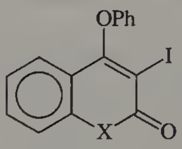
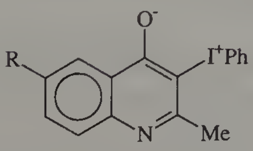
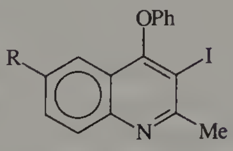
Dipole	Partner	Product	Yield (%)	Ref.
	$Me_2C{=}CMe_2$		30	[57]
	$PhC{\equiv}CH$		18	[57]
	CS_2		73	[58]
	PhNCS		71	[59]
	$Me_2C{=}CHMe$		23	[55]
	$PhC{\equiv}CH$		20	[60]
			15	[61]

TABLE 10.7

Iododiaryl ethers from 1,4-phenyliodonium dipoles

Dipole	Product	Yield (%)	Ref.
		83	[56]
 (X=H, NO_2, Ac)		47–70	[61]
		60–65	[62]
 (Y=O, NH, NPh)		88–93	[63]
		63–69	[64]
 (X=O, NH, NMe, NPh)		88–92	[65]
		70–75	[66]

A suspension of the dipole (402 mg, 1 mmol) in commercial acetonitrile (20 ml) was refluxed for 2 h. After removal of the solvent the residue was washed with petroleum ether and recrystallized from chloroform–petroleum ether to afford 2-phenyl-2-cyclopentene-1,4-dione (146 mg, 85%), m.p. 127–129°C.

Another unexpected rearrangement was observed from 3-phenyliodonio-1,4-naphthoquinone-3-imide which upon treatment with sodium alkoxides was transformed to (2-carbalkoxybenzoyl)acetonitriles [67].

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–11–

Reagents of Iodine(V)

Among iodine(V) compounds rather few have been used as reagents. These include iodylbenzene (formerly named iodoxybenzene) and some substituted iodylarenes, 2-iodylbenzoic acid (which is actually cyclic) and its triacetoxy derivative, better known as Dess–Martin reagent.

11.1 REACTIONS WITH IODYLARENES

The powerful oxidizing character of iodine(V) is not amply manifested in iodylarenes, the synthetic applications of which are limited. This is partly due to their polymeric nature which makes them insoluble in most ordinary solvents, with the exception of water. Nevertheless, iodylbenzene and also 3-iodylbenzoic acid in the presence of catalytic amounts of other reagents can be of considerable synthetic utility.

11.1.1 Dehydrogenations of ketones

A fruitful area of application was the efficient dehydrogenation of steroidal 3-ketones to 1,4-dien-3-ones using benzeneseleninic anhydride, $(PhSeO)_2O$, generated *in situ* by oxygen atom transfer from iodylbenzene to catalytic amounts of diphenyl diselenide. The use of 3-iodylbenzoic acid instead of iodylbenzene had the advantage of avoiding chromatographic separation, allowing recovery of both reagents.

Steroidal 1,4-dien-3-ones from ketones [1]

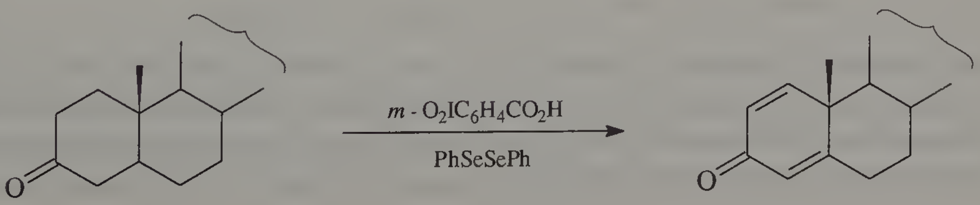
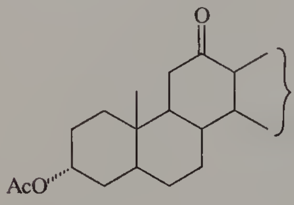
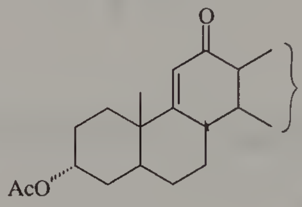
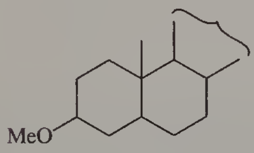
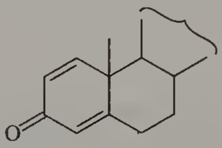
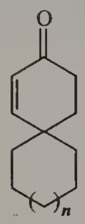
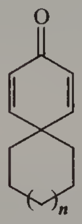
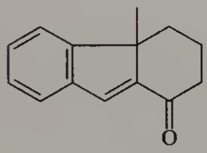
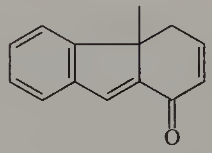


TABLE 11.1

Dehydrogenations using iodylarenes-diphenyl diselenide

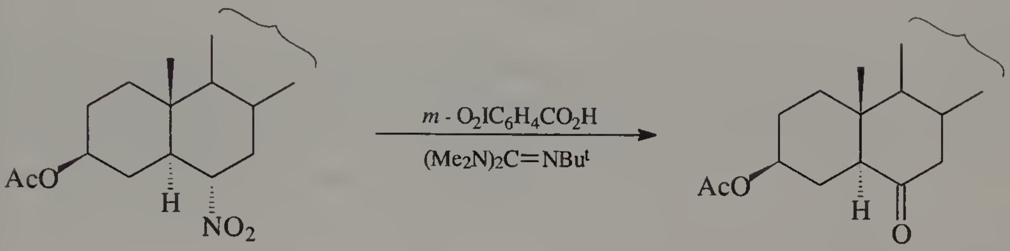
Substrate	Product	Yield (%)	Ref.
		90	[1]
			[3]
 (*n* = 1, 2)		77–85	[1]
		‘good’	[4]

3-Iodylbenzoic acid (720 mg, 2.57 mmol) and diphenyl diselenide (50 mg, 0.16 mmol) were refluxed with stirring in benzene or toluene or chlorobenzene (20 ml) until the yellow colour of the diselenide disappeared (about 15 min). The steroid (300 mg) was added and heating with stirring continued until completion of the reaction. The reaction mixture was washed with water and dried. Concentration and recrystallization gave steroidal 1,4-dien-3-ones in 70–89% yield. From the combined aqueous extracts 3-iodylbenzoic acid and diphenyl diselenide could be recovered. Not only steroidal ketones [1,2] but also substrates with similar features were dehydrogenated in this way, sometimes to provide only enones (Table 11.1).

11.1.2 Conversion of nitro compounds to ketones

3-Iodylbenzoic acid in the presence of an excess of *N,N,N′,N′*-tetramethyl-*N″*-t-butylguanidine converted efficiently secondary nitro compounds into ketones; primary nitro compounds similarly gave aldehydes but in lower yields (30–40%). This Nef-type transformation was applied to nitrosteroids, in which because of the mild character of the oxidizing system easily oxidizable groups, such as hydroxyl, double bonds and a dithiolane moiety, were unaffected.

3-β-Acetoxy-6-ketocholestane [5]



To a mixture of 3-β-acetoxy-6-nitrocholestane (250 mg, 0.56 mmol) and 3-iodylbenzoic acid (400 mg, 1.05 mmol) in dichloromethane (7 ml) was added the guanidine base (0.4 ml). After stirring at room temperature for 5 h, the reaction mixture was poured into 0.5 N sodium hydroxide and the organic layer separated and then washed with dilute hydrochloric acid and water. Drying, filtration through a silica plug and concentration afforded 3-β-acetoxy-6-ketocholestane (227 mg, 95%), m.p. not given.

11.1.3 Allylic oxidation

Iodylbenzene with catalytic amounts of 2,2′-dipyridyl diselenide converted alkenes into allylic ketones directly; the actual oxygenating agent was 2-pyridineseleninic anhydride, formed *in situ.*

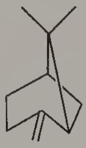
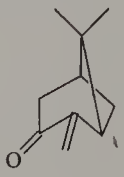
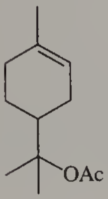
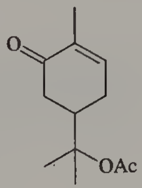
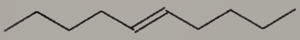
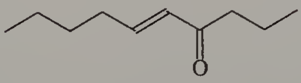
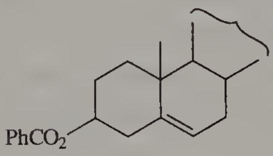
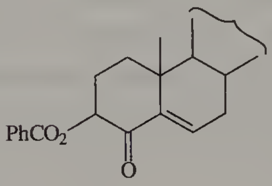
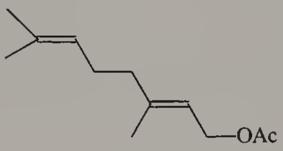
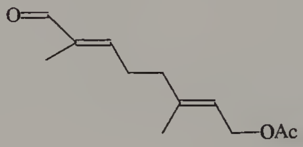
Allylic ketones from alkenes [6]

$$RCH{=}CHCH_2R \xrightarrow[(2\text{-pySe})_2]{PhIO_2} RCH{=}CHCOR$$

Iodylbenzene (708 mg, 3 mmol) and 2,2′-dipyridyl diselenide (31 mg, 0.1 mmol) were added to a solution of the substrate (1 mmol) in benzene (10 ml). The solution was heated to reflux with stirring under nitrogen for 1–8 h. The cooled reaction mixture was filtered on celite and concentrated; the products were isolated by flash

TABLE 11.2

Allylic oxidation using iodylbenzene and 2,2'-dipyridyldiselenide [6]

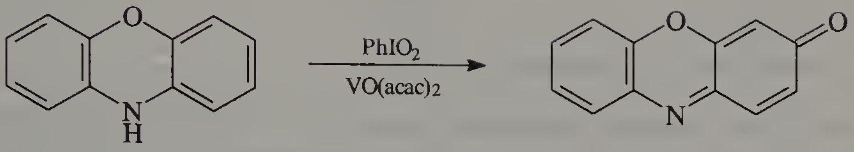
Substrate	Product	Yield (%)
		95
		55
		81
		67
		55

chromatography on silica gel in 55–95% yield. Relevant examples are illustrated in Table 11.2.

11.1.4 Oxygenation of aromatic compounds

Iodylbenzene in hot nitrobenzene effected some oxidations mimicking its isoelectronic ozone. Among them, the most interesting was with pyrene which was converted into a mixture of three isomeric pyrenequinones; this method was advantageous for the preparation of the 4,5-isomer, despite its low yield (14%) [7]. The system iodylbenzene and catalytic amounts of vanadyl acetylacetonide was used for the synthesis of some quinone-imines from phenothiazines and related heterocycles; also *N*-phenyl-phenylsulphonamide was converted into *N*-(phenylsulphonyl)-1,4-benzoquinone-imine.

Phenoxazine-3-one [8]



Phenoxazine (28 mg, 0.25 mmol), iodylbenzene (118 mg, 0.25 mmol) and vanadyl acetylacetonide (13 mg, 0.05 mmol) were refluxed in benzene for 4 h. After concentration, the residue was chromatographed (silica gel, hexane–ethyl acetate, 8:2) to give the title compound (22 mg, 72%), m.p. 214°C.

11.1.5 Nucleophilic aromatic substitution

The iodyl group (IO_2) is a good nucleofugue. Under mild conditions, the conversion of several iodylarenes into benzoic acids was realized in good yields, via carbonylation. Carbon monoxide was used at atmospheric pressure and 40–50°C, in aqueous sodium carbonate, with palladium catalysis [9]:

$$\mathrm{ArIO_2} + \mathrm{CO} \xrightarrow[\substack{\mathrm{Na_2PdCl_4} \\ 55-89\%}]{\text{aq. } \mathrm{Na_2CO_3}} \mathrm{ArCOOH}$$

It should be noted that some nucleophilic aromatic substitutions were performed using 2,4-dinitroiodylbenzene already in 1937 [10].

11.1.6 Miscellaneous

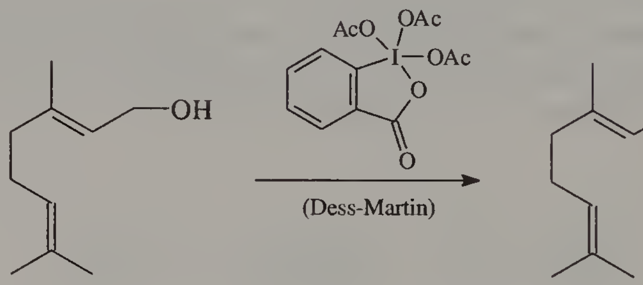
The reactivity of iodylbenzene was increased in the presence of trifluoroacetic acid; for example, $PhSCH_2CH_2NO_2$ was converted into its sulphoxide (97%) at room temperature [11]. 4-t-Butyliodylbenzene in hot chlorobenzene oxidized tetralin to α-tetralone (97%) [12]; it also brought about the opening of the pyrrole ring in a derivative of tryptophan [13].

11.2 REACTIONS WITH DESS–MARTIN REAGENT AND *o*-IODYLBENZOIC ACID

11.2.1 Oxidation of alcohols

A newcomer in the family of oxidants, introduced in 1983, Dess–Martin reagent is presently a well-established oxidant. Its main function is the extremely facile oxidation of primary and secondary alcohols to carbonyl compounds, at room temperature; no further oxidation of aldehydes occurs. The reaction is conveniently carried out in dichloromethane (also, chloroform or acetonitrile) using only 5–10% excess of reagent. Although dry solvents were originally recommended, a systematic study revealed that small amounts of water are beneficial, increasing the oxidation rate as well as the yield [14]. A representative procedure involving a base-sensitive oxidation product illustrates the easiness of experimental work.

Oxidation of geraniol to geranial [15]

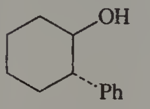
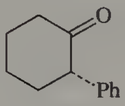
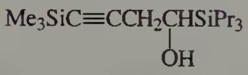
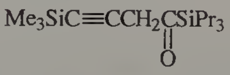
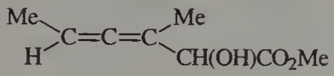
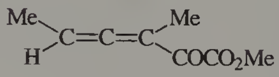


A solution of geraniol (2.67 g, 17.3 mmol) in dichloromethane (14 ml) was added to a stirred solution of Dess–Martin reagent (8.4 g, 19.8 mmol) in the same solvent (52 ml) over 5 min; a spontaneous boil occurred for 5 min. After 20 min the reaction mixture was diluted with ether (100 ml) and poured into a saturated aqueous solution of sodium bicarbonate (100 ml) containing sodium thiosulphate (25 g). The mixture was stirred for 5 min and more ether was added (100 ml); the ether layer was then extracted with saturated sodium bicarbonate solution (100 ml) and water (100 ml) and dried. Concentration followed by Kugelrohr distillation gave geranial (2.22 g, 84%).

In Table 11.3 are collected some examples of oxidation of relatively simple alcohols to illustrate the scope of the reaction. With few exceptions, saturated alcohols are oxidized within 2 h, whereas allylic or benzylic alcohols react within 30 min and some other substrates in only 1–2 min. Hydroxy groups were selectively oxidized in

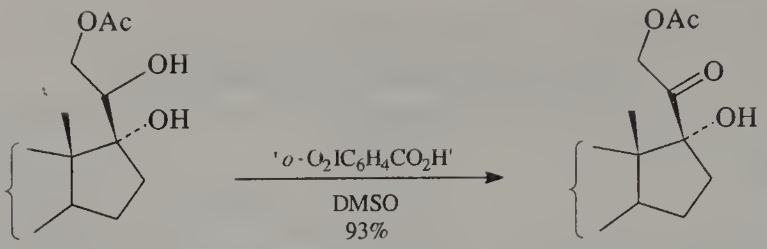
TABLE 11.3

Oxidations of alcohols by Dess–Martin reagent

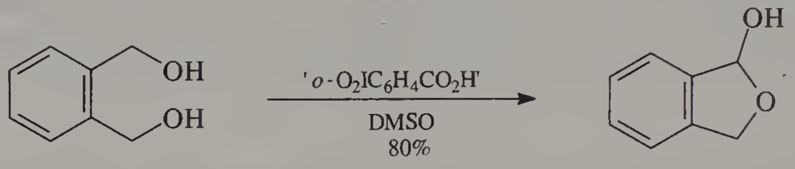
Substrate	Product	Yield (%)	Ref.
1-octanol	octanal	93	[16]
cyclooctanol	cyclooctanone	86	[16]
2,5-dimethoxybenzyl alcohol	2,5-dimethoxybenzaldehyde	94	[16]
$PhSCH_2CH_2OH$	$PhSCH_2CHO$	76	[15]
cholesterol	5-cholesten-3-one	91	[14]
1-(9-anthryl)-2-propanol	9-anthrylacetone	89	[17]
$RCHOHCF_3$	$RCOCF_3$	75–95	[18]
		97	[14]
 $Me_3SiC{\equiv}CCH_2\underset{\displaystyle OH}{\underset{\vert}{C}}HSiPr_3$	 $Me_3SiC{\equiv}CCH_2\underset{\displaystyle O}{\underset{\Vert}{C}}SiPr_3$	72	[19]
		92	[20]
$HC{\equiv}CCH(OH)CMe_2CH_2CH{=}CH_2$	$HC{\equiv}CCOCMe_2CH_2CH{=}CH_2$	84	[21]
O-silyl nucleosides	*O*-silyl 2'- or 3'-ketonucleosides	75–93	[22]

the presence of oxidation-sensitive functionality such as sulphides, enol ethers, furans, etc. Oxidations performed with Dess–Martin reagent are numerous, since it has become the oxidant of choice in many natural product syntheses. In several applications it was the only suitable oxidant for the desired oxidation. Generally, it seems to be superior to chromium(VI) and manganese(IV) oxidants, as well as to Swern and Moffat reagents.

Another useful iodine(V) compound is the cyclic '*o*-iodylbenzoic acid' precursor of Dess–Martin reagent (Section 2.4). This may become a cheaper alternative, despite its potentially explosive nature, since it smoothly oxidized alcohols to carbonyl compounds in high yields under mild conditions, in DMSO. In some cases, such as with γ,δ-unsaturated alcohols it was actually superior to Dess–Martin reagent. However, its main advantage is that it oxidizes 1,2-glycols to α-ketols or α-diketones without cleaving the glycol carbon–carbon bond. Among the several substrates successfully oxidized in this way, an example from the field of steroids is illustrated [23]:



It should be noted that several sensitive groups (amino, heteroaromatic, etc.) were unaffected [24]. The same reagent effected the highly selective oxidation of a number of 1,4-diols to cyclic hemiacetals (γ-lactols), a conversion not previously possible in one step, for example [25]:



A mixture of DMSO and acetone was more convenient and economical for these oxidations, with a simplified isolation procedure and higher yields [26]. Some analogues of Dess–Martin reagent showed distinct advantages for the oxidation of alcohols [15,27]. However, their preparation from simple precursors involved several steps.

11.2.2 Oxidation to 1,2,3-tricarbonyl compounds

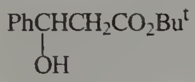
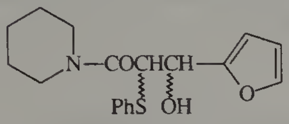
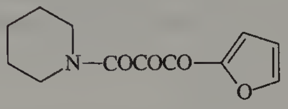
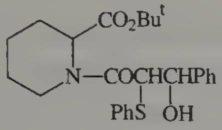
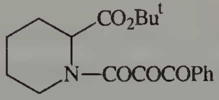
Some multifunctional alcohols were further oxidized by Dess–Martin reagent, for example, the ester $PhCH(OH)CH_2CO_2Bu^t$; although it was converted into the expected $PhCOCH_2CO_2Bu^t$ (86%), with an excess of reagent and some added water the products were either $PhCOCHOHCO_2Bu^t$ (72%) or $PhCOCOCO_2Bu^t$ (80%) [28]. In fact, not only β-hydroxycarbonyl but also α-phenylthio-β-carbonyl and β-dicarbonyl compounds when treated with Dess–Martin reagent and pyridine were transformed to tricarbonyl compounds, obtained as mixtures with their hydrates (Table 11.4).

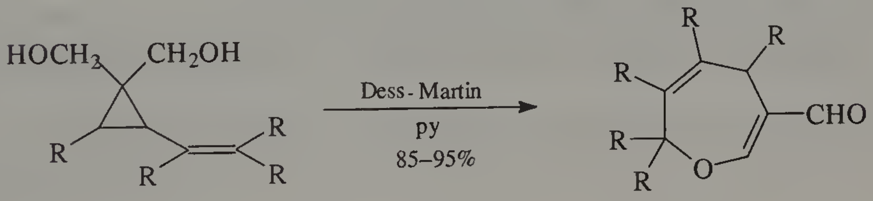
11.2.3 Rearrangements

A number of vinyl cyclopropane diols upon treatment with Dess–Martin reagent and pyridine underwent oxidation accompanied by rearrangement to give formyl dihydro-oxepins [30]:

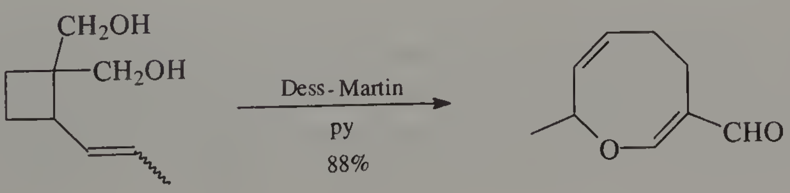
TABLE 11.4

1,2,3-Tricarbonyl compounds by Dess–Martin oxidation of various precursors

Substrate	Product	Yield (%)	Ref.
 $\mathrm{Ph}\underset{\mathrm{OH}}{\mathrm{C}}\mathrm{HCH_2CO_2Bu^t}$	$PhCOCOCO_2Bu^t$	80	[28]
		80	[29]
		62	[29]
$PhCOCH_2COOEt$	$PhCOCOCO_2Et$	80	[28]
$PhCOCH_2COPh$	PhCOCOCOPh	57	[28]
$PhCH(OH)CH_2COOBu^t$	$PhCOCOCOOBu^t$	80	[14]


HOCH2
CH2OH
R
R
R
R
Dess - Martin
py
85–95%
R
R
R
CHO
R
R
O

Similar rearrangement occurred in some related substrates bearing one hydroxymethyl and one cyano or phenylsulphonyl group. Also, a cyclobutane homologue was transformed to a formyl dihydro-oxocin:


CH2OH
CH2OH
Dess - Martin
py
88%
CHO
O

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– 12 –

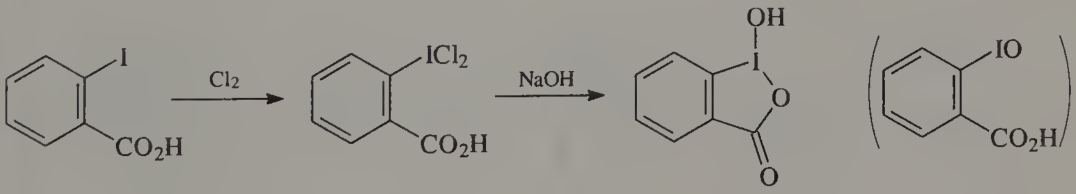
Some Further Reagents of Iodine(III)

This chapter contains assorted hypervalent iodine compounds which have been sporadically used in reactions of synthetic interest. Although they cannot be considered presently as fully fledged reagents, comparable in scope to those appearing in previous chapters, it is possible that in the future they will be further developed. It is hoped that this separate presentation of minor reagents will serve as a source of inspiration for new useful applications.

12.1 *o*-IODOSYLBENZOIC ACID AND ITS DERIVATIVES

o-Iodosylbenzoic acid is actually cyclic in the crystalline state. In some of its alkyl-substituted analogues, cyclic as well as open structure forms have been obtained separately; they are distinct chemical entities and result from the oxidation of the corresponding *o*-iodo-substituted benzoic acids with different oxidants [1].

Iodosylbenzoic acid [2]



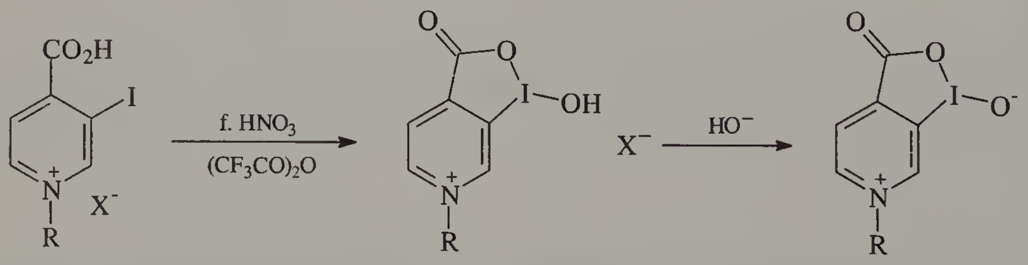
Chlorine was passed into a cold solution of *o*-iodobenzoic acid (15 g, 60 mmol) in chloroform (400 ml) until no more precipitate was formed. The yellow crystalline mass formed (16 g, 82%) was collected and dissolved in aqueous sodium hydroxide; on careful acidification with dilute hydrochloric acid iodosylbenzoic acid precipitated (10 g, 62%) as colourless crystals, m.p. 230–231°C (from water). An alternative improved method involved oxidation of *o*-iodobenzoic acid with acetyl nitrate in acetic anhydride; the *o*-acetyl derivative formed was subsequently hydrolysed to iodosylbenzoic acid (65–70%) [3].

The α-hydoxylation of ketones, accompanied by acetalization, should preferably be performed using *o*-iodosylbenzoic acid rather than DIB (Section 3.2.2). In fact, this type of transformation has reached Organic Syntheses status for acetophenone [4]:

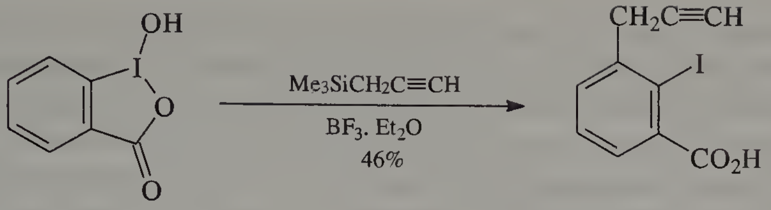
$$\mathrm{PhCOMe} \xrightarrow[\substack{\mathrm{MeOH\,/\,KOH} \\ 65\%}]{o\text{-}\mathrm{OIC_6H_4CO_2H}} \mathrm{PhC(OMe)_2CH_2OH}$$

The procedure was applied to several enolizable ketones with yields slightly better than those obtained with DIB. However, the main advantage of *o*-iodosylbenzoic acid is that its use avoids chromatographic separation; the solubility of the *o*-iodobenzoic acid produced in alkali allows the isolation of the hydroxy dimethylacetals by direct extraction. For large-scale preparations the acid may be recycled.

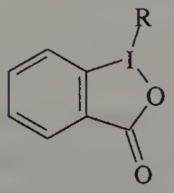
Whereas α,*β*-unsaturated ketones afforded with DIB α-hydroxy-*β*-methoxy dimethylacetal derivatives (Section 3.2.2), some steroidal ketones of this kind showed a deviation when treated with *o*-iodosylbenzoic acid; for example, 4-androstene-3,17-dione gave a mixture of two methoxy derivatives and a diene [5]. Several sulphides were oxidized efficiently to sulphoxides by *o*-iodosylbenzoic acid in acetic acid–sulphuric acid, at room temperature [3]. *o*-Iodosylbenzoic acid is an excellent reagent for the rapid, catalytic cleavage of reactive esters, especially phosphates, some of which are in stock in big quantities for use as potential nerve gases. This kind of reactivity has drawn considerable attention, and several analogues of the parent acid showed better catalytic activity; among them, a series of structurally interesting pyridinium 1,5-zwitterions should be mentioned [6]:



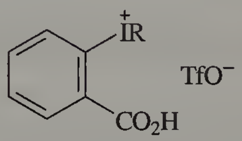
The reaction of *o*-iodosylbenzoic acid with 1-(trimethylsilyl)-2-propyne led to a reductive iodonio-Claisen rearrangement (Section 3.8.3), permitting the preparation of 2-iodo-3-prop-2-ynylbenzoic acid [7]:



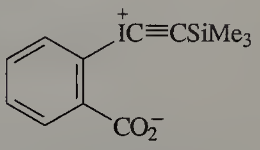
Another silylated alkyne unexpectedly afforded an alkynyl peroxy derivative of *o*-iodosylbenzoic acid [8]. Generally, several cyclic and non-cyclic derivatives of the acid are known, some of which are shown below:



R=Ph [9], RC≡C[10], MeO [2], Bu^tOO [11], N_3[12], $O_2P(OPh)_2$[13]



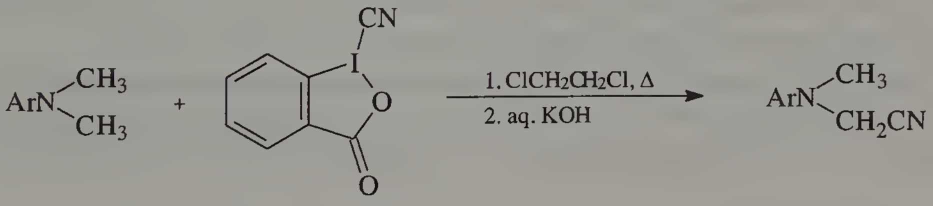
R=CN [14], N_3 [12], RC≡C [15]



[16]

These compounds are expected to exhibit interesting reactivity. For example, 1-cyanobenziodoxole constitutes an excellent reagent for the transfer of the cyano group toward *N,N*-dimethylanilines.

Cyanation of N,N-*dimethylanilines* [14]



A stirred mixture of cyanobenziodoxole (225 mg, 0.824 mmol) in dry 1,2-dichloroethane (20 ml) was treated with *N,N*-dimethylaniline (0.824 mmol) under nitrogen. After 1 h reflux, the reaction mixture was washed with aqueous potassium hydroxide (0.5 M, 2 × 20 ml) and water (20 ml), dried and evaporated to give N-cyanomethyl-N-methylanilines as oils, in 80–96% yield.

An analogous reagent with an azido instead of a cyano group was generated *in situ* and used for the azidation of polycyclic hydrocarbons such as adamantane and norbornane; catalysis by benzoyl peroxide was necessary, in refluxing chlorobenzene [17].

Another cyclic derivative, 1-t-butylperoxy-benziodoxole, was easily prepared and stable; it showed good oxidizing properties, for example, it oxidized diphenylsulphide to its sulphoxide (84%) at room temperature (other reagents failed to react under these conditions) and it dehydrogenated 1,2,3,4-tetrahydroisoquinoline to 3,4-dihydroisoquinoline (83%) [11].

12.2 REAGENTS WITH IODINE–OXYGEN BONDS

12.2.1 [Hydroxy(phosphoryloxy)iodo]benzenes

The above collective name refers to compounds of the general formula $PhI(OH)[(O_2P(OR)_2]$ where R is an alkyl, benzyl or phenyl group. Their preparation is very easy; for example, DIB is simply stirred with diphenyl phosphate in acetonitrile, or HTI reacts with sodium diethyl phosphate in methanol to give the corresponding phosphoryloxy compounds, in high yields [18,19].

Ketones and terminal alkynes have been converted into ketol phosphates on treatment with these reagents.

[Bis(phenyloxy)phosphoryloxy]acetone [18]

$$CH_3COCH_3 + PhI(OH)[O_2P(OPh)_2] \longrightarrow CH_3COCH_2O_2P(OPh)_2$$

To a solution of acetone (10 ml) and acetonitrile (40 ml) the iodine reagent (2.4 g, 5.04 mmol) was added. The mixture was heated under reflux for 30 min. After removal of volatiles the residual oil was taken in dichloromethane, washed successively with water, 5% sodium bicarbonate and water, dried and concentrated to give [bis(phenyloxy)phosphoryloxy]acetone (1.3 g, 81%) as an oil.

The same reagent with terminal alkynes also afforded α-ketol phosphates [20], or alkynyl dialkyl phosphates (see Section 9.4.3) [19], depending on the conditions. 4-Pentenoic acids underwent phosphoryloxylactonization [18].

12.2.2 Oxygen-bridged reagents

In addition to the oxygen-bridged compound derived from BTI (Section 4.6.2), several related analogues are known (μ-compounds), some of which have found synthetic applications. These are of the general formula PhI(X)OI(X)Ph where X is TfO, ClO_4, BF_4, PF_6 and AsF_6, of ionic rather than covalent character; they may be written in short as $(PhI^+)_2O\ 2X^-$. The bis triflate (Zefirov's reagent, Section 2.3) is relatively stable; however, when left in solution for a few hours it isomerizes to a derivative of 1,4-diiodobenzene [21}. Its use provides a mild procedure for the conversion of alkenes into vicinal triflates. The high reactivity of this reagent, which was also used *in situ*, was applied to selective activation of thioglycosides (Section 5.4.1).

1,2-Bis-trifyloxyethane [22]

$$(PhI^+)_2O\ 2TfO^- + CH_2{=}CH_2 \longrightarrow TfOCH_2CH_2OTf$$

In a flame-dried 30 ml standard reaction bulb were placed the iodine reagent (227 mg, 0.31 mmol) and dichloromethane (8 ml). After degassing on a vacuum line, ethylene (9 mg, 0.31 mmol) was condensed into the bulb and stirred at room temperature for 64 h. The reaction mixture then became homogeneous and after another 24 h it grew cloudy as a white precipitate formed. The solution was concentrated to about 3 ml and filtered through a plug of silver-impregnated silica. The solvent was removed completely to yield 1,2-bis-trifyloxyethane (71 mg, 71%) as an oil.

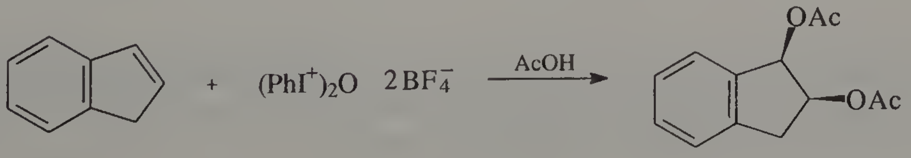
The reaction with cyclohexene was highly stereoselective, since 99% *syn* addition was observed. By contrast, the propargyl ether $MeC{\equiv}2OCH_2SiMe_3$ gave a *trans*-vinyl iodonium salt [23].

Alkenes such as cyclohexene and indene reacted with $(PhI^+)_2O\ 2BF_4^-$ and its analogues in the presence of external nucleophiles (methanol, acetic acid, lithium perchlorate) to afford products of vicinal addition, either *cis* or mixtures of *cis,trans*.

a. *μ-Oxo-bis phenyliodine tetrafluoroborate* [24]

b. *cis-1,2-Diacetoxyindan* [24]

$$2\,PhI(OAc)_2 + 2\,HBF_4 \longrightarrow (PhI^+)_2O\ \ 2BF_4^-$$



a. To a stirred solution of (diacetoxyiodo)benzene (3.22 g, 10 mmol) in chloroform (5 ml) was added tetrafluoroboric acid (2 ml of 48% aqueous solution, 12 mmol), at room temperature. The resulting solution was evaporated *in vacuo* for 30 min at 50°C to give an oil, which was crystallized by addition of chloroform (10 ml) and water (2 ml). The yellow crystals formed were filtered, washed with chloroform (30 ml) and water (30 ml) and dried over P_4O_{10} *in vacuo* to yield the μ-reagent (2.1 g, 70%). HAZARD: Although a melting point of 130–140°C has been reported, an explosion of this compound occurred at room temperature [25].

b. The iodine reagent (300 mg, 0.5 mmol) was added to a stirred solution of indene (120 mg, 1 mmol) in acetic acid (3 ml), at room temperature. Stirring was continued for 30 min, until the disappearance of the yellow colour. The reaction mixture was diluted with water (15 ml) and extracted with dichloromethane. The extract was dried and concentrated to an oil. This was purified by column chromatography on silica gel (ethyl acetate–hexane, 1:2) to give *cis*-1,2-diacetoxyindan (200 mg, 85%), m.p. not given.

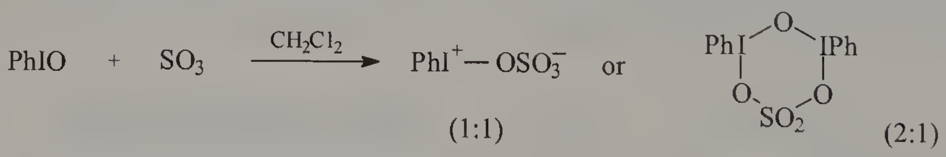
This reaction of cyclohexene with $(PhI^+)_2O\ 2BF_4^-$ and lithium perchlorate gave exclusively the *cis*-bis-perchlorate adduct (92%). Also, silyl enol ethers underwent efficient oxidative coupling to 1,4-diketones [24]:

$$2\ ArC(OSiMe_3){=}CH_2 \xrightarrow[80\text{–}94\%]{(PhI^+)_2O\ \ 2BF_4^-} ArCOCH_2CH_2COAr$$

The same reagent was used as a deprotective agent of silylated [4] radialene [26].

12.2.3 Adducts of iodosylbenzene with sulphur trioxide

The reaction of iodosylbenzene with sulphur trioxide at −50°C leads to the formation of two isolable very hygroscopic compounds, depending on the stoichiometry of the reactants [27]:



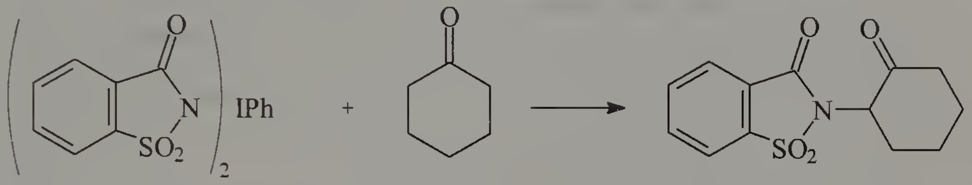
Both readily entered into reaction with ethylene, 1-hexene and methyl methacrylate to afford cyclic 1,2-sulphates in 50–85% yield; with norbornadiene a mixture of adducts were formed, depending on the conditions.

12.3 REAGENTS WITH IODINE–NITROGEN BONDS

12.3.1 [Bis(saccharinyl)iodo]benzene

This compound was obtained from BTI and sodium saccharinate. It belongs to a category of iodobenzene derivatives in which two imidyl groups are attached to iodine through nitrogen; its main utility was the transfer of a saccharinyl group to the α-position of enolizable ketones.

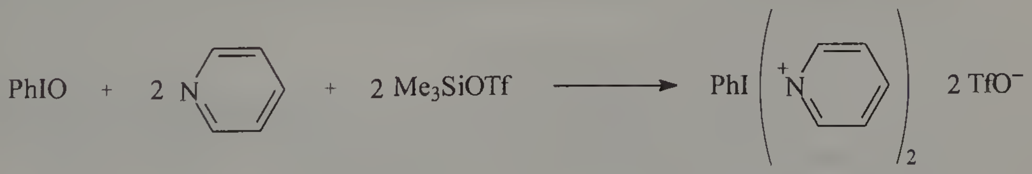
2-Saccharinyl cyclohexanone [28]



A suspension of the iodine reagent (0.4 g, 0.7 mmol) in an excess of cyclohexanone (2 ml) was heated at 65°C for 5 h. The clear reaction mixture, without concentration, was passed through a silica gel column, using cyclohexanone as eluant, to afford 2-saccharinyl cyclohexanone (105 mg, 51%), m.p. 195–197°C.

12.3.2 [Bis(pyridinio)iodo]benzene triflate

When DIB or iodosylbenzene were treated with pyridine and trimethylsilyl triflate under strictly anhydrous conditions, at room temperature, the title compound precipitated almost quantitatively. Similar compounds were formed using substituted pyridines, quinoline and *N*-methyl-imidazole [29]:



[Bis(pyridinio)iodo]benzene triflate is a potent oxidant, as corroborated from polarographic measurements; indeed, its $E_{1/2}$ value, +0.34 V, exceeds enormously that of DIB which has only −1.0 V. For example, it converted hydrazones into diazo compounds and 1,2-bis hydrazones into alkynes, in good to excellent yields;

also, electron-deficient hydroquinones, including 2,3-dichloro-5,6-dicyano-1,4-hydroquinone were oxidized to quinones. Its superiority was shown in another case (see Section 3.8.1). Generally, it is expected that it will effect difficult oxidations.

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This book describes the fascinating chemistry of the many kinds of organic compounds of hypervalent iodine. Each chapter deals with a particular iodine compound or families of compounds which have been used as reagents in a plethora of useful transformations. These include assorted oxidation, such as with the precious Dess-Martin reagent, as well as a wide range of further reactions.

Prominent features of hypervalent iodine reagents derived from iodobenzene are: ready availability, operational simplicity, mild reaction conditions and high efficiency. They are environmentally safe and can be recycled. New species may be easily prepared by introducing substituents in the benzene ring or changing the ligand attached to iodine. Their combination with other reagents broadens considerably their synthetic potential. Today, no synthetic chemist can afford to ignore the valuable hypervalent iodine reagents.

Anastasios Varvoglis obtained his Ph.D. from Cambridge University, UK. He has been Professor of Organic Chemistry at the University of Thessaloniki, Greece since 1974. He has had several articles published in the field of hypervalent iodine.

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