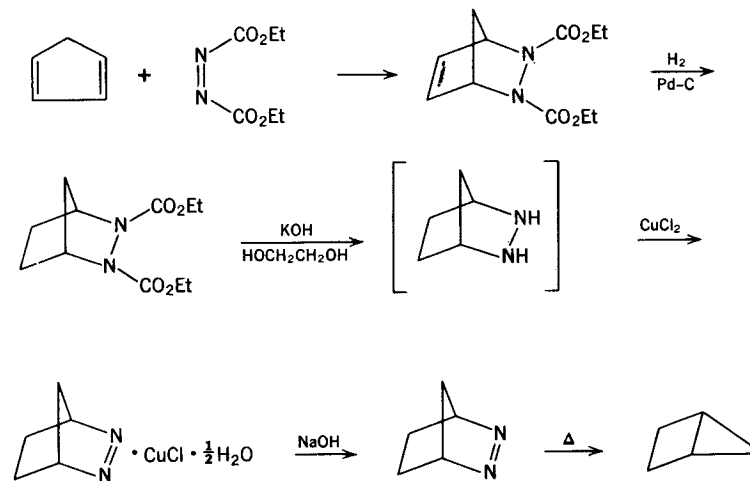


BICYCLO[2.1.0]PENTANE



Submitted by P. G. GASSMAN and K. T. MANSFIELD¹
 Checked by G. N. TAYLOR and K. B. WIBERG

1. Procedure

A. *Diethyl 2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate*.
 In a 1-l., three-necked, round-bottomed flask equipped with a constant-pressure dropping funnel, a mechanical stirrer, and a reflux condenser is placed 174 g. (1.0 mole) of ethyl azodicarboxylate² in 150 ml. of ether. Freshly prepared cyclopentadiene³ (70 g., 1.06 moles) is added dropwise over a 1-hour period to the stirred ethereal solution of diethyl azodicarboxylate. During the addition a gentle reflux is maintained by external cooling with an ice-water bath as needed. When the addition is complete, the reaction mixture is allowed to stand for 4 hours, or less if the yellow color of the azodicarboxylic acid ester disappears. The dropping funnel and condenser are replaced by a glass stopper and a short distillation head, respectively. The ether and unreacted diene are distilled off on a steam bath and the

residue is transferred to a 500-ml. round-bottomed boiling flask equipped with a 30-cm. Vigreux column. After a small forerun the diethyl 2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate distills to give 218–228 g. (91–95%) of a colorless or very pale yellow, viscous liquid, b.p. 119–120° (0.4 mm.).

B. Diethyl 2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate. A mixture of 112 g. (0.47 mole) of diethyl 2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate and 125 ml. of absolute ethanol is placed in a standard Paar bottle along with 0.2 g. of 5% palladium on carbon catalyst (Note 1). The bottle is attached to the Paar hydrogenation apparatus, and shaking is begun using an initial pressure of 60 p.s.i. After 2 hours, hydrogen uptake ceases. The mixture is gravity-filtered twice and the ethanol is removed using a rotary evaporator. The entire procedure is repeated on a second batch and the crude product from the combined runs is placed in a 500-ml. round-bottomed boiling flask fitted with a 15-cm. Vigreux column. Fractional distillation gives 218–223 g. (95–97%) of diethyl 2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate, b.p. 107–108° (0.05 mm.), $n_D^{22} = 1.4730$.

C. 2,3-Diazabicyclo[2.2.1]hept-2-ene. A slow stream of nitrogen is bubbled through 1.2 l. of ethylene glycol (Note 2) for 20 minutes in a mechanically stirred 2-l. three-necked flask with mild heating (Note 3). The gas inlet tube is replaced with a condenser and a thermometer which reaches below the level of the ethylene glycol, and 275 g. (4.2 moles) of reagent grade potassium hydroxide pellets (85% pure) is added in four portions. A constant-pressure dropping funnel containing 223 g. (0.92 moles) of diethyl 2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate is connected and the reaction vessel is flushed with nitrogen. The ethylene glycol solution is heated to 125° and the diethyl 2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate is added as rapidly as is permitted by its viscous nature. The heating source is removed whenever the reaction temperature approaches 130°. After the addition is complete, the reaction mixture is stirred at 125° for 1 hour. The reaction mixture is allowed to cool and then poured *slowly* into a 4-l. beaker which contains 1 kg. each of ice and water and 450 ml. of concentrated hydrochloric acid (*Caution. Vigorous foaming occurs*) (Note 4).

When the acidification is complete, the reaction mixture is warmed to about 40° and neutralized with 5*N* ammonium hydroxide. Half of this neutral solution is transferred to a second 4-l. beaker and subsequent operations are carried out on both batches.

The solution is stirred slowly and *ca.* 25 ml. of 2*N* cupric chloride solution is added slowly. The blue-green color of the cupric chloride is rapidly discharged and a brick red coloration occurs, followed by the precipitation of voluminous bright red crystals of the cuprous chelate of 2,3-diazabicyclo[2.2.1]hept-2-ene. The pH is adjusted to 5–6 by the addition of 5*N* ammonium hydroxide. Addition of 25 ml. of the cupric chloride solution followed by neutralization of the generated hydrochloric acid with 5*N* ammonium hydroxide is repeated five times. The precipitate is collected by filtration and the filtrate is again treated with 25-ml. portions of cupric chloride solution and 5*N* ammonium hydroxide. The procedure is repeated until the filtrate is clear red at pH 3–4 and returns to a cloudy green at pH 6 with no further formation of precipitate (Note 5).

The combined precipitate from the two batches is carefully washed with 500 ml. of 20% ammonium chloride solution, two 400-ml. portions of 95% ethanol, and two 300-ml. portions of cold water. The product is sucked as dry as possible in the suction funnel.

The damp product is broken up and transferred to a 1-l. flask containing a magnetic stirring bar and 400 ml. of water. A cold solution of 60 g. of sodium hydroxide in 100 ml. of water is added slowly with magnetic stirring. The stirred yellow-orange suspension is then continuously extracted with 700 ml. of pentane for 48 hours.

The pentane extract is dried over 10 g. of anhydrous potassium carbonate. After removal of the drying agent by filtration, the pentane is slowly removed from the product by distillation through a 20-cm. Hempel column packed with glass helices (Note 6). When the pentane is removed, a white crystalline residue remains which weighs 78–83 g. (88–94% yield based on the hydrogenated Diels-Alder adduct). This 2,3-diazabicyclo[2.2.1]hept-2-ene melts at 98.0–99.5° (Note 7).

D. *Bicyclo[2.1.0]pentane*. Finely powdered 2,3-diazabicyclo[2.2.1]hept-2-ene (83 g., crude product from above) is placed in a 500-ml., one-necked, round-bottomed flask. The flask is heated at 130–140° in a oil bath to completely remove any traces of pentane. A 25-cm. unpacked Hempel column is installed and connected directly to a 100-ml. receiver flask having a side arm to which is attached a drying tube packed with silica gel. The receiver is cooled in a dry ice-acetone bath. The azobicyclic is pyrolyzed by heating the oil bath to 180–195°. At the preferred rate of pyrolysis, the starting material condenses about one fourth of the way up the column. Occasional flaming of the column may be necessary to prevent plugging of the column by the solidifying starting material. At the end of the pyrolysis (8 hours) only a small, black, nonvolatile residue remains. The condensed bicyclo[2.1.0]pentane is allowed to warm to room temperature, dried over anhydrous magnesium sulfate, and the drying agent removed by filtration through glass wool into a 100-ml. distillation flask. (Caution! *Bicyclo[2.1.0]pentane is a very volatile hydrocarbon and requires appropriate handling for high yields.*) Distillation leaves a residue of about 1 g. of the starting azobicyclic and affords 53.5–55.5 g. (90.0–93.5%) of bicyclo[2.1.0]pentane, b.p. 45.5°, n_D^{20} 1.4220 (Note 8).

2. Notes

1. The submitters effected the hydrogenation using a medium-capacity, rocker-type, high-pressure hydrogenator with an initial hydrogen pressure of 700 p.s.i. By employing these conditions, the reaction time is reduced to 20–30 minutes. The yield is unchanged.

2. Technical grade ethylene glycol such as that sold by Union Carbide Corp. is suitable for this purpose.

3. A large oil bath supported by a laboratory jack is used for this and subsequent operations when rapid removal of the heat source might be necessary.

4. Foaming may easily be controlled even with rapid addition of the basic solution by vigorous stirring employing the mechanical stirrer used during the reaction.

5. The precipitation of copper oxides in slightly alkaline solution should not be confused with the formation of the bright red crystals of the organocuprous complex.

Recrystallization of the crude copper complex from boiling 20% ammonium chloride (pH 4) affords lustrous brick red needles. Analytically pure material is obtained on a second recrystallization from 0.001*N* hydrochloric acid followed by drying over phosphorous pentoxide.

6. If the supersaturated pentane solution tends to foam toward the end of the distillation, the pot should be allowed to cool. This causes the product to crystallize. Once the crystals start to form, foaming is no longer a problem.

7. This material may be further purified (m.p. 99.5–100.0°) by recrystallization from pentane or methanol, or by sublimation at 85° (60 mm.). Owing to the unusually high vapor pressure of this product, large losses may be encountered on recrystallization or sublimation unless due care is exercised.

8. If all the pentane is removed before pyrolysis, the bicyclo[2.1.0]pentane shows no impurities on vapor phase chromatography with a 20% Dow 710 on 50/60 U Anaprep column. Analysis by n.m.r. also revealed the absence of any traces of cyclopentene in the spectrum consisting of three complex multiplets at 0.3–0.8, 1.1–1.7, and 1.9–2.4 p.p.m. (downfield from internal tetramethylsilane reference).

3. Discussion

The procedure described is a modification of that developed by Diels⁴ and Criegee.⁵ Bicyclo[2.1.0]pentane has been prepared by the pyrolysis of 2,3-diazabicyclo[2.2.1]hept-2-ene,^{5,6} the photolysis of 2,3-diazabicyclo[2.2.1]hept-2-ene,⁷ the pyrolysis of *N*-phenyl-2-oxo-3-azabicyclo[2.2.1]heptane,⁸ and the addition of methylene to cyclobutene.⁹

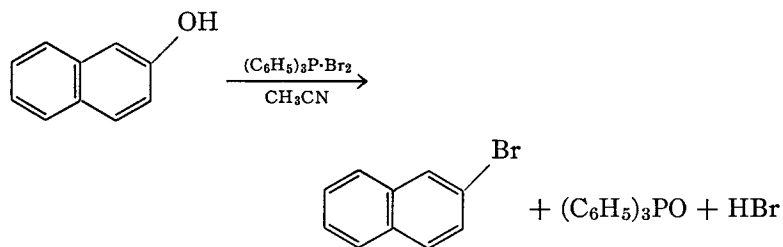
The procedure described is suitable for the preparation of bicyclo[2.1.0]pentane on a large scale. The product is obtained free of impurities and the general method is relatively safe. The starting materials are readily available. The hydrolysis of the diester is very reproducible, a feature that was not true of the literature

procedure.⁴ The pyrolysis step is much simpler and cleaner than the published description.⁵ In addition, the procedure described gives a general method of hydrazo oxidation and for the pyrolysis of azo compounds.

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2-BROMONAPHTHALENE

(Naphthalene, 2-bromo-)



Submitted by J. P. SCHAEFER, JERRY HIGGINS, and P. K. SHENOY¹
 Checked by JAMES P. NELSON, WAYLAND E. NOLAND,
 and WILLIAM E. PARHAM

1. Procedure

A 500 ml., three-necked, round-bottomed flask is equipped with a Trubore stirrer, a pressure-compensating dropping funnel, and a reflux condenser with drying tube. The flask is charged with 144 g. of triphenylphosphine (0.55 mole) (Note 1) and 125

ml. of acetonitrile (Notes 2 and 3). The solution is stirred and cooled in an ice bath and 88 g. of bromine is added dropwise over a period of 20–30 minutes (Note 4). After the addition of the bromine (Note 5) is complete, the ice bath is removed and 72 g. (0.50 mole) of β -naphthol (Note 6) in 100 ml. of acetonitrile (Note 7) is added in one portion and the reaction mixture is heated to 60–70° for at least 30 minutes (Note 8). The flask is now fitted for a simple distillation, stirring is discontinued, and the acetonitrile is distilled (Note 9) under aspirator pressure until the oil bath temperature reaches 110° (Note 10). After all the acetonitrile has been removed, the condenser is replaced by a short, large glass tube (Note 11) connected to a 500-ml. flask half-filled with water, and the oil bath is replaced by a Wood's metal bath. The bath temperature is now raised to 200–220° and kept at this temperature until all the solid has melted (Note 12). The mixture is stirred and the bath temperature is raised to 340° (Note 13) and held at this temperature until evolution of hydrogen bromide ceases (approximately 20–30 minutes). The Wood's metal bath is removed and the reaction mixture is cooled to approximately 100° and then poured into a 1-l. beaker and cooled to room temperature. Pentane (300 ml.) (Note 14) is added and the solid is broken into a fine precipitate (Note 15). The solid is filtered by suction and washed thoroughly with two 300-ml. portions of pentane. The pentane filtrates are combined, washed with 200 ml. of 20% sodium hydroxide, and dried over anhydrous magnesium sulfate. The pentane extract is then passed through a 25 mm. diameter column filled to 35 cm. in depth with alumina; distillation of the pentane at reduced pressure gives 72–81 g. (70–78%) (Note 16) of 2-bromonaphthalene, a white solid melting at 45–50° (reported:² 55–56.4°) (Notes 17, 18).

2. Notes

1. Triphenylphosphine was obtained from M and T Chemicals Inc. and was used without further purification.
2. The acetonitrile was *cautiously* distilled from phosphorus pentoxide. The solid phosphorus pentoxide may cause bumping

during the distillation of the acetonitrile. This can be avoided if the solution is stirred during the distillation.

3. The triphenylphosphine is only partially dissolved.

4. The temperature is kept below 40° and the reaction mixture thoroughly stirred during this addition.

5. If a small amount of free bromine remains, as evidenced by color, then a sufficient amount of triphenylphosphine is added to take up the bromine.

6. Practical grade β -naphthol was obtained from Matheson Coleman and Bell and distilled at atmospheric pressure before use.

7. Warming the acetonitrile is necessary to dissolve the β -naphthol.

8. All the precipitate dissolves at this point. The checkers heated the mixture for 2 hours. The solids appeared to dissolve; then there was some reprecipitation. All solids had not dissolved after 2 hours at 70°.

9. The checkers encountered severe bumping during distillation of the acetonitrile. The acetonitrile may be removed with only moderate bumping if no external heat is applied.

10. The checkers did not remove all the acetonitrile at 110°, a factor which contributed to foaming later (Note 12).

11. If a tube smaller than $\frac{1}{2}$ inch in diameter is used, it may become plugged later in the reaction.

12. If temperature is higher than 220°, initial foaming may become troublesome. The checkers heated the solid to 240–270°, since melting did not occur at 200–220°; foaming was encountered.

13. Evolution of hydrogen bromide begins at about 280°.

14. The checkers used petroleum ether (b.p. 65–67°).

15. The checkers obtained a somewhat tarry precipitate.

16. The submitters obtained 85–87 g. (82–86% yield).

17. The checkers' product retained solvent. The product was heated for a short period at 120° (20 mm.) and a crystalline solid, free of solvent, was obtained.

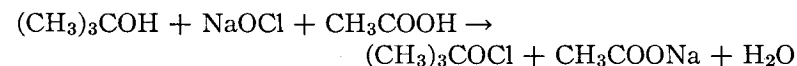
18. Purity was checked by analytical vapor phase chromatography (98–99%). This product can be used for most reactions without further purification. If further purification is desired, 2-bromonaphthalene can be recrystallized from aqueous methanol (95% recovery) to give a product melting at 53–55°.

3. Discussion

2-Bromonaphthalene has been prepared from 2-aminonaphthalene by the reaction of mercuric bromide with the diazonaphthalene.^{2, 3} The reaction described in this preparation appears to be fairly general and provides a useful alternative method for introducing bromine into the aromatic nucleus. Using conditions similar to those outlined, the following have been prepared from the corresponding aryl alcohols:^{4, 5} α -bromonaphthalene (72%), 3-bromopyridine (76%), 2-bromopyridine (61%), 8-bromoquinoline (48%), *o*-bromotoluene (72%), *p*-chlorobromobenzene (90%), *p*-nitrobromobenzene (60%), and *p*-methoxybromobenzene (59%). The use of the triphenylphosphine-halogen complex to convert alcohols to alkylhalides is described elsewhere in this series.⁶

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t-BUTYL HYPOCHLORITE



Submitted by M. J. MINTZ¹ and C. WALLING²
 Checked by LOIS A. ABLIN and HENRY E. BAUMGARTEN

1. Procedure

Caution! This preparation should be carried out in a hood to avoid exposure to the hypochlorite produced. To avoid vigorous decomposition the product should be handled only in dim light and should not be heated above its boiling point or be exposed to rubber.

In a 1-l. Erlenmeyer or round-bottomed flask equipped with a mechanical stirrer is placed 500 ml. of a commercial household

bleach solution (Note 1). The flask is placed in a pail of ice and rapidly stirred until the temperature drops below 10°. At this point the lights in the vicinity of the apparatus should be turned off (Note 2). A solution of *t*-butyl alcohol (37 ml., 0.39 mole) and glacial acetic acid (24.5 ml., 0.43 mole) (Note 3) is added in a single portion to the rapidly stirred bleach solution, and stirring is continued for about 3 minutes (Note 4).

The entire reaction mixture is poured into a 1-l. separatory funnel. The lower aqueous layer (Note 5) is discarded, and the oily yellow organic layer is washed first with a 50-ml. portion of 10% aqueous sodium carbonate and then with 50 ml. of water. The product is dried over 1 g. of calcium chloride and filtered. The yield of *t*-butyl hypochlorite, 99–100% pure, is 29.6–34 g. (70–80%) (Notes 1, 6). The product can be stored conveniently in a freezer or refrigerator over calcium chloride in amber glass bottles (Note 7).

2. Notes

1. Both the submitters and checkers used the commercial household bleach solution, Clorox (Proctor and Gamble Co.). This solution is stated to be 5.25% sodium hypochlorite (NaOCl). The submitters found it to be 0.75–0.80*M* by iodometric titration for total oxidant (assumed to be NaOCl). Thus 500 ml. of this solution would contain 0.375–0.400 mole of NaOCl. The checkers found that as little as 440 ml. of fresh Purex (Purex Corp., Ltd., stated to be 6% sodium hypochlorite) gave the stated yield. However, samples from different bottles from one case of "Purex" gave consistently lower yields, 57–70%. Probably the lower yield was due to a lowering of the hypochlorite concentration on standing. The submitters and checkers recommend either discarding bleach solution over 6 months old or checking the titer before use. Presumably other household bleaches will give comparable results with possible small variations in yield.

2. Whereas the inorganic hypochlorite is rather stable to photodecomposition, *t*-butyl hypochlorite is much more readily decomposed. It is not necessary to work in a totally darkened room,

but the incidence of strong light should be avoided—both for reasons of safety and to ensure that hypochlorite of high purity will be isolated.

3. The *t*-butyl alcohol was a commercial product obtained from Matheson Coleman and Bell, and the glacial acetic acid a commercial product obtained from Union Carbide.

4. The submitters have carried out runs using up to 4 l. of the commercial bleach solution (3 moles)—as the largest scale conveniently run in the laboratory—and found no change in the reaction behavior.

5. The checkers observed that the aqueous layer was colorless when Clorox was used and was yellow when Purex was used.

6. The purity of the hypochlorite may be determined by iodometric titration. This titration is run conveniently by weighing out a small portion of the hypochlorite (<0.5 g.) in a 4-ml. vial and then dropping the vial and its contents into an iodine flask containing 20 ml. of glacial acetic acid, 10 ml. of water, and 3 g. of potassium iodide. The titration is then conducted in the usual fashion.

7. The product isolated by this procedure is sufficiently pure for almost any purpose. It was found that distillation did not change the product purity and often led to product of lower purity.

3. Discussion

t-Butyl hypochlorite has been prepared by treatment of an alkaline solution of *t*-butyl alcohol with chlorine,³⁻⁷ and a recent warning^{8, 9} cautions against allowing the temperature to rise above 20° during this reaction. *t*-Butyl hypochlorite has been prepared in solution by shaking a solution of the alcohol in carbon tetrachloride,¹⁰ fluorotrichloromethane (Freon 11), and other solvents¹² with aqueous hypochlorous acid. It has also been prepared by the action of chlorine on an aqueous *t*-butyl alcohol suspension of calcium carbonate,¹³ and by the action of chlorine monoxide on a carbon tetrachloride solution of the alcohol.¹¹

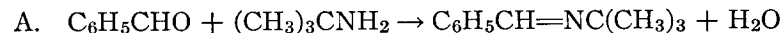
The procedure described here has previously been reported by Mintz¹⁴ and was adapted from work by Geneste and Kergo-

mard,¹⁵ Kergomard,¹⁶ Sumner,¹⁷ and Clark.¹⁸ It eliminates the dangers in working with a compressed gas (chlorine) and the danger from explosion due to poor temperature control during the addition of chlorine.^{3, 8, 9} The availability and low cost of the commercial bleach solution (NaOCl), the simplicity of the equipment needed, the short time involved, and the high purity of the *t*-butyl hypochlorite produced accrue additional merit to this preparation. The submitters have also prepared benzyldimethylcarbinyl hypochlorite, cumyl hypochlorite, and isopropyl hypochlorite by this procedure. The checkers have used essentially the same procedure (with twice as much sodium hypochlorite solution and acetic acid) to prepare N,N-dichloro-*t*-butylamine.

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2-*t*-BUTYL-3-PHENYLOXAZIRANE

(Oxaziridine, 2-*t*-butyl-3-phenyl-)



Submitted by W. D. EMMONS and A. S. PAGANO¹
Checked by G. RYAN and RONALD BRESLOW

1. Procedure

Caution! The preparation and distillation of the oxazirane, like that of any active oxygen compound, should be carried out behind a safety screen.

A. *N-t*-butylbenzaldimine. A 1-l. three-necked flask equipped with stirrer, thermometer, and condenser for downward distillation is charged with 109.5 g. (1.5 moles) of *t*-butylamine (Note 1). Benzaldehyde (106 g., 1.0 mole) is then added in four increments to the stirred solution over a 20-minute period. A mild exotherm is noted which raises the temperature to 40–50°. Benzene (150 ml.) is then added and the solution is heated until distillation commences. Solvent (a mixture of amine, water, and benzene) is removed by distillation until a pot temperature of 110° is reached. The product mixture is then cooled to room temperature, dried over magnesium sulfate, and stripped free of solvent at aspirator pressure. Distillation of the yellow liquid so obtained yields 120–151 g. (78–94%) of colorless *N-t*-butylbenzaldimine, b.p. 59–63° (1 mm.), n_D^{26} 1.5174, n_D^{20} 1.5260 (Note 2).

B. 2-*t*-Butyl-3-phenyloxazirane. A 1-l. three-necked flask equipped with an addition funnel, stirrer, and condenser is charged with 68.0 g. (0.422 mole) of *N-t*-butylbenzaldimine (Note 3) and 50 ml. of benzene. The stirred solution is cooled

in an ice bath and a solution of 61 g. (0.445 mole) of perbenzoic acid in 315 ml. of benzene is added dropwise over a 40-minute period. After one additional hour the stirrer is stopped, and the reaction mixture is allowed to stand overnight with the concurrent melting of the ice bath. The light blue benzene solution is then filtered to remove the precipitated benzoic acid and is washed sequentially with three 100-ml. portions of sodium carbonate, 100 ml. of 5% hydrochloric acid, 100 ml. of saturated sodium bisulfite solution, and finally with 100 ml. of water. The solution is dried over magnesium sulfate, and the solvent is evaporated at room temperature (Note 4) at aspirator pressure. There is obtained 46–60 g. (60–78%) of crude oxazirane, n_D^{26} 1.5065. This product assays 96–98% purity by iodimetric titration (Note 5) and is sufficiently pure for many purposes. Distillation of the crude product through a short Vigreux column yields, after a few drops of forerun, 42–55 g. (56–74%) of pure oxazirane, n_D^{26} 1.5062, n_D^{20} 1.5144, b.p. 55–58° (0.05 mm.), 74–76° (0.2 mm.). Iodimetric assay of this product indicates a purity of 99–100%.

2. Notes

1. Eastman Kodak white label reactants are satisfactory. The benzaldehyde should be freshly distilled before use.

2. The checkers handled and stored this material under nitrogen.

3. The charge of *N-t*-butylbenzalimine is adjusted according to the amount of perbenzoic acid available. The perbenzoic acid in benzene is prepared by the procedure of Silbert, Siegel, and Swern,² and a 5% excess of this reagent is employed in the oxidation. In one attempt with commercial *m*-chloroperbenzoic acid instead, the checkers obtained only a 34% yield of oxazirane.

4. A rotary evaporator is very convenient for this operation.

5. A 0.200–0.300 g. sample of the oxazirane is weighed into a stoppered flask to which is added 15 ml. of glacial acetic acid and 2 ml. of saturated aqueous sodium iodide solution. After 5–10 minutes 25 ml. of deionized water is added, and the liberated iodine is titrated with 0.1*N* sodium thiosulfate with freshly pre-

pared starch as indicator. Each milliliter of thiosulfate solution is equivalent to 0.00885 g. of 2-*t*-butyl-3-phenyloxazirane.

3. Discussion

This procedure is an adaptation of that described by Emmons for the preparation of oxaziranes from imines using peracetic acid.³ Other procedures which may be more useful for oxazirane preparation in specific instances are the oxidation of imines with *m*-chloroperbenzoic acid⁴ and the reaction of aldehydes or ketones with hydroxylamine *O*-sulfonic acid in alkaline solution.⁵ 2-*t*-Butyl-3-phenyloxazirane has also been prepared by photolysis of α -phenyl-*N-t*-butylnitrone⁶ (a general reaction of considerable theoretical interest since it represents direct conversion of electromagnetic energy to chemical energy) and in low yields by ozonolysis of *N-t*-butylbenzalimine.⁷

Oxaziranes are in a real sense active oxygen compounds and exhibit many reactions grossly analogous to those of organic peroxides. Thus they undergo one electron transfer reaction with ferrous salts and on pyrolysis they are converted to amides. Oxaziranes are also useful synthetic intermediates since in appropriate cases they may be isomerized to aromatic nitrones which are a convenient source of *N*-alkylhydroxylamines.³ The reaction of oxaziranes with peracids also provides a source of nitrosoalkanes and is in many instances the method of choice for preparation of these compounds.⁸

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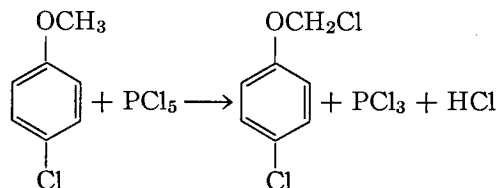
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***p*-CHLOROPHENOXYMETHYL CHLORIDE**(Anisole, *p*- α -dichloro-)Submitted by H. GROSS and W. BÜRGER¹

Checked by J. LONGANBACH and K. B. WIBERG

1. Procedure

This preparation must be carried out in an efficient hood.

A 250-ml. round-bottomed flask with a side arm is equipped with a distillation head and condenser. The receiving flask is attached to the condenser with an adapter, and the exit from the flask goes to a bubble counter containing high-boiling petroleum ether. A thermometer is inserted in the side arm of the distillation flask, and it reaches to the bottom. With exclusion of moisture, 147 g. (0.704 mole) of phosphorus pentachloride and 100 g. (0.704 mole) of *p*-chloroanisole are added to the flask. The flask is heated in an oil bath; the reaction begins when the inside temperature reaches 120° and occurs rapidly at 140°. The temperature is raised to 160° over a period of 2 hours, thereby distilling the phosphorus trichloride (Note 1). After the gas evolution subsides, the reaction mixture is heated to 175° for a short time. About 73–75 g. of phosphorus trichloride is collected.

The residue is distilled through a 30-cm. column packed with glass beads giving 10 g. of a fraction, b.p. 85–105° (10 mm.), containing mainly *p*-chloroanisole, and 85–99 g. (68–80%) of *p*-chlorophenoxyethyl chloride, b. p. 105–108° (10 mm.), $n_D^{25} = 1.5496$, m.p. 28–29° (Notes 2, 3). The n.m.r. spectrum [CCl_4 , $(\text{CH}_3)_4\text{Si}$ reference] had bands at δ 5.6 (s, 2H) and 6.6–7.3 p.p.m.

2. Notes

1. Some phosphorus pentachloride may solidify in the upper part of the condenser. This may be removed by rotating the condenser.

2. The literature values are b.p. 120–124 (18 mm.), m.p. 29–30°.²

3. Gas chromatography analysis using a silicone gum column indicated the product to be 97% pure.

3. Discussion

Aryloxymethyl chlorides may be prepared by the reaction of sodium aryloxymethanesulfonates with phosphorus pentachloride.^{2, 3} The chlorination of anisole does not, as previously reported,⁴ give phenoxyethyl chloride, but rather a mixture of *p*- and *o*-chloroanisoles.⁵ Similarly, anisole and other unsubstituted methyl aryl ethers undergo ring chlorination with phosphorus pentachloride and chlorine,⁶ whereas ring-chlorinated anisoles, such as *p*-chloroanisole, undergo chlorination at the methyl group with chlorine at 190–195° in the presence of a catalytic amount of phosphorus pentachloride.⁶

The present method is simple, proceeds easily and in good yield to give a single product. It is applicable to other cases, such as the preparation of 2,4-dichlorophenoxyethyl chloride (89–92%). The chlorination of *p*-chloroanisole with chlorine and phosphorus pentachloride gives considerable amounts of *p*-chlorophenoxydichloromethane which is difficult to separate from the desired compound by distillation.

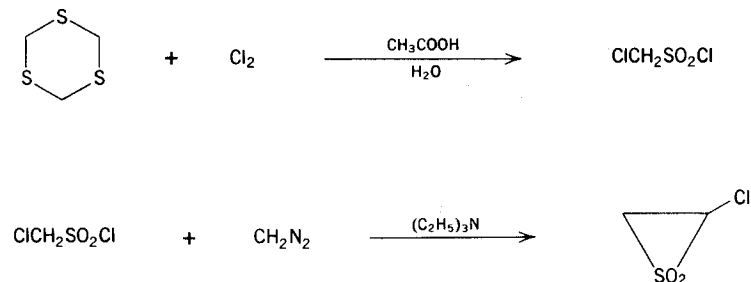
The reaction of chloromethyl aryl ethers with nucleophilic reagents has been described by Barber *et al.*² Thus, by reaction with thiourea, potassium thiocyanate, or sodium cyanide, there are obtained aryloxyalkylisothiuronium salts, aryloxyalkyl thiocyanates, and aryloxyalkylacetonitriles, respectively.² The reaction of chloromethyl aryl ethers with butyllithium leads to an aryloxy carbene which on reaction with olefins gives aryloxy-cyclopropanes.³ The ethers react with triphenylphosphine and a base to give phenoxyethylene ylides which are useful in con-

verting carbonyl compounds to aromatic enol ethers.⁷ The reaction of the chloro ethers with trialkylphosphites gives aryl-oxy-methanephosphonates.⁸ Most of these reactions have been studied with phenoxymethyl chloride and the *p*-methyl derivative; they also proceed well and in good yield with the readily obtainable *p*-chlorophenoxymethyl chloride.⁸

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2-CHLOROTHIIRANE 1,1-DIOXIDE

(Thiirane, 2-chloro-, 1,1-dioxide)



Submitted by LEO A. PAQUETTE and LAWRENCE S. WITTENBROOK¹
 Checked by JOHN J. MILLER and WILLIAM D. EMMONS

1. Procedure

Caution! Because of the toxic nature of chlorine and diazomethane and the lachrymatory properties of chloromethanesulfonyl chloride, both steps of this preparation should be carried out in a well-ventilated hood. Diazomethane is also explosive; follow the directions for its handling given in earlier volumes.^{2, 3}

A. *Chloromethanesulfonyl chloride*. A slurry of 210 g. (1.52 moles) of *s*-trithiane (Note 1) in a mixture of 1 l. of glacial acetic acid and 210 ml. of water is prepared in a 2-l., three-necked, round-bottomed flask equipped with an efficient mechanical stirrer, a thermometer, a coarsely fritted gas inlet tube (Note 2), and an exit tube by which excess fumes are carried to the rear of the hood. The flask is immersed in an ice bath, and the stirrer is started. A stream of chlorine is introduced at such a rate (Note 3) that the temperature of the mixture is maintained between 40° and 50° by the mildly exothermic reaction. After 1–2 hours a yellow solution results. To this solution is added 300 ml. of water, at which point the temperature rises to *ca.* 60°.

Chlorine is again introduced, and the stirred reaction mixture is cooled to maintain the temperature initially in the vicinity of 40°. During 3 hours the temperature slowly returns to that of the surroundings, and the stream of chlorine is stopped. The yellow solution is allowed to stand overnight at room temperature and is then transferred to a 4-l. Erlenmeyer flask and diluted with 1.5 l. of ice water. The flask is stoppered and placed in a refrigerator for 2–3 hours. The aqueous phase is decanted from the denser, organic layer that has separated (Note 4) and is extracted with four 300-ml. portions of methylene chloride. The methylene chloride extracts are combined with the original organic layer, dried over anhydrous magnesium sulfate, filtered, and evaporated on a rotary evaporator at 20–30°. The material that remains is distilled through a 15-cm. Vigreux column. Chloromethanesulfonyl chloride is collected as a colorless, lachrymatory liquid, b.p. 80–81° (25 mm.), *n*_D²⁶ 1.4840–1.4850; yield 135–220 g. (20–32%) (Note 5).

B. *2-Chlorothiirane 1,1-dioxide*. In a 500-ml., three-necked, round-bottomed flask fitted with an efficient mechanical stirrer, a thermometer, and two pressure-equalizing addition funnels is placed an ethereal solution of 4.6 g. (0.11 mole) of diazomethane (Note 6). The system is blanketed with nitrogen, the stirrer is started, and the solution is cooled to –10° with an ice-methanol bath. A solution of 14.9 g. (0.100 mole) of chloromethanesulfonyl chloride in 40 ml. of ether and a solution of 10.0 g. (0.099 mole) of triethylamine in 40 ml. of ether are simultaneously added

dropwise from the two addition funnels. The addition requires about 45 minutes. The insoluble triethylamine hydrochloride is separated by filtration and washed with 25 ml. of cold ether. The combined filtrate and washings are evaporated at reduced pressure below 25° to give white crystalline 2-chlorothiirane 1,1-dioxide, m.p. 49–51° (Note 7); yield 10.0–10.5 g. (80–84%). The product may be further purified by recrystallization from ether-hexane at –70°; m.p. 53–54° (8.9 g. after two recrystallizations) (Notes 8 and 9).

2. Notes

1. *s*-Trithiane obtained from Eastman Organic Chemicals was used without further purification.

2. The gas inlet tube must be sufficiently long to allow the chlorine to enter near the bottom of the flask, and sufficiently coarse to prevent the pores from becoming clogged by the suspended *s*-trithiane. A 6-mm. glass tube with a slightly constricted orifice has been found to be equally satisfactory.

3. The rate of addition of chlorine appears to be important. With rates adequate to maintain the temperature between 40° and 50°, addition times of 1–2 hours are required.

4. This separation is most conveniently achieved by first decanting as much water as possible from the 4-l. Erlenmeyer flask. The remaining mixture is then placed in a 4-l. separatory funnel, and the lower layer is collected. The separatory funnel is then used in the ensuing extractions.

5. The yield is based on the assumption that 3 molecules of chloromethanesulfonyl chloride arise from each molecule of *s*-trithiane. The checkers obtained a yellow product which had to be redistilled to provide material with the reported refractive index.

6. The ethereal diazomethane is prepared by the method of Arndt.⁴ The checkers employed undistilled material as described in Note 3 of the preparation cited.

7. Use of undistilled diazomethane solution gives a less pure product, m.p. 38–42°, which can be recrystallized as described.

8. The characteristic infrared maxima of 2-chlorothiirane

1,1-dioxide (Nujol) occur at 3.24, 7.53, and 8.56 μ . Its n.m.r. spectrum (CDCl₃) shows a doublet of doublets at δ 3.17 (J = 9.5 and 5.5 Hz), a triplet at δ 3.75 (J = 9.5 Hz), and a doublet of doublets at δ 4.85 (J = 9.5 and 5.5 Hz).

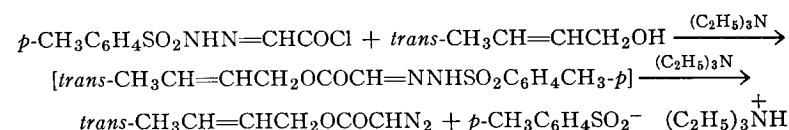
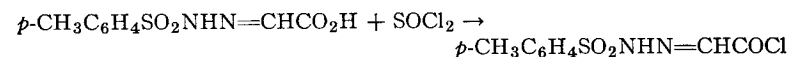
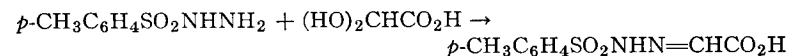
9. A characteristic property of thiirane 1,1-dioxides is the ease with which such molecules fragment into sulfur dioxide and the related olefin on standing for several hours at room temperature. The title compound is no exception; however, the rate of decomposition may be reduced substantially by storage under an inert atmosphere in a freezing compartment (*ca.* –5°). Under such conditions the product may be kept for many months.

3. Discussion

2-Halothiirane 1,1-dioxides are known to be intermediates in the Ramberg-Bäcklund rearrangement of α,α -dihalo sulfones.^{5, 6, 9, 10} These three-membered cyclic sulfones are not isolable from such reactions, however, because they are not stable under the conditions of the rearrangement and they undergo further transformations. The present procedure represents the only means presently available for the preparation of halogen-substituted thiirane dioxides.⁵⁻⁷ The addition of halosulfenes to diazoalkanes is a convenient and general synthesis which may be extended to the preparation of a variety of thiirane 1,1-dioxides with relative ease.⁸

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CROTYL DIAZOACETATE

(Acetic acid, diazo-, *trans*-2-butenyl ester)Submitted by C. JOHN BLANKLEY, FREDERICK J. SAUTER,
and HERBERT O. HOUSE¹

Checked by J. H. HAM and R. E. IRELAND

1. Procedure

A. *Glyoxylic acid p-toluenesulfonylhydrazone*. A solution of 46.3 g. (0.50 mole) of 80% glyoxylic acid (Note 1) in 500 ml. of water is placed in a 1-l. Erlenmeyer flask and warmed on a steam bath to approximately 60°. This solution is then treated with a warm (approximately 60°) solution of 93.1 g. (0.50 mole) of *p*-toluenesulfonylhydrazide (Note 2) in 250 ml. (0.63 mole) of aqueous 2.5*M* hydrochloric acid. The resulting mixture is heated on a steam bath with continuous stirring until all the hydrazone, which initially separates as an oil, has solidified (about 5 minutes is required). After the reaction mixture has been allowed cool to room temperature and then allowed to stand in a refrigerator overnight, the crude *p*-toluenesulfonylhydrazone is collected on a filter, washed with cold water, and allowed to dry for 2 days (Note 3). The crude product (110–116 g., m.p. 145–149° dec.) is dissolved in 400 ml. of boiling ethyl acetate, filtered to remove any insoluble material, and then diluted with 800 ml. of carbon tetrachloride and allowed to cool. After the mixture has been

allowed to stand overnight in a refrigerator, the *p*-toluenesulfonylhydrazone is collected and washed with cold mixture of ethyl acetate and carbon tetrachloride (1:2 by volume). The yield is 92.4–98.5 g. (76–81%) of the hydrazone as white crystals, m.p. 148–154° dec. (Note 4).

B. *The p-toluenesulfonylhydrazone of glyoxylic acid chloride*. *Caution!* Since hydrogen chloride and sulfur dioxide are liberated during this reaction, it should be conducted in a hood. To a suspension of 50.2 g. (0.21 mole) of glyoxylic acid *p*-toluenesulfonylhydrazone in 250 ml. of benzene is added 30 ml. (49 g. or 0.42 mole) of thionyl chloride (Note 5). The reaction mixture is heated under reflux with stirring until vigorous gas evolution has ceased and most of the suspended solid has dissolved (about 1.5–2.5 hours is required, Note 6). The reaction mixture is then cooled immediately (Note 6) and filtered through a Celite mat on a sintered-glass funnel. After the filtrate has been concentrated to dryness under reduced pressure, the residual solid is mixed with 40–50 ml. of anhydrous benzene, warmed, and the solid mass is broken up to give a fine suspension. This suspension is cooled and filtered with suction. The crystalline product is washed quickly with two portions of cold benzene to remove most of the residual colored impurities, and then the remaining crude acid chloride is transferred to a flask for recrystallization.

The combined benzene filtrates from this initial washing procedure are concentrated under reduced pressure, and the washing procedure with benzene is repeated to give a second crop of the crude acid chloride which is transferred to a flask for recrystallization.

For recrystallization each crop of the crude acid chloride is dissolved in a minimum volume of boiling anhydrous benzene (about 100 ml. is required for the first crop) and petroleum ether (b.p. 30–60°; about 50 ml. is required for the first crop) is added to the hot solution. Crystallization begins on cooling. After the mixture has cooled to room temperature, it is allowed to stand overnight at room temperature and the acid chloride is collected on a filter and washed with a small portion of cold benzene. The yield of recrystallized acid chloride from the first crop of crude

acid chloride is 27.6–33.4 g. (50–61%) of pale yellow prisms, m.p. 101–112° (Note 4). The product obtained from crystallization of the second crop of acid chloride amounts to 3.3–3.6 g. (6–7%), m.p. 104–108°.

C. *Crotyl diazoacetate*. A solution of 10.0 g. (0.038 mole) of the *p*-toluenesulfonylhydrazone of glyoxylic acid chloride in 100 ml. of methylene chloride is cooled in an ice bath. Crotyl alcohol (2.80 g. or 0.038 mole) (Note 7) is added to this cold solution, and then a solution of 7.80 g. (0.077 mole) of redistilled triethylamine (b.p. 88.5–90.5°) in 25 ml. of methylene chloride is added to the cold reaction mixture dropwise and with stirring over a 20-minute period. During the addition a yellow color develops in the reaction mixture and some solid separates near the end of the addition period. The resulting mixture is stirred at 0° for 1 hour and then the solvent is removed at 25° under reduced pressure with a rotary evaporator. A solution of the residual dark orange liquid in approximately 200 ml. of benzene is thoroughly mixed with 100 g. of Florisil (Note 8) and then filtered. The residual Florisil, which has adsorbed the bulk of the dark colored by-products, is washed with two or three additional portions of benzene of such size that the total volume of the combined benzene filtrates is 400–500 ml. This yellow benzene solution of the diazoester is concentrated under reduced pressure at 25° with a rotary evaporator, and the residual yellow liquid is distilled under reduced pressure. (*Caution! This distillation should be conducted in a hood behind a safety shield*) (Note 9). The diazo ester is collected as 2.20–2.94 g. (42–55%) of yellow liquid, b.p. 30–33° (0.15 mm.), n_D^{24} 1.4853 – 1.4856 (Note 10).

2. Notes

1. The submitters used a practical grade of material containing 80% glyoxylic acid purchased from Eastman Organic Chemicals.
2. The submitters used *p*-toluenesulfonylhydrazide prepared as described in *Organic Syntheses*.² This material may be purchased from Eastman Organic Chemicals.
3. Difficulty was encountered in the subsequently described recrystallization if the crude product was not dry.

4. The broad melting range is presumably due to the presence of a mixture of stereoisomers.

5. If the thionyl chloride is not taken from a freshly opened bottle, it should be redistilled before use.

6. The heating period is critical to the success of this reaction. After a heating period of 45–90 minutes the initially white suspension begins to turn yellow and the color gradually deepens as heating is continued. The correct heating period is normally reached about 10 minutes after vigorous gas evolution ceases; at this time the color of the reaction mixture is yellow-orange to orange. At this point the mixture is not clear, but relatively little suspended material separates when the stirrer is stopped for a short period. If heating is stopped too soon, a large amount of acid is lost during the filtration and the product is difficult to crystallize. If heating is continued too long, the product is contaminated with a brown-colored impurity and is difficult to crystallize.

7. The submitters used material purchased from the Aldrich Chemical Company.

8. This material was purchased from Fisher Scientific Company.

9. Although this distillation has been performed repeatedly without incident, the product is potentially explosive and the operator should take suitable precautions including surrounding the distillation apparatus with a hood and a safety shield and wearing an effective face shield.

10. A pot residue amounting to 2–3 g. of orange liquid remains at the end of this distillation.

3. Discussion

Crotyl diazoacetate has been prepared by the procedure described here³ and by the reaction of diazomethane with crotyl chloroformate.³ The lower homolog, allyl diazoacetate, has been prepared by the reaction of allyl glycinate with nitrous acid⁴ and by the successive conversion of allyl chloroacetate to the corresponding azide, iminophosphorane, and, finally, the diazo ester.⁵

Other methods for the preparation of diazoacetic acid esters

include the diazotization of glycine esters,⁶ the thermal or base-catalyzed decomposition of N-acyl-N-nitrosoglycine esters,⁷ the base-catalyzed cleavage of α -diazo- β -keto acetates,⁸ the reaction of carboalkoxymethylenephosphoranes with arylsulfonyl azides,⁹ the acid-catalyzed decomposition of acetic esters with α -aryl-triazene substituents,¹⁰ and the reaction of chloroformate esters with diazomethane.^{3, 11} The present procedure is unique in that a diazoacetic ester may be prepared in one step by reaction of the desired alcohol with a relatively stable, solid acylating agent which may be prepared in quantity and stored (in a desiccator). Consequently, the method is of particular value for alcohols which are not readily available or for alcohols containing other functional groups which would be incompatible with the reaction conditions required in other diazoacetate syntheses.

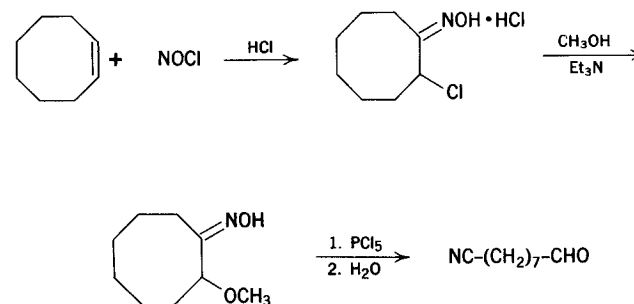
Although the present procedure illustrates the formation of the diazoacetic ester without isolation of the intermediate ester of glyoxylic acid *p*-toluenesulfonylhydrazone, the two geometric isomers of this hydrazone can be isolated if only one molar equivalent of triethylamine is used in the reaction of the acid chloride with the alcohol.³ The extremely mild conditions required for the further conversion of these hydrazones to the diazo esters should be noted. Other methods for decomposing arylsulfonylhydrazones to form diazocarbonyl compounds have included aqueous sodium hydroxide,¹² sodium hydride in dimethoxyethane at 60°,¹³ and aluminum oxide in methylene chloride or ethyl acetate.¹⁴ Although the latter method competes in mildness and convenience with the procedure described here, it was found not to be applicable to the preparation of aliphatic diazoesters such as ethyl 2-diazopropionate. Hence the conditions used in the present procedure may offer a useful complement to the last-mentioned method when the appropriate arylsulfonylhydrazone is available.

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7-CYANOHEPTANAL

(Heptanal, 7-cyano-)



Submitted by MASAJI OHNO, NORIO NARUSE, and ISAO TERASAWA¹
 Checked by E. J. COREY and I. VLATTAS

1. Procedure

A. 2-Chlorocyclooctanone oxime hydrochloride. In a 2-l. three-necked, round-bottomed flask, fitted with a mechanical stirrer, a gas inlet tube, and a tube fitted with a thermometer and a calcium chloride tube, is placed 55 g. (0.50 mole) of freshly distilled cyclooctene and 600 ml. of trichloroethylene. The solution is cooled with ice water to 5°, and 36 g. (0.55 mole) of nitrosyl chloride (Note 1) and excess of hydrogen chloride gas (about 400-600 ml. per minute) are bubbled into the solution, keeping the reaction temperature between 5-10°. The solution gradually

becomes light reddish brown. The addition of nitrosyl chloride should be carried out in about 1.5 hours. After completion of the addition of nitrosyl chloride, hydrogen chloride gas is bubbled in for another 15 minutes. A light brown oily material is obtained after evaporation of the solvent under an aspirator pressure below 35° (Note 2) by using an efficient rotatory evaporator. On cooling this product in a refrigerator, 107.2 g. (ca. 100%) of crude 2-chlorocyclooctanone oxime hydrochloride is obtained as a solid.

B. 2-Methoxycyclooctanone oxime. In a 500-ml., three-necked, round-bottomed flask, fitted with a mechanical stirrer, a dropping funnel, and a reflux condenser equipped with a calcium chloride tube, is placed a solution of 53.5 g. (0.252 mole) of crude 2-chlorocyclooctanone oxime hydrochloride in 250 ml. of methanol. While cooling the vessel with running water, 60.7 g. of triethylamine (0.60 mole) is added dropwise during 40 minutes. The reaction temperature is kept below 50° and the reaction is continued for 30 minutes with stirring. After removal of methanol under reduced pressure using an efficient rotatory evaporator, a light brown semisolid is obtained; it is treated with 200 ml. of ether and 200 ml. of water to effect complete solution. The ether layer is separated and the aqueous layer is further extracted twice with ether. The combined ether solution is washed with saturated sodium chloride and dried over sodium sulfate. Removal of ether affords 42.8 g. of crude 2-methoxycyclooctanone oxime (Note 3) as a brown oil.

C. Beckmann fission of 2-methoxycyclooctanone oxime. In a 500-ml., three-necked, round-bottomed flask equipped with a mechanical stirrer, a dropping funnel, and a calcium chloride tube is placed a suspension of 62.5 g. (0.30 mole) of phosphorus pentachloride (Note 4) in 150 ml. of absolute ether, and the reaction vessel is cooled with ice. A solution of 42.8 g. of crude 2-methoxycyclooctanone oxime (0.25 mole) in 100 ml. of absolute ether is added over 30 minutes with vigorous stirring and the reaction is continued for 50 minutes at 5°. The reaction mixture, which becomes a transparent reddish brown solution (Note 5), is poured with mechanical stirring into 500 g. of ice in a 2-l. beaker. Stirring is continued for 1.5 hours at 5° (Note 6). The ether layer is separated and the aqueous layer is extracted with

methylene chloride three times. The combined organic extracts are neutralized with dilute sodium carbonate solution and dried over sodium sulfate (Note 7). Removal of the solvent below 40° affords a reddish brown oil which is distilled to give 29.6 g. (85.2%) of 7-cyanoheptanal (Note 8), b.p. 109–115° (0.3 mm.) $n_D^{26} = 1.4456$. The 2,4-dinitrophenylhydrazone has m.p. 74–75° after recrystallization from ethanol.

2. Notes

1. Solid nitrosyl chloride stored in a dry-ice box is quickly melted by warming, and as rapidly as possible the liquid nitrosyl chloride is weighed into a flask contained in a hood. Nitrosyl chloride is simply allowed to volatilize into the reaction from this flask under ambient conditions; rapid addition of nitrosyl chloride causes a decrease of the yield of α -chlorooxime. It may sometimes be necessary to control the rate of addition by cooling the nitrosyl chloride container with ice water.

2. 2-Chlorocyclooctanone oxime hydrochloride is unstable to heat. Therefore the temperature during removal of methanol should be kept below 35°.

3. The methanol-triethylamine reagent is superior to the previously used ² methanolic sodium methoxide, and the crude 2-methoxycyclooctanone oxime thus obtained can be used for the Beckmann fission reaction without further purification. However, it is easily purified by distillation, b.p. 101° (0.7 mm.).

4. Thionyl chloride can also be used as the reagent for the Beckmann fission.

5. A very small amount of excess of phosphorus pentachloride is sometimes observed at the bottom of the reaction vessel.

6. If necessary, the temperature is kept at 5–10° by adding ice occasionally.

7. If the solution is acidic, the yield of ω -cyanoaldehyde is diminished by the occurrence of aldo condensation.

8. Although this distilled product, a pale yellow oil, is pure enough to use for most purposes, pure 7-cyanoheptanal, a colorless oil, is obtained by redistillation, b.p. 85–87° (0.013 mm.), $n_D^{26} = 1.4451$.

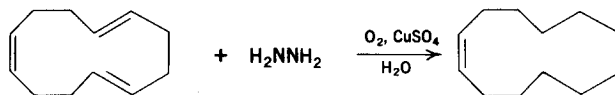
3. Discussion

The only preparation reported for 7-cyanoheptanal is that described by the submitters.³ The present procedure starting from 2-methoxycyclooctanone oxime is superior to modifications employing 2-alkylamino- or 2-ethylthiocyclooctanone oxime in the Beckmann cleavage step.

ω -Cyanoaldehydes are not easily accessible by other routes but are interesting synthetic intermediates,⁴ since the two terminal function groups are in different oxidation states which readily allow separate modification or elaboration.^{5,6} The general applicability of the method described herein allows the synthesis of a wide variety of ω -cyanoaldehydes from available cycloolefins.

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cis-CYCLODODECENE



Submitted by MASAJI OHNO and MASARU OKAMOTO¹

Checked by FREDERICK J. SAUTER and HERBERT O. HOUSE

1. Procedure

In a 2-l., three-necked, round-bottomed flask equipped with a mechanical stirrer, an efficient condenser, and an air inlet tube (Note 1) are placed 60.0 g. (0.370 mole) of *cis,trans,trans*-1,5,9-

cyclododecatriene (Note 2), 224.4 g. (7.00 moles) of 95% hydrazine (Note 3), 350 ml. of 95% ethanol, and 3.0 g. (0.012 mole) of copper(II) sulfate pentahydrate (Note 4). Air is bubbled through the reaction mixture (Note 5) with vigorous stirring for 8–12 hours or longer until the reaction mixture contains primarily the desired *cis*-monoolefin (Note 6). During the early stages in the reaction a considerable amount of heat is generated and the temperature of the reaction mixture rises to 50–60°.¹⁹

When the reaction has progressed to the desired stage (Note 6), the flow of air is stopped and the mixture is filtered. After the filtrate has been extracted with two 350-ml. portions of petroleum ether (b.p. 30–60°), the combined hydrocarbon extracts are washed successively with two 100-ml. portions of 2*N* hydrochloric acid and three 100-ml. portions of water. The petroleum ether is distilled from the solution, heated in a water bath, through a 60-cm. Vigreux column, and the residual liquid is distilled under reduced pressure. The fraction, b.p. 64–65° (1.0 mm.) or 132–134° (35 mm.), is collected as 39.5–52.0 g. (64–85%) of colorless liquid, *n*_D²⁵ 1.4846–1.4850. This distillation fraction contains (Note 6) 80–90% of the *cis*-cyclododecene (51–76%) accompanied by 10–20% of a mixture of cyclododecane and *cis,trans*-1,5-cyclododecadiene (Note 7). If desired, the *cis*-cyclododecene may be further purified by preparative chromatography or separation of the silver nitrate-olefin addition complex (Note 8).

2. Notes

1. An air inlet tube with a sintered-glass disk or cylinder at the end immersed in the solution is recommended.

2. The submitters used material available from Hüls Company in Germany. This material was contaminated with 1–3% of the more easily reduced *trans,trans,trans*-1,5,9-cyclododecatriene. The checkers purchased the starting triene from Aldrich Chemical Company, Inc. The gas chromatogram (see Note 6) of this material exhibited no peak corresponding to the all-*trans*-triene, an indication that less than 1% of this contaminant was present.

3. The submitters had specified the use of either hydrazine hydrate (aqueous 85% hydrazine) or aqueous 80% hydrazine.

The checkers observed only partial reduction of the triene and intermediate diene under these conditions, apparently because sufficient water was present in the reaction mixture to prevent adequate partitioning of the olefins between the hydrocarbon layer and the aqueous ethanolic layer containing the diimide. The checkers avoided this difficulty by use of hydrazine containing less than 5% water (95+ % hydrazine) available from Olin Mathieson Chemical Company or from Eastman Organic Chemicals. This difficulty could probably also be avoided by use of absolute ethanol rather than 95% ethanol.

4. Copper(II) acetate can also be used.

5. The rate of air flow, measured with a precalibrated mercury flow meter in the gas inlet tube, was adjusted to 400–450 ml. per minute.

6. In order to stop the reaction when the amount of monoolefinic product in the reaction mixture is highest, aliquots of the reaction mixture are removed at intervals and analyzed by infrared spectrometry or by gas chromatography. In the infrared spectrum the relative intensities of bands at 965 cm^{-1} (*trans*-CH=CH) and 702 cm^{-1} (*cis*-CH=CH) are observed in successive aliquots. The reaction is stopped when the band at 965 cm^{-1} , attributable to the *trans* double bonds of the starting triene, has almost completely disappeared and the band at 702 cm^{-1} (*cis*-olefin) remains.

Gas chromatographic analyses are obtained at about 120° with a 2 m. x 7 mm. column packed with a suspension of 5% (by weight) of silver nitrate and 15% (by weight) of Carbowax 6000 (polyethylene glycol) on either Chromosorb P or Celite 545. With this column the relative retention times of the various possible components in the reaction mixture are: cyclododecane, 1.00; *trans,trans,trans*-1,5,9-cyclododecatriene, 1.20; *trans*-cyclododecene, 1.13; *cis*-cyclododecene, 1.33; *cis,trans*-1,5-cyclododecadiene, 1.51; *cis,trans-trans*-1,5,9-cyclododecatriene, 1.72. The reaction should be stopped when the rate of reduction of *cis,trans*-1,5-cyclododecadiene to *cis*-cyclododecene has become approximately equal to the rate of conversion of the *cis*-monoolefin to cyclododecane.

7. The submitters reported obtaining a product after a 60–72

hour reaction period which contained 91%–95% of the *cis*-monoolefin and 5–9% of cyclododecane with no *trans*-monoolefin being detected. The checkers found the maximum amount of *cis*-monoolefin was present in the reaction mixture after a reaction period of 8–12 hours. At this time the resulting distilled product had the approximate composition: cyclododecane, 8%; *trans*-cyclododecene, 3%; *cis*-cyclododecene, 80%; and *cis,trans*-1,5-cyclododecadiene, 9%. The use of longer reaction times resulted in the further reduction of the *cis*-monoolefin to cyclododecane more rapidly than it was produced from the residual *cis,trans*-diene.

8. The conversion of the *cis*-monoolefin to its silver nitrate complex¹⁶ was accomplished by adding 1.66 g. (0.010 mole) of the distilled reaction product to a solution of 1.70 g. (0.010 mole) of silver nitrate in 50 ml. of boiling methanol. The resulting solution, when cooled, deposited the complex as white needles, m.p. 79° dec.; recrystallization from methanol separated 1.0 g. of the complex, m.p. 80° dec. After this complex had been partitioned between water and ether, the ether phase was separated, dried over magnesium sulfate, and concentrated. Distillation of the residual liquid in a short path still separated 0.45 g. of the pure (Note 6) *cis*-cyclodecene, b.p. 70° (1.0 mm.), n_D^{25} 1.4852.

3. Discussion

Cyclododecene may be prepared from 1,5,9-cyclododecatriene by the catalytic reduction with Raney nickel and hydrogen diluted with nitrogen,² with nickel sulfide on alumina,³ with cobalt, iron, or nickel in the presence of thiophene,⁴ with palladium on charcoal,⁵ with palladium chloride in the presence of water,⁶ with palladium on barium sulfate,⁷ with cobalt acetate in the presence of cobalt carbonyl,⁸ and with cobalt carbonyl and tri-*n*-butyl phosphine.⁹ It may also be obtained from the triene by reduction with lithium and ethylamine,¹⁰ by disproportionation,^{11, 12} by epoxidation followed by isomerization to a ketone and Wolff-Kishner reduction,¹³ and from cyclododecanone by the reaction of its hydrazone with sodium hydride.¹⁴

These methods generally afford a mixture of *cis*- and *trans*-

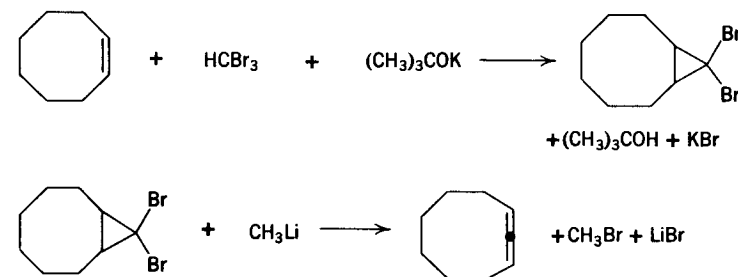
cyclododecene. *cis*-Cyclododecene has also been prepared by the reduction of cyclododecyne with Lindlar catalyst,^{15, 16} and from 1,5-cyclododecadiene¹⁷ or from 1,2-dichlorocyclododecane.¹⁸ The *cis*-olefin is usually obtained as a minor product from the Hofmann degradation of cyclododecyltrimethylammonium hydroxide¹⁵ and from the pyrolysis of cyclododecyl acetate.

The procedure described is based on the selective reduction with diimide described by Ohno and Okamoto¹⁹ and by Nozaki and Noyori.²⁰ It illustrates the generation of diimide from the air oxidation of hydrazine and the use of diimide for the selective reduction of the *trans* double bond in *cis,trans,trans*-1,5,9-cyclododecatriene, the product of trimerization of butadiene.²¹

The use of diimide provides a particularly convenient and general method for the selective reduction of *trans* double bonds of medium ring systems.²² The *cis*-cyclododecene produced in this selective reduction is thermodynamically less stable than the corresponding *trans*-isomer.²³

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1,2-CYCLONONADIENE



Submitted by L. SKATTEBØL and S. SOLOMON¹
 Checked by L. S. KELLER and K. B. WIBERG

1. Procedure

A. *9,9-Dibromobicyclo[6.1.0]nonane*. A dry 3-l. three-necked flask is fitted with a glass stopper, stirrer, and condenser. The flask is kept under a positive nitrogen pressure by means of a gas-trap arrangement connected to the top of the condenser (Note 1). The flask is quickly charged with 2 l. of anhydrous *t*-butyl alcohol (Note 2) and 73 g. (1.87 g. atoms) of potassium metal. (*Caution! See earlier volume² for handling of this metal.*) The flow of nitrogen is stopped and the mixture is stirred and boiled under reflux until the potassium is reacted, hydrogen being liberated through the trap. The condenser is arranged for distillation by means of an adapter. The glass stopper is replaced by a pressure-equalized dropping funnel with the nitrogen inlet connected to the top. About 1.5 l. of *t*-butyl alcohol (Note 3) is then distilled into a predried flask under an atmosphere of nitrogen. A water pump is then connected, the nitrogen inlet is closed, and the distillation is continued under reduced pressure while the three-necked flask is gradually heated to 150° in an oil bath. Finally, the water pump is replaced by an oil pump and the white remaining solid is heated at 150° under a pressure of

0.1–1 mm. for 2 hours. The connection to the vacuum system is closed, the oil bath removed, and nitrogen again introduced. The condenser with adapter is replaced by a glass stopper, and the flask is cooled in an ice-salt bath.

Freshly distilled *cis*-cyclooctene, 178 g. (214 ml., 1.62 moles) (Note 4) and 200 ml. of sodium-dried pentane (Note 5) are introduced to the flask, and the dropping funnel is charged with 420 g. (148 ml., 1.66 moles) of bromoform (Note 6). The bromoform is added dropwise to the stirred slurry over a period of 6–7 hours, the color of the reaction mixture changing gradually from light yellow to brown. When the addition is complete, the reaction mixture is allowed to warm to room temperature and left stirring overnight. Water (400 ml.) is added to the reaction mixture followed by enough 10% aqueous hydrochloric acid to neutralize the slightly basic solution. The reaction mixture is transferred to a separatory funnel and the organic layer is separated. The aqueous layer is extracted with three 50-ml. portions of pentane, and the combined pentane solutions are washed with three 50-ml. portions of water. The pentane solution is dried over anhydrous magnesium sulfate, filtered, and stripped of solvent on a rotary evaporator. Distillation of the residue yields 237–299 g. (52–65%) of 9,9-dibromobicyclo[6.1.0]nonane, b.p. 62° (0.04 mm.), n_D^{25} 1.5493–1.5507 (Note 7).

B. *1,2-Cyclononadiene*. A dry 2-l. three-necked flask is equipped with mechanical stirrer, pressure-equalized dropping funnel, and a nitrogen inlet tube connected to a gas-trap arrangement (Note 1). To the flask are added 187 g. (116 ml., 0.66 mole) of 9,9-dibromobicyclo[6.1.0]nonane and 100 ml. of anhydrous ether. The dropping funnel is charged with 450 ml. of 1.9*M* ether solution of methyllithium (0.85 mole) (Note 8). The flask is cooled by means of an acetone-dry ice bath maintained at –30° to –40°, and the methyllithium is added dropwise with stirring during 1 hour (Note 9). After the addition is complete, the reaction mixture is stirred for 30 minutes, and excess lithium reagent is decomposed by dropwise addition of 100 ml. of water. An additional 400 ml. of water is then added, and the ether layer is separated. The aqueous layer is extracted with three 30-ml. portions of ether. The combined ether solutions are washed with

30-ml. portions of water until neutral and dried over magnesium sulfate. The latter is filtered and the ether is distilled through a 40-cm Vigreux column. Distillation of the residue (Note 10) yields 66–73 g. (81–91%) of 1,2-cyclononadiene, b.p. 62–63° (16 mm.), n_D^{20} 1.5060 (Note 11).

2. Notes

1. A suitable gas-trap has been described.³ Mercury can conveniently be replaced by paraffin oil.

2. Reagent grade *t*-butyl alcohol distilled from calcium hydride was used.

3. The *t*-butyl alcohol thus recovered can be used for a second preparation without further purification.

4. *cis*-Cyclooctene was obtained from Columbia Organic Chemicals or Aldrich Chemical Co. It was distilled from sodium and a fraction, b.p. 81–82° (95 mm.), n_D^{25} 1.4682, was used. Gas chromatography showed 98% purity, the impurity being mainly cyclooctane.

5. Pentane is added as a diluent in order to obtain an easily stirred slurry. Amounts varying from 100 to 250 ml. per mole of olefin have been used with no appreciable change in yield of product.

6. Reagent grade bromoform was used without further purification.

7. The submitters have also used commercially available dry potassium *t*-butoxide with varying success in this reaction; with a sample purchased from M.S.A. Research Corporation a 65% yield of product was obtained. The submitters reported a 65–76% yield range for this step.

8. An ethereal solution of methyllithium was either prepared from lithium metal and methyl bromide or purchased from Alfa Inorganics, Inc. Concentrations of 0.5–2*M* were used with no change in result.

9. Solid methyllithium and lithium halide occasionally separate out on the tip of the dropping funnel, probably owing to the low temperature, and this may cause plugging. It can be avoided by using a faster rate of addition.

10. The submitters used a 40-cm. spinning band column. Owing to polymerization of the product, the checkers obtained consistently low yields when this column was used. Distillation through a 40-cm. Vigreux column gave the indicated yield without a significant decrease in product purity.

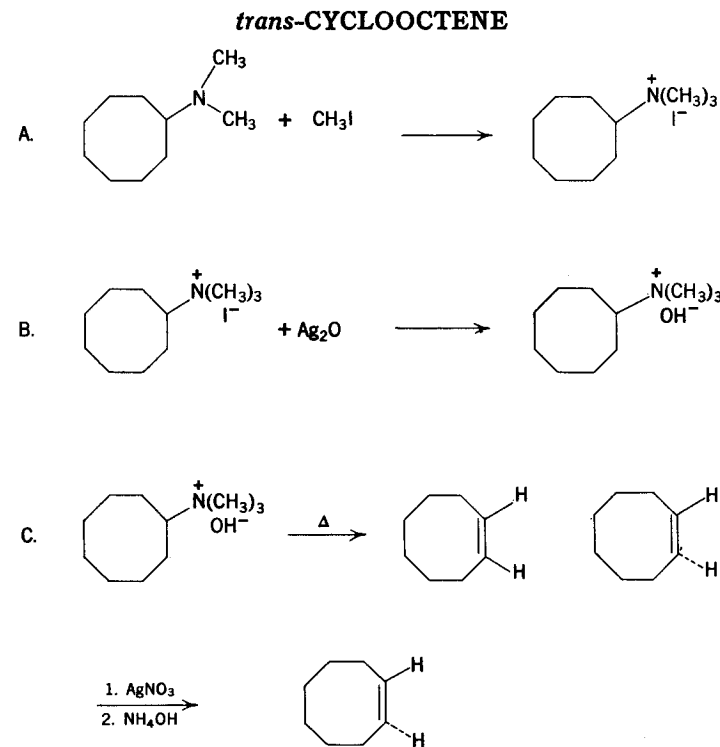
11. The product is more than 99% pure as shown by gas chromatography.

3. Discussion

Cyclic allenes have previously been obtained only admixed with the isomeric acetylenes.⁴ The present two-step synthesis is a practical method for the preparation of cyclic allenes, and at the same time it describes a general method for the preparation of allenes.^{5, 6} It is based on the original work of Doering and co-workers.⁷ Examples of the reaction sequence above are known in which allenes are not produced,⁸ or they represent only a part of the reaction products.⁹ A one-step synthesis of 1,2-cyclononadiene has been reported.¹⁰

Reduction of 1,2-cyclononadiene with sodium in liquid ammonia gives *cis*-cyclononene in almost quantitative yield.¹¹

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Submitted by ARTHUR C. COPE¹ and ROBERT D. BACH²
 Checked by A. DEMEIJERE and K. B. WIBERG

1. Procedure

A. *N,N,N*-Trimethylcyclooctylammonium iodide. To a 2-l., three-necked, round-bottomed flask equipped with a stirrer, condenser, drying tube, and pressure-equalizing dropping funnel are added 155.3 g. (1 mole) of *N,N*-dimethylcyclooctylamine (Note 1) and 700 ml. of reagent grade methanol. To the stirred solution is added 170.3 g. (1.2 moles) of iodomethane (Note 2) dropwise over a 30-minute period. The flask is cooled intermittently with an ice bath to keep the reaction temperature at approximately

25° (Note 3). After 1 hour the bath is removed and the reaction mixture is allowed to stir at 25° for an additional 3 hours.

The light yellow solution is transferred to a 2-l. round-bottomed flask, and the solvent is removed under reduced pressure (Note 4) with slight warming. The solid product is triturated with 500 ml. of diethyl ether, filtered, and washed with three 200-ml. portions of diethyl ether. The white solid (291–296 g.) is dried under reduced pressure, m.p. 269–270° dec. (Note 5).

B. *N,N,N*-Trimethylcyclooctylammonium hydroxide. To a 1-l. round-bottomed flask equipped with a stirrer are added 100 g. (0.34 mole) of *N,N,N*-trimethylcyclooctylammonium iodide, 76 g. of silver oxide (Note 6), and 35 ml. of distilled water. The suspension is stirred at room temperature for 5 hours and is filtered through a Buchner funnel. The filter cake is washed with four 35-ml. portions of distilled water. The light yellow filtrate is transferred to a 1-l. round-bottomed flask and the volume is reduced to approximately 90 ml. employing a rotary evaporator and a 40° water bath. The viscous *N,N,N*-trimethylcyclooctylammonium hydroxide solution is transferred (Note 7) to a 200-ml. dropping funnel, with a pressure-equalizing side arm, for use in the next step in the synthesis (Note 8).

C. *trans*-Cyclooctene. A 500-ml., three-necked, round-bottomed flask is equipped with a nitrogen inlet capillary tube (Note 9), a short (10–20 cm.) unpacked column (Note 10), and a pressure-equalizing dropping funnel. The round-bottomed flask is connected by the unpacked column to a 100-ml. trap cooled in an ice bath. This trap is then connected to a 200-ml. trap cooled in dry ice-acetone (Note 11). The flask is heated in an oil bath to 110–125°, and the apparatus is evacuated to a pressure of *ca.* 10 mm. under a constant sweep of nitrogen. The hydroxide solution is added dropwise at approximately the rate of decomposition of the quaternary ammonium hydroxide (Note 12).

The combined distillates from the cold traps are allowed to come to room temperature (Note 13) and are placed in a 1-l. separatory funnel with 200 ml. of 5% hydrochloric acid solution. The mixture of *cis*- and *trans*-cyclooctenes (Note 14) is extracted with 200 ml. of *n*-pentane and subsequently with two 50 ml.

portions of *n*-pentane. The *n*-pentane extracts are combined and washed with 170 ml. of 5% sodium bicarbonate solution.

To a 1-l. separatory funnel is added *ca.* 500 ml. of 20% aqueous silver nitrate solution (100 g. of Mallinckrodt C.P. crystals to *ca.* 500 ml. of water). The pentane solution is added to the separatory funnel in five approximately equal portions, with intermittent shaking until all the silver nitrate complex has gone into solution (Note 15).

The silver nitrate solution is extracted as described above with three portions of *n*-pentane to remove *cis*-cyclooctene (Note 16). The aqueous silver nitrate solution is added slowly to 300 ml. of concentrated ammonium hydroxide containing cracked ice. The hydrocarbon that separates is extracted with 300 ml. of *n*-pentane as described above and the pentane solution is dried over anhydrous magnesium sulfate and the pentane distilled through a 23 x 250 mm. column packed with glass beads.

The product is distilled under reduced pressure through a short (8 cm.) Vigreux column (Note 17) and has b.p. 75° (78 mm.), 44° (23 mm.), $n_D^{25} = 1.4741$, $d_4^{25} = 0.8456$. The yield of pure *trans*-cyclooctene is 15.0 – 15.3 g. (40%) (Notes 18, 19, 20).

2. Notes

1. Cyclooctylamine was purchased from Aldrich Chemical Co. It was converted to *N,N*-dimethylcyclooctylamine in 74% yield using a procedure analogous to that for β -phenylethyldimethylamine.³

2. Fischer reagent grade methanol and Eastman Organic Chemicals iodomethane were used.

3. The molar ratio of iodomethane to *N,N*-dimethylcyclooctylamine may be reduced if precautions are taken to prevent loss of iodomethane due to vaporization.

4. It is convenient to use a rotary evaporator for removal of the solvents.

5. After one recrystallization from an acetone-methanol mixture, the compound melts at 273–275° dec. The compound is sufficiently pure for the next step in the synthesis without recrystallization.

6. Mallinckrodt purified silver oxide powder was used. The reaction flask should be protected from direct sunlight with a suitable wrapping.

7. The flask may be rinsed with a minimum of water and transferred to the dropping funnel. The total volume of hydroxide solution at this point should not exceed 100 ml.

8. The conversion of the quaternary ammonium iodide to the hydroxide may also be carried out using a strongly basic ion exchange resin.⁴

9. The decomposition should be carried out under a constant sweep of nitrogen. The nitrogen may be introduced through the pressure-equalizing dropping funnel if that is more convenient.

10. The unpacked column should be wrapped with a heating tape, or Nichrome heating wire, and kept at *ca.* 110° throughout the decomposition.

11. The reaction is stopped and the trap, cooled in dry ice-acetone, is emptied when the reaction is *ca.* one half finished to prevent plugging by ice. Most of the olefinic products are found in the first trap. The second trap contains mostly trimethylamine and water.

12. About 3 hours is required to add the hydroxide solution. The rate of addition may be increased, but considerable foaming occurs during the decomposition, and caution should be taken that the hydroxide does not foam over into the traps.

13. This part of the experiment should be carried out in a hood because trimethylamine is evolved.

14. The decomposition of N,N,N-trimethylcyclooctylammonium hydroxide forms a mixture of *cis*- and *trans*-cyclooctenes which contains *ca.* 60% of the *trans*- and 40% of the *cis*-isomer (see Note 19). The mixture is separated by extraction of the *trans*-isomer with aqueous silver nitrate.⁵

15. If the pentane solution is added to the silver nitrate solution too rapidly, the *trans*-cyclooctene forms a dark precipitate that is difficult to get into solution. This situation can, however, be remedied by the addition of more silver nitrate solution and continued shaking.

16. The pentane is removed and *ca.* 11 g. of *cis*-cyclooctene is obtained on distillation, b.p. 65° (59 mm.); $n_D^{25} = 1.4684$.

17. Considerable foaming occurs during distillation of *trans*-cyclooctene. The distillation may therefore be facilitated by use of a distilling adapter with a foam trap. The distilling adapter (5225) may be purchased from Ace Glass Incorporated, Vineland, New Jersey. The bath temperature should be kept below 100° owing to the possibility of isomerization to *cis*-olefin and polymerization.⁶ The distillation should be carried out as rapidly as possible because the condensed product evaporates under prolonged exposure to reduced pressure.

18. The submitters carried out this preparation on a 1.0-mole scale and obtained 49–51 g. (45–46%) of *trans*-cyclooctene.

19. The purity of the *trans*-cyclooctene may be determined by infrared spectroscopy⁵ or by gas chromatography using an NMPN (3-nitro-3-methylpimelonitrile) column.⁷ A low injection port temperature is desirable (<200°).

20. *trans*-Cyclooctene is stable for at least 1 year if kept under refrigeration and if a free radical inhibitor is used (*e.g.* di-*t*-butyl-resorcinol). The compound has a very disagreeable odor.

3. Discussion

trans-Cyclooctene has been prepared by the Hofmann elimination of N,N,N-trimethylcyclooctylammonium hydroxide,^{5, 8} the present method; by the treatment of N,N,N-trimethylcyclooctylammonium bromide with phenyllithium, methyllithium, and potassium amide;⁹ and by the treatment of *trans*-1,2-cyclooctene thiocarbonate with triisooctyl phosphite.¹⁰

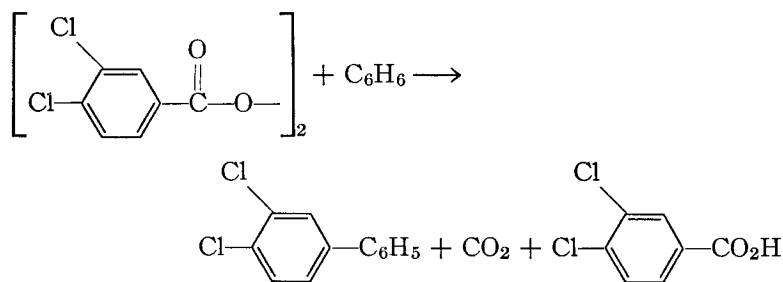
This procedure illustrates a general method for preparing olefins by the elimination of an amine and a β -hydrogen atom.¹¹ The present method is more convenient for adaptation to large-scale laboratory preparation than is the Wittig modification, which utilizes liquid ammonia; both methods give essentially the same overall yield of *trans*-cyclooctene.

The preparation of olefins *via* their thiocarbonate¹⁰ is a stereospecific elimination reaction which may be used to advantage when a mixture of *cis*- and *trans*-olefins is difficult to separate. However, all the reagents required to prepare the thiocarbonate are not readily available.

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ARYLBENZENES: 3,4-DICHLOROBIPHENYL

(Biphenyl, 3,4-dichloro-)



Submitted by D. H. HEY and M. J. PERKINS¹

Checked by K. K.-W. SHEN and K. B. WIBERG

1. Procedure

Thirty-eight grams (0.1 mole) of bis-3,4-dichlorobenzoyl peroxide (Note 1) is added to a boiling solution of 3 g. of *m*-dinitrobenzene in 800 ml. of dry reagent grade benzene contained in a 1-l. round-bottomed flask, and the resulting solution is boiled under reflux for 40 hours. The solvent is then distilled from the red solution until the residual volume is about 200 ml. (Note 2), and the mixture is allowed to cool. The 3,4-dichlorobenzoic acid

which separates is removed by suction filtration, washed with a little cold benzene, and then with 100 ml. of petroleum ether (b.p. 80–100°). The combined filtrate and washings are further concentrated by distillation (Note 2) to about 60 ml., cooled, and a small second crop of 3,4-dichlorobenzoic acid is removed and washed with a little benzene followed by a little petroleum ether. The total yield of acid, m.p. 208–210° (Lit.² m.p. 208–209°), is 18.2 g. (95%) (Note 3). The filtrate and washings are combined (Note 4) and chromatographed on a column of basic alumina (30 cm. x 3.5 cm.) which is eluted with petroleum ether (b.p. 40–60°). Solvent is distilled from the eluate (Note 5), and the residual crude 3,4-dichlorobiphenyl is distilled under reduced pressure using a short air condenser and a receiver chilled in ice. There is obtained 17.3–18.0 g. (78–81%) of almost pure 3,4-dichlorobiphenyl (b.p. 146–150° at 2 mm.) which sets to a colorless solid, m.p. 44–47° (Note 6).

2. Notes

1. The bis-3,4-dichlorobenzoyl peroxide may be prepared as follows.^{3, 4} To a 2-l. beaker containing 400 ml. of water which is cooled to 0–5° in an ice bath is added slowly 40 g. (0.51 mole) of sodium peroxide. A dropping funnel containing 167.6 g. (0.8 mole) of 3,4-dichlorobenzoyl chloride in 400 ml. of dry toluene is supported over the beaker. The peroxide solution is cooled and stirred vigorously while the toluene solution is added dropwise over a 1-hour period. The solution is stirred for an additional 2 hours. The precipitate is filtered using a suction funnel, washed with 600 ml. of cold water, and dried in air overnight. There is obtained 114 g. (75%) of bis-3,4-dichlorobenzoyl peroxide, m.p. 135° dec. The crude product is purified by dissolving it in chloroform and precipitating by the addition of methanol, m.p. 139° dec.

2. Solvent removal may conveniently be carried out with a rotary evaporator to obviate bumping caused by separation of the dichlorobenzoic acid from the boiling solution.

3. In syntheses of other arylbenzenes, in which the acid by-product is more soluble, it may be extracted from the reaction

mixture with aqueous sodium bicarbonate or removed in the subsequent chromatography.

4. At this point the solvent is largely petroleum ether. Appreciable quantities of benzene in the mixture to be chromatographed tend to carry some of the dinitrobenzene through the alumina.

5. After removal of the solvent from the eluate, almost pure white 3,4-dichlorobiphenyl crystallizes, m.p. 44–48°. It may be purified by recrystallization from methanol as an alternative to vacuum distillation.

6. The product may be freed from a trace (~1%) of biphenyl present as an impurity by recrystallization from methanol which raises the melting point to 47–48°. The literature values range from 46°⁵ to 49–50°.⁶

3. Discussion

3,4-Dichlorobiphenyl has been prepared by the arylation of benzene using the Gomberg procedure starting with 3,4-dichloroaniline,⁵ and using the acid-catalyzed decomposition of 1-(3,4-dichlorophenyl)-3,3-dimethyltriazene in benzene.⁶ The arylation procedure given above, which utilizes a diaryl peroxide as the aryl radical source, provides a route to arylbenzenes which involves simple operations and gives a good yield of pure product. In the absence of the nitro compound, the mode of action of which has been discussed in terms of two somewhat different mechanisms,^{7, 8} the yields of aroic acids and arylbenzenes are commonly below 50%,⁹ and the arylbenzene may be contaminated with aryldihydrobenzenes.¹⁰ The present procedure has been used to prepare a variety of simple arylbenzenes in isolated yields ranging from 70 to 90%. If a nitro substituent is present in the peroxide, high yields are obtained without the addition of further nitro compound.⁹

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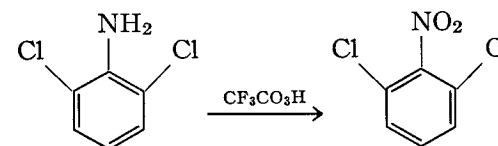
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2,6-DICHLORONITROBENZENE

(Benzene, 1,3-dichloro-2-nitro-)



Submitted by A. S. PAGANO and W. D. EMMONS¹

Checked by V. Z. WILLIAMS, JR. and K. B. WIBERG

1. Procedure

Caution! The preparation and handling of peroxytrifluoroacetic acid should be carried out behind a safety screen. Precautions to be observed with 90% hydrogen peroxide are described in Note 3 and should be carefully followed.

A 300-ml. three-necked flask equipped with a Trubore stirrer, dropping funnel, and reflux condenser protected with a calcium chloride drying tube is charged with 100 ml. of methylene chloride (Note 1). To this solvent is added without stirring 5.4 ml. (0.20 mole) of 90% hydrogen peroxide (Notes 2, 3, 4, 5). The hydrogen peroxide is not miscible with the solvent and separates as the lower layer at the bottom of the flask. The flask is then cooled in an ice bath, and the stirrer is started. To this cold solution over a 20-minute period is added 34.0 ml. (0.24 mole) of trifluoroacetic anhydride. After addition is complete, the ice bath is removed and the solution is stirred at room temperature for 30 minutes.

A solution is then prepared from 8.1 g. (0.05 mole) of 2,6-dichloroaniline (Note 6) and 80 ml. of methylene chloride. This

solution is added dropwise over a 30-minute period to the previously prepared peroxytrifluoroacetic acid reagent (Note 7). During this addition the exothermic reaction causes the mixture to reflux. After addition is complete, the mixture is heated under reflux for 1 hour. It is then cooled and poured into 150 ml. of cold water. The organic layer is separated, washed with 100 ml. of water, with two 100-ml. portions of 10% sodium carbonate solution (Note 8), and finally with 50 ml. of water. The organic extract is treated with activated charcoal and anhydrous magnesium sulfate. After standing overnight, the volatile solvent is removed at aspirator pressure with the aid of a warm water bath. There is obtained 8.6–8.8 g. (89–92%) of yellow 2,6-dichloronitrobenzene, m.p. 63–68°. The product is recrystallized from a minimum volume (12–15 ml.) of ethanol and washed on the filter with 10 ml. of cold ethanol to give 5.7–7.0 g. (59–73%) of a slightly off-white product, m.p. 69–70° (reported,⁴ 70.5°).

2. Notes

1. Reagent grade methylene chloride was used without further purification.

2. Available from Becco Chemical Division, Food, Machinery and Chemical Co., Buffalo 7, New York.

3. The precautions to be observed with 90% hydrogen peroxide have been described in detail.² In essence, it is important to prevent contact of this reagent with any easily oxidizable substrate such as wood, alcohols, and sugars and with heavy metal salts since these substances catalyze its decomposition. Storage of hydrogen peroxide in the laboratory should be arranged in such a way that, even if the bottle containing the reagent breaks, the hydrogen peroxide will not come into contact with any material of this kind. Small samples of 90% hydrogen peroxide are regularly shipped in vented glass bottles provided with a protective outside metal container, and it is desirable to use this container while storing the reagent in the laboratory. In the event that spillage of the reagent occurs, dilution with at least several volumes of water is recommended. In weighing out 90% hydro-

gen peroxide it is good practice never to return excess reagent to the stock bottle; rather, it should be diluted with water and discarded to avoid any possibility that the stock bottle will be contaminated.

4. It is convenient to measure out the hydrogen peroxide by a 10-ml. graduate or by a 10-ml. pipet actuated by a glass syringe connected via a ground-glass joint.

5. The procedure described here for the preparation of peroxytrifluoroacetic acid in methylene chloride has been carried out by the submitters several hundred times without incident and is believed to be the best available. However, it has been pointed out that suspensions of 90% hydrogen peroxide in methylene chloride can be detonated by impact under certain conditions.³ Accordingly, the use of the recommended safety screen is imperative, and the preparation should not be scaled up without special precautions. The homogeneous solution of peroxytrifluoroacetic acid, once obtained, is undoubtedly much safer to handle than the suspension of hydrogen peroxide in methylene chloride. The latter suspension is not transferred, however, and exists for only a brief time period during the preparation.

6. Available from Aldrich Chemical Company, Inc.

7. Addition of the peracid solution to the aniline invariably resulted in a poor-quality product in low yield.

8. The sodium carbonate extracts are quite dark.

3. Discussion

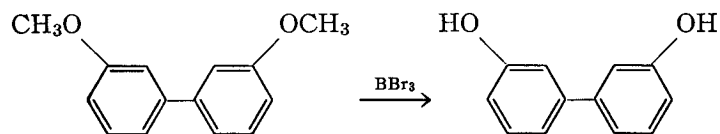
2,6-Dichloronitrobenzene has been prepared by deamination of 3,5-dichloro-4-nitroaniline⁴ and of 2,4-dichloro-3-nitroaniline.⁵ This procedure is an example of the rather general oxidation of anilines to nitrobenzenes with peroxytrifluoroacetic acid.^{6,7} Use of this reagent is frequently the method of choice for carrying out this transformation, and it is particularly suitable for oxidation of negatively substituted aromatic amines. Conversely, those aromatic amines, such as *p*-anisidine and β -naphthylamine, whose aromatic nuclei are unusually sensitive to electrophilic attack give intractable mixtures with this reagent.⁶ This is not

a serious limitation, however, and many of the nitrobenzenes which are available from this procedure have in the past required tedious multistep syntheses.

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3,3'-DIHYDROXYBIPHENYL

(m,m'-Biphenol)



Submitted by J. F. W. McOMIE and D. E. WEST¹
 Checked by J. E. HIATT and K. B. WIBERG

1. Procedure

3,3'-Dimethoxybiphenyl² (8 g., 0.037 mole) is dissolved in 120 ml. of methylene chloride in a 250-ml. conical flask, and the flask is placed in an acetone-dry ice bath at -80° . The flask is fitted with an air condenser. A solution of 15.9 g. (6.0 ml., 0.063 mole) of boron tribromide (Notes 1, 2) in 40 ml. of methylene chloride (Notes 3, 4) is added carefully to the stirred solution through the condenser. When the addition is complete, a calcium chloride tube is fitted to the top of the air condenser in order to protect the reaction mixture from moisture. As the solution of boron tribromide is added, a white precipitate is formed. The reaction mixture is allowed to attain room temperature overnight with stirring, when a clear, brownish yellow solution is obtained. The reaction mixture is then hydrolyzed

by careful shaking with 130 ml. of water, thus precipitating a white solid which is dissolved by the addition of 500 ml. of ether. The organic layer is separated and extracted with 240 ml. of 2*N* sodium hydroxide; the alkaline extract is neutralized with dilute hydrochloric acid, extracted with 300 ml. of ether, and the ether extract is dried over anhydrous magnesium sulfate. On removal of the ether under reduced pressure, a brownish yellow oil remains which soon crystallizes to give an off-white solid; this is recrystallized twice from hot benzene, the first time with the addition of charcoal, and gives 3,3'-dihydroxybiphenyl as white needles with a pinkish tint, m.p. $126-127^{\circ}$ (Note 5). The yield is 5.4–6.0 g. (77–86%).

2. Notes

1. Boron tribromide of 99.9% purity, from Koch-Light Laboratories Ltd., Colnbrook, Bucks, England, was used.

2. Boron tribromide is a heavy, colorless liquid ($d = 2.6$) when pure but begins to decompose on exposure to light, liberating free bromine. It fumes vigorously in air, being rapidly hydrolyzed to boric acid, with the evolution of considerable heat.

3. Demethylation reactions proceed equally well using dry *n*-pentane or dry methylene chloride as the solvent for both the ether and the boron tribromide; methylene chloride, having by far the more powerful solvent action, is to be preferred.

4. When making up the solution of boron tribromide in methylene chloride, it has been found best to stand the vessel containing the solvent in an acetone-dry ice bath at -80° and to add the required amount (it is difficult to measure accurately) to the methylene chloride as rapidly as possible.

5. In order to obtain a perfectly white product, recrystallization from water is necessary;^{3, 5} prismatic needles several centimeters long are obtained. The compound is moderately soluble in boiling water and slightly soluble in cold water.

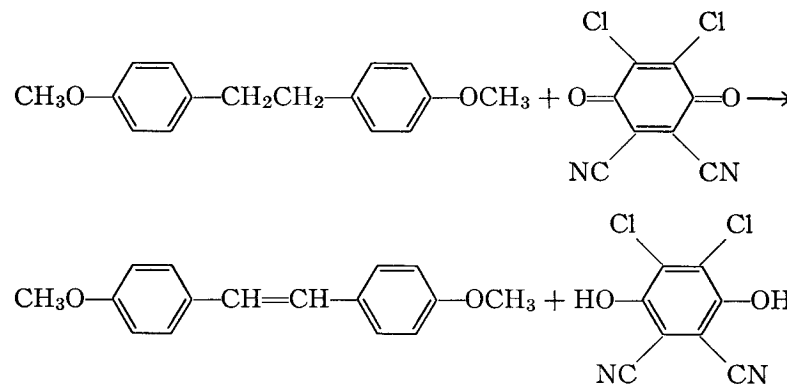
3. Discussion

The above preparation of 3,3'-dihydroxybiphenyl is a good example of the utility of boron tribromide for the cleavage of

aryl methyl ethers; it is based on the method of McOmie, Watts, and West.⁴ 3,3'-Dihydroxybiphenyl has been prepared previously by diazotization³ of 3,3'-diaminobiphenyl and subsequent boiling with water, by the fusion of biphenyl-3,3'-disulfonic acid with potassium hydroxide,⁶ and by heating 3,3'-dimethoxybiphenyl with hydriodic acid.⁵

Almost all the methods previously employed⁷ for the demethylation of aromatic methyl ethers have involved fairly high temperatures, *e.g.*, hydrogen halides in water or acetic acid at reflux temperature, whereas the present method is effective at, or well below, room temperature although in a few cases it has been found necessary to boil the solution (b.p. of methylene chloride, 40°). Boron tribromide does not effect cleavage of methylenedioxy groups nor of diphenyl ethers. It can be used for the demethylation of aryl methyl ethers in the presence of many functional groups without affecting these.⁴ It is especially valuable for the demethylation of iodinated ethers⁴ and of methoxy biphenylenes⁸ where the usual reagents are either ineffective or else cause decomposition. Boron tribromide was the reagent of choice for the final (demethylation) step in the synthesis of the naturally occurring macrolide, Zearalenone.⁹

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trans*-4,4'-DIMETHOXYSTILBENE*(*trans*-Stilbene, 4,4'-dimethoxy-)**Submitted by J. W. A. FINDLAY and A. B. TURNER¹

Checked by R. E. IRELAND and G. BROWN

1. Procedure

A solution of 100 mg. (0.41 mmole) of 4,4'-dimethoxybiphenyl (Note 1) in 1.5 ml. of anhydrous dioxane (Note 2) was placed in a 10-ml. round-bottomed flask. To this was added 103 mg. (0.45 mmole) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; Note 3) dissolved in 1.5 ml. of anhydrous dioxane. The flask was fitted with a reflux condenser and heated in an oil bath at 105° for 18 hours. The solution, which was initially deep green, became pale yellow as the hydroquinone crystallized out. The mixture was cooled, and the solid was filtered off. It was washed with 1 ml. of warm benzene followed by 6 ml. of warm chloroform (Note 4), and dried at 100° to give 95 mg. (91%) of pure 2,3-dichloro-5,6-dicyanohydroquinone (Note 5). The filtrate and washings were combined and evaporated under reduced pressure. The semisolid residue was dissolved in 5 ml. of ethyl acetate and passed through a short column of neutral alumina

(2.0 g.; Note 6). The column was eluted with 100 ml. of ethyl acetate (Note 7). Evaporation of the solvent under reduced pressure left the crude product, which was recrystallized from 35 ml. of ethanol to give 82–84 mg. (83–85%) of *trans*-4,4'-dimethoxystilbene as colorless plates, m.p. 212–213.5°.

2. Notes

1. The starting bibenzyl was prepared from *p*-methoxybenzyl chloride by a modified Wurtz reaction.² The checkers found the procedure described by Buu-Hoï and Lavit² inadequate and used the copper(I) chloride-catalyzed coupling of *p*-methoxyphenyl magnesium chloride in its place.

2. Dioxane was purified by the method of Vogel³ and stored over molecular sieves.

3. DDQ was obtained from Koch-Light Laboratories, Ltd. It can be recrystallized from benzene if required.

4. Washing with chloroform is necessary to dissolve some of the stilbene which crystallizes out with the hydroquinone. In many reactions, washing the hydroquinone with hot benzene is sufficient, as the dehydrogenation products crystallize to a limited extent from dioxane.

5. The amount of precipitated hydroquinone is a convenient measure of the extent of hydrogen transfer. DDQ is readily regenerated in good yield from the hydroquinone by oxidation with nitric acid.⁴

6. Woelm neutral alumina, activity grade 1.

7. The volume of ethyl acetate required to elute the product can be reduced considerably for more soluble products.

3. Discussion

DDQ was first introduced for the dehydrogenation of hydroaromatic compounds, such as tetralin and bibenzyl, which yield naphthalene and stilbene, respectively.⁵ A benzene ring or an olefinic bond provides sufficient activation, although it is sometimes difficult to force the reaction to completion. This high-potential quinone has since found wide application,⁶ particularly

in the steroid field, and its scope has been extended by the dehydrogenation of carbonyl compounds (ketones and lactones) and alcohols. DDQ is also useful for preparing stable cations and radicals. These reactions are commonly carried out in refluxing benzene or dioxane, and the procedure described here is a general one. An alternative workup procedure involves washing with alkali.

A number of compounds react rapidly with DDQ at room temperature. They include allylic and benzylic alcohols, which can thus be selectively oxidized, and enols and phenols, which undergo coupling reactions or dehydrogenation, depending on their structure. Rapid reaction with DDQ is also often observed in compounds containing activated tertiary hydrogen atoms. The workup described here can be used in all these cases.

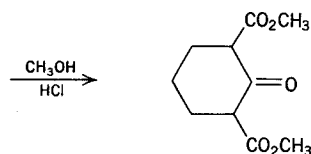
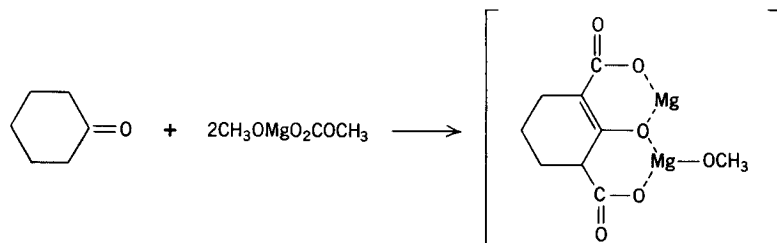
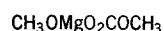
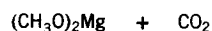
A number of side products can arise with this quinone. They include Diels-Alder adducts (DDQ is a powerful dienophile) and Michael adducts derived from the hydroquinone.

General methods for the preparation of *trans*-stilbenes have been covered previously.⁷ 4,4'-Dimethoxystilbene has been prepared from deoxyanisoin and *n*-propylmagnesium iodide,⁸ by treatment of thiophenol with 2-bromo-1,1-di-*p*-methoxyphenylethane,⁹ and by the action of nitrous acid on the corresponding amine.¹⁰

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DIMETHYL CYCLOHEXANONE-2,6-DICARBOXYLATE

(Cyclohexanone-2,6-dicarboxylic acid, dimethyl ester)



Submitted by S. N. BALASUBRAHMANYAM and M. BALASUBRAMANIAN¹

Checked by FREDERICK J. SAUTER and HERBERT O. HOUSE

1. Procedure

Caution! Since hydrogen is liberated in the first step of this reaction, it should be conducted in a hood. A dry 2-l. three-necked flask is fitted with a Trubore mechanical stirrer, an Allihn condenser, and a 1-l. pressure-equalizing dropping funnel, the top of which is fitted with a gas inlet tube. After 40.0 g. (1.64 g. atoms) of clean, dry magnesium ribbon (Note 1) has been placed in the flask, the system is flushed with nitrogen and 600 ml. of anhydrous methanol (Note 2) is added. As soon as the vigorous reaction begins, the nitrogen flow is stopped; if necessary, the reaction may be moderated by external cooling with wet towels. When the hydrogen evolution has ceased, a slow stream of nitrogen is passed through the reaction system and the condenser is replaced by a total condensation-partial take-off distillation head. The nitrogen flow is stopped, and the bulk of the methanol

is distilled from the solution under reduced pressure (Note 3) with stirring while the reaction flask is heated to 50–55° with a water bath. This distillation is stopped when stirring of the pasty suspension of magnesium methoxide is no longer practical. Nitrogen is readmitted to the system, and the outlet from the distillation head is attached to a small trap containing mineral oil so that the volume of gas escaping from the reaction system can be estimated. Anhydrous dimethylformamide (700 ml.; Note 4) is added to the reaction flask, and the resulting suspension is stirred vigorously while a stream of anhydrous carbon dioxide (Note 5) is passed into the reaction vessel through the gas inlet tube attached to the dropping funnel. The dissolution of the carbon dioxide is accompanied by an exothermic reaction with the suspended magnesium methoxide to form a solution. When the absorption of carbon dioxide has stopped (Note 6), the colorless solution is heated with a mantle under a slow stream of anhydrous carbon dioxide gas until the temperature of the liquid distilling from the flask reaches 140°, indicating that the residual methanol has been removed from the reaction mixture. The flow of carbon dioxide is stopped, and a slow stream of nitrogen is passed through the system while the resulting solution (Note 7) is cooled below 100° with a water bath. Cyclohexanone (20.0 g., 0.204 mole) (Note 8) is added to the reaction mixture, and the solution is heated under reflux for 2 hours while a slow stream of nitrogen (2–3 bubbles per second) is passed over the reaction mixture. The resulting solution is cooled first to room temperature with a water bath and then to –5° with a dry ice-acetone bath (Note 9).

Meanwhile, 700 ml. of anhydrous methanol is placed in a 2-l. flask fitted with a gas inlet tube extending approximately 5 mm. below the surface of the methanol and a calcium chloride tube to protect the contents of the flask from atmospheric moisture. The methanol is cooled with an external cooling bath prepared from ice and calcium chloride (Note 10) and saturated with anhydrous hydrogen chloride (Note 10) (290–300 g. of hydrogen chloride is required). This solution is transferred to the dropping funnel by means of a gooseneck adapter and the methanolic hydrogen chloride solution is then added, dropwise and with stirring, to the

reaction flask, the temperature of the reaction being maintained at $0^{\circ} \pm 5^{\circ}$ by means of a cooling bath. This addition is accompanied by the vigorous evolution of carbon dioxide and the separation of a white solid. After the addition is complete, the reaction mixture is allowed to stand overnight at room temperature and then the bulk of the methanol is removed from the solution by distillation under reduced pressure with stirring. During the distillation the temperature of the reaction mixture is kept below 55° . The remaining suspension is poured into a 4-l. beaker containing 1 kg. of crushed ice. The crude product separates as shiny white flakes which are collected on a filter and washed with water. A small second crop of the crude material may be obtained by cooling the aqueous filtrates to 0° overnight. The total crude product (25–26 g.) is dissolved in 250 ml. of boiling methanol, and this solution is concentrated to 125–150 ml. and allowed to cool. The keto diester separates as flat white needles, m.p. $128\text{--}132^{\circ}$ (Note 11), yield 19.3–19.7 g. (44–45%). Concentration of the mother liquors affords an additional 2.2–2.5 g. of crude product, m.p. $122\text{--}128^{\circ}$ (Note 11).

2. Notes

1. Magnesium ribbon is conveniently cleaned by immersion in aqueous 10% hydrochloric acid, rinsing the ribbon with distilled water and with acetone, and drying it in an oven at 120° .

2. To ensure a rapid reaction with the magnesium, the methanol should be heated to reflux over magnesium methoxide for 12 hours and then distilled and transferred to the reaction vessel with a siphon or a large pipet. If necessary, a crystal of iodine may be added to initiate the reaction of methanol with magnesium.

3. If a water aspirator is used, a calcium chloride tube or tower should be included in the line connecting the distillation head and the aspirator.

4. The dimethylformamide may be purified by distillation at atmospheric pressure. The checkers distilled material purchased from the J. T. Baker Company and used the fraction collected at $153\text{--}155^{\circ}$.

5. Carbon dioxide obtained from a cylinder of the compressed gas was passed through a tube packed with calcium chloride and either activated silica gel or Drierite (containing an indicator) to remove water.

6. If the gas flow is turned off while carbon dioxide is still being absorbed, the pressure inside the flask falls below atmospheric pressure. This pressure change is readily observed with the mineral oil-filled trap fitted to the gas exit tube of the system.

7. The submitters found that this solution of methyl magnesium carbonate in dimethylformamide could be stored for long periods in a well-stoppered bottle without loss of potency.

8. The checkers employed cyclohexanone purchased from Eastman Organic Chemicals and distilled before use, b.p. $155\text{--}157^{\circ}$. The ratio of cyclohexanone to methylmagnesium carbonate is fairly critical; a proportion of ketone larger than the ratio 1:8 ketone:magnesium salt specified yields a pasty product presumably contaminated with monocarboxylated material. A smaller proportion of ketone lowers the yield.

9. The checkers measured the temperature of this solution by sliding a thermometer through the distillation head so that the thermometer bulb was immersed in the reaction mixture.

10. The checkers used a cooling bath prepared from ice and sodium chloride and dried the hydrogen chloride obtained from a compressed-gas cylinder by passing the gas through a trap filled with concentrated sulfuric acid.

11. The submitters reported that the addition of eight volumes of warm (35°) water to a warm solution of the keto diester in ten volumes of methanol followed by gradual cooling to 0° separated, on one occasion, a product, m.p. $142\text{--}143^{\circ}$, which was presumably one pure isomer. The checkers found that the product recrystallized readily from methanol, aqueous methanol, or benzene in good crystalline form, but invariably with a wide melting range ($129\text{--}136^{\circ}$) which varied with the rate of heating. It would appear that the checkers invariably obtained the product as a mixture of two or more of the three readily interconvertible forms: keto *cis*-diester, keto *trans*-diester, and enol diester. The thin-layer chromatogram of the recrystallized product, determined on a plate coated with silica gel and eluted with a mixture

of carbon tetrachloride and ethyl acetate (1:1 v/v), indicated the absence of monocarbomethoxycyclohexanone in the product. Also, the elemental composition of the product and the mass spectrum of the product are consistent with the idea that the product contains only stereoisomeric and tautomeric forms. The mass spectrum exhibits a molecular ion peak at m/e 214 with abundant fragment peaks at m/e 182, 154, 126, 95, 67, and 55 but exhibits a peak of relatively low abundance at m/e 156, the mass of the molecular ion derived from 2-carbomethoxycyclohexanone. An ethanol solution of the recrystallized keto diester product initially exhibits an ultraviolet maximum at 255 $m\mu$ with a molecular extinction coefficient within the range 6000–11,000; on the addition of excess sodium hydroxide the ultraviolet maximum is shifted to 287.5 $m\mu$ (ϵ 12,600). A chloroform solution of the recrystallized product has infrared absorption at 1750 (strong), 1712 (medium), 1675 (weak), and 1610 (weak) cm^{-1} ; an ethanol solution of the product, when treated with ferric chloride, gives no immediate color, but a brown color develops after the solution is allowed to stand for 10 to 20 minutes. These observations suggest that the crystalline product obtained in this preparation is primarily a mixture of the *cis*- and *trans*-isomers of the keto tautomer.

3. Discussion

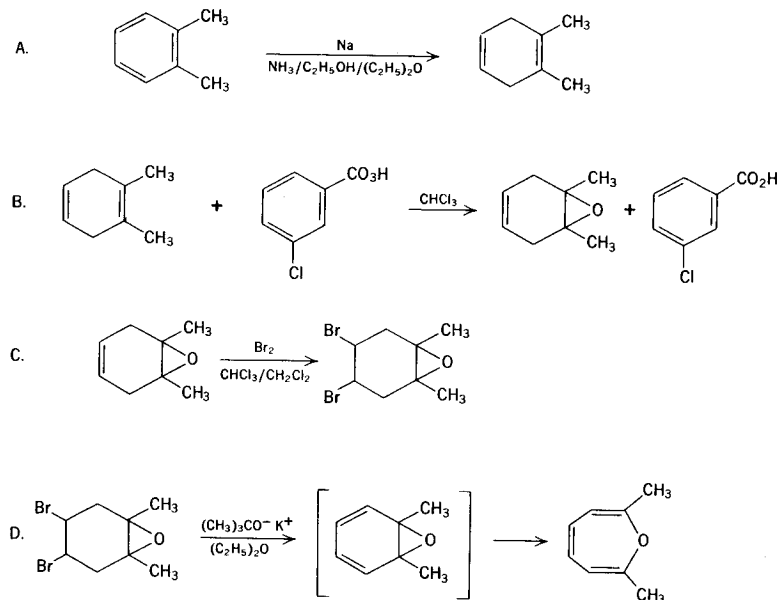
Dimethyl cyclohexanone-2, 6-dicarboxylate has been prepared by the alkylation of dimethyl acetonedicarboxylate with trimethylene dibromide² and by the carboxylation of cyclohexanone.³ The present preparation gives a general procedure for carboxylation of active methylene compounds.^{3–6} The method has been used for carboxylation of methylene groups activated by ketones,^{3–5} nitro groups,^{3, 4} and certain amide functions.⁶ The success of the procedure is attributed to the formation of a magnesium enolate which is stabilized by chelation with an adjacent carboxylate anion.^{4, 6} In certain cases^{3, 6} the magnesium enolate has been alkylated in the original reaction mixture, thereby avoiding the necessity for isolating an intermediate ester. Although the present example illustrates the fact that when two

equivalent active methylene groups are present both positions may be carboxylated, the submitters were unsuccessful in obtaining a pure keto diester when the procedure was applied to cyclopentanone.

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2,7-DIMETHYLOXEPIN

(Oxepin, 2,7-dimethyl-)

Submitted by L. A. PAQUETTE and J. H. BARRETT¹

Checked by JON MALMIN and RONALD BRESLOW

1. Procedure

A. *1,2-Dimethyl-1,4-cyclohexadiene.* *Caution!* This step should be conducted in a hood to avoid exposure to ammonia fumes. A 5-l. three-necked flask, cooled in a dry ice-isopropyl alcohol bath, is fitted with an efficient stirrer and a dry ice condenser. The flask is charged with approximately 2.5 l. of liquid ammonia, the stirrer is started, and 450 g. of anhydrous diethyl ether, 460 g. (10 moles) of absolute ethanol, and 318.5 g. (3.0 moles) of *o*-xylene (Note 1) are added slowly in that order (Note 2). Then 207 g. (9.0 g. atoms) of sodium is added in small pieces over a 5-hour

period (Note 3). The ammonia is allowed to evaporate overnight. The flask is now equipped with a reflux condenser, and approximately 800 ml. of ice water is slowly added with stirring to dissolve the salts (Note 4). The two layers which form are separated and the upper organic layer is washed three times with 800-ml. portions of water and dried over anhydrous magnesium sulfate. The liquid is separated from the drying agent and is distilled through a 20-cm. Vigreux column. The fraction boiling at 70–72° (48 mm.) is collected and weighs 250–300 g. (77–92%). The 1,2-dimethyl-1,4-cyclohexadiene is sufficiently pure for the epoxidation reaction (Note 5).

B. *1,2-Dimethyl-1,2-epoxycyclohex-4-ene.* A 2-l. three-necked flask equipped with an efficient stirrer, a reflux condenser, and a dropping funnel is charged with 41 g. (0.38 mole) of 1,2-dimethyl-1,4-cyclohexadiene. Over a period of 2 hours 80 g. (0.46 mole of 85% assay) of *m*-chloroperbenzoic acid (Note 6) dissolved in 1 l. of chloroform is added with vigorous stirring. The mixture is heated to reflux on a steam bath for 3 hours and kept overnight. The contents of the flask are cooled in an ice bath and the precipitated *m*-chlorobenzoic acid is removed by filtration. The organic layer is washed with 25 ml. of 20% sodium bisulfite solution, three 100-ml. portions of 10% sodium bicarbonate solution (Note 7), and 100 ml. of saturated sodium chloride solution, in that order. The organic layer is dried over anhydrous magnesium sulfate, filtered, concentrated under reduced pressure, and distilled through a 30-cm. glass bead-packed column (Note 8) to afford 32.3–36.8 g. (68–78%) of the epoxide, b.p. 55–57° (15 mm.); *n*_D²⁰ 1.4642–1.4650 (Note 9).

C. *4,5-Dibromo-1,2-dimethyl-1,2-epoxycyclohexane.* Into a 1-l. three-necked flask fitted with an efficient stirrer, an alcohol thermometer, a dropping funnel, and a drying tube are placed 32 g. (0.26 mole) of the epoxide and 500 ml. of an anhydrous chloroform-methylene chloride mixture (1:1). The solution is cooled to –65° and 34 g. (0.21 mole) of bromine in 50 ml. of the same solvent is added dropwise while maintaining the temperature below –60° (Note 10). When the addition is complete, the reaction mixture is stirred for 30 minutes and the solvent is removed at room temperature under reduced pressure. The

resulting oil (or solid) is recrystallized from a minimum amount of *n*-hexane to give 47–51 g. (80–86%) of lustrous white needles, m.p. 82–83°.

D. *2,7-Dimethyloxepin*. In a 1-l. three-necked flask fitted as above, except that the dropping funnel is replaced by a 125-ml. Erlenmeyer flask connected to the reaction flask by means of Gooch tubing, is placed a solution of 42.1 g. (0.15 mole) of the purified dibromoepoxide in 500 ml. of anhydrous ether. The solution is cooled to 0° and 33.2 g. (0.30 mole) of potassium *t*-butoxide (Note 11) is added portionwise through the Gooch tubing over a period of 1 hour while maintaining the temperature below 5°. The resulting mixture is stirred for 30 minutes and filtered. The ether is removed under reduced pressure, and the residual liquid is distilled to give 9.7–12.2 g. (52–67%) of 2,7-dimethyloxepin as an orange oil, b.p. 49–50° (15 mm.), n_{D}^{27} 1.5010 (Note 12).

2. Notes

1. Eastman Organic Chemicals, white label grade, was used without further purification.

2. It is advisable to precool these reagents before their addition to minimize excessive boiling of the liquid ammonia.

3. Only five or six pieces of sodium should be added at one time in order to avoid an almost uncontrollable exothermic reaction. The solution turns blue and then white as the sodium is consumed. When the solution turns white, another portion of sodium may be added. The last 50 g. of sodium may be added without waiting between portions because the reaction is much slower at this point.

4. Because dissolution of the salts is a highly exothermic process, the water should be added slowly. A stream of nitrogen may be passed through the reaction during the addition of the water to ensure that no fire is started by bits of sodium that may be adhering to the upper walls of the flask.

5. The product is readily analyzed by vapor phase chromatography. Since the only impurity is *o*-xylene (conversions range from 80% to 100%), the percentage of reduction product was

calculated from the gas chromatogram and this value was used to determine the amount of *m*-chloroperbenzoic acid to be used in the epoxidation.

6. *m*-Chloroperbenzoic acid was obtained from Aldrich Chemical Company, Milwaukee, Wisconsin.

7. The separatory funnel must be vented frequently because of the large volume of carbon dioxide liberated at this point.

8. It appears necessary to effectively remove the residual *o*-xylene during this distillation in order that it not interfere (by liberation of hydrogen bromide) with the subsequent bromination of the epoxide. The checkers used a spinning-band column for this distillation.

9. The submitters worked at four times this scale with similar yields and purity.

10. Best yields are obtained if the bromination mixture is never allowed to become orange in color. If a calculated amount of bromine is added to the epoxide, the yields of dibromide are greatly diminished.

11. Potassium *t*-butoxide may be obtained from MSA Research Corporation, Callery, Pennsylvania.

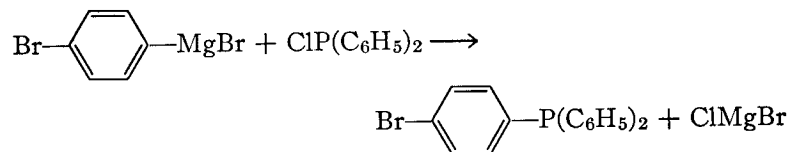
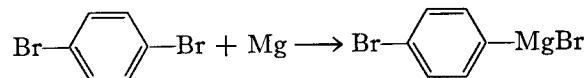
12. 2,7-Dimethyloxepin is stable for long periods when stored under nitrogen at 0–5°.

3. Discussion

The procedure described is patterned after the method suggested by Vogel, Schubart, and Böll,² and it illustrates a general method of preparing oxepins. Furthermore, the first step represents an example of the Birch reduction of an aromatic hydrocarbon.³ The second step is illustrative of the selective epoxidation of a diene system.³

Oxepins themselves are interesting examples of cyclic conjugated molecules with $4n$ π -electrons.

1. Department of Chemistry, The Ohio State University, Columbus, Ohio 43210.
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DIPHENYL-*p*-BROMOPHENYLPHOSPHINE[Phosphine, (*p*-bromophenyl)diphenyl]Submitted by G. P. SCHIEMENZ¹

Checked by V. Z. WILLIAMS, JR., and K. B. WIBERG

1. Procedure

A dry 1-l. round-bottomed flask with five outlets is equipped with a sealed stirrer, a 500-ml. dropping funnel, a reflux condenser attached to a calcium chloride tube, an inlet for dry nitrogen (a weak stream of which is maintained through all the reaction until the hydrolysis step), and a thermometer reaching close to the bottom. In the flask are placed 9.0 g. (0.38 g. atom) of magnesium turnings, a crystal of iodine, and about 25 ml. of dry ether. With stirring, about 15 ml. of a solution of 88.5 g. (0.38 mole) of *p*-dibromobenzene (Note 1) in 500 ml. of dry ether (Note 2) is added at once. When the reaction has started, the remaining ether solution is added at a rate which maintains rapid refluxing. After the *p*-dibromobenzene has been added, the mixture is stirred at room temperature for 1.5 hours.

The mixture is then cooled by means of an ice-sodium chloride bath. When the internal temperature has reached -7° , a solution of 71.8 g. (0.33 mole) of chlorodiphenylphosphine (Note 3) in 100 ml. of dry ether is added at such a rate that the internal temperature does not exceed $+10^\circ$. The addition requires about 1.25 hours. The cooling bath is then removed and stirring con-

tinued for 1.5 hours. The flask is then again immersed in an ice-sodium chloride bath, and 150 ml. of a cold saturated aqueous ammonium chloride solution is added slowly. The ether is decanted and the remainder acidified with hydrochloric acid and extracted three times with 125 ml. of benzene each (Note 4). From the combined ether and benzene solutions, the solvents are evaporated and the residue is distilled at reduced pressure. After the low-boiling material, some *p*-dibromobenzene distills and crystallizes in the distillation bridge. At 2×10^{-2} mm., heating is continued until the phosphine reaches the stillhead. At this stage the distillation is interrupted, the stillhead and condenser containing *p*-dibromobenzene replaced by a clean, short distillation bridge without condenser, and the phosphine distilled at 2×10^{-2} to 10^{-3} mm., no forerun being taken (Note 5). The main bulk distills at $180-185^\circ$ (2×10^{-2} mm.). The colorless, oily distillate begins to crystallize in the receiving flask during or shortly after the distillation (Note 6) and weighs 81–83 g. (73–77% yield) (Note 7), m.p. $64-71^\circ$. This material is sufficiently pure for further reactions, e.g., Grignard reaction. A sample may be recrystallized from methanol to give colorless needles, m.p. $79-80^\circ$.

2. Notes

1. A commercial product, m.p. $88-89^\circ$, was used without purification.
2. The *p*-dibromobenzene may be dissolved by heating the ether to reflux. If substantially less ether is used, part of the compound will crystallize out at room temperature.
3. A commercial product from Aldrich Chemical Company was used without purification.
4. When a larger excess of Grignard reagent was used, a polymer insoluble in either phase was observed.
5. Dividing the distillate into a forerun and a constant-boiling main fraction did not improve the melting point of the latter, 66 g. (62%) of phosphine being obtained. The forerun likewise consisted mainly of the phosphine.
6. The distillation apparatus should be taken apart and

cleaned immediately after the distillation, while still hot. The distillation flask contains a polymer which, on cooling, solidifies to a hard glass which blocks the joints and can hardly be removed from the flask.

7. No improvement of the yield was obtained when a 50% excess of Grignard reagent was used.

3. Discussion

This preparation ² is an example of the general and versatile synthesis of *t*-phosphines of Michaelis ³ which, however, is usually not applicable for aromatic phosphines substituted with $-M$ substituents. The synthesis is an interesting case of the Grignard reaction in that it includes the addition of a Grignard reagent to an "inorganic" single bond and makes use of the mono-Grignard reagent of a dihalogen compound with two equivalent halogen atoms. Similarly, from the mono-Grignard reagents of *m*-dibromobenzene in ether ⁴ and of *p*-dichlorobenzene in tetrahydrofuran,⁵ diphenyl-*m*-bromophenyl-⁴ and diphenyl-*p*-chlorophenylphosphine ² were prepared in yields of 58 and 84%, respectively.

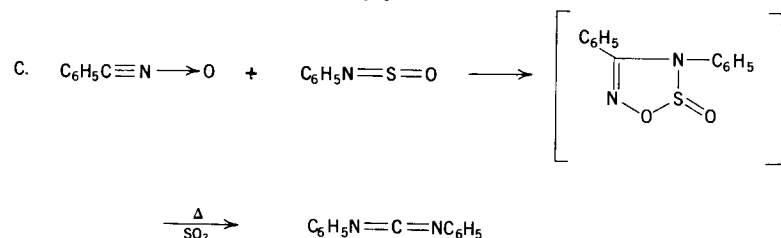
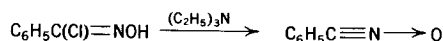
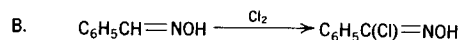
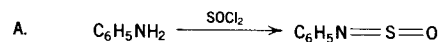
A slightly higher yield of diphenyl-*p*-bromophenylphosphine has been reported using more expensive reagents (tetrahydrofuran and butyllithium rather than ether and magnesium turnings).⁶ An alternative route consists of a Friedel-Crafts type of reaction of bromobenzene with phosphorus trichloride and reaction of the resulting dichloro-*p*-bromophenylphosphine with phenylmagnesium bromide. The submitter found this sequence less convenient, and the overall yield is given as only 21%.⁷⁻⁹ In addition, this path fails for the *meta* isomer, and with other substituents the first step yields a mixture of isomers.¹⁰ On the other hand, some phosphines containing $-M$ substituents were prepared by making use of the second step.^{11, 12} A more facile synthesis of such phosphines starts from the title compound ² or its *meta* isomer,⁴ the key step being a second Grignard reaction with subsequent carbonation to give the diphenylphosphinobenzoic acids ^{2, 4} which are also accessible by several other, apparently less convenient and more expensive, routes.^{8, 11, 14} *p*-Diphenylphosphinobenzoic acid has been used in place of tri-

phenylphosphine in a modification of the Wittig olefination, giving rise to a phosphine oxide which is scarcely soluble in organic solvents and easily soluble in aqueous carbonate solution, and therefore facilitates separation of the olefin from the phosphine oxide.¹⁵

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DIPHENYLCARBODIIMIDE

(Carbodiimide, diphenyl)

Submitted by P. RAJAGOPALAN, B. G. ADVANI, and C. N. TALATY¹

Checked by A. ESCHENMOSER, R. SCHEFFOLD, and P. MAYER

1. Procedure

Caution! All the following operations should be carried out in a well-ventilated hood.

A. *N*-Sulfinylaniline (Note 1). A solution of 82.5 g. (0.69 mole) of pure thionyl chloride (Note 2) in 100 ml. of anhydrous benzene is added slowly to a solution of 46.5 g. (0.5 mole) of freshly distilled aniline in 250 ml. of anhydrous benzene contained in a 1-l. round-bottomed flask, with swirling and occasional cooling in an ice bath (if necessary). An immediate precipitation of aniline hydrochloride occurs. After the addition of the thionyl chloride solution is complete, the mixture is heated to reflux, protected from moisture, on a heating mantle until a clear solution is obtained (2–5 hours). The solvent and excess thionyl chloride are evaporated under reduced pressure (Note 3)

at 50° and the residual brownish yellow liquid is distilled under vacuum to yield 63–65 g. (91–94%) of yellow *N*-sulfinylaniline, b.p. 88–95° (17–20 mm.), n_D^{21} 1.6253.

B. *Benzohydroxamoyl chloride* (Note 4). A four-necked flask equipped with a rubber-sealed stirrer, a thermometer, an inlet tube, and an outlet tube attached to a calcium chloride tube (Note 5) and containing a solution of 50 g. (0.41 mole) of benzal-doxime (Note 6) in 450 ml. of pure chloroform (Note 7) is cooled in a dry ice-acetone bath (Note 8). When the temperature of the solution reaches –2°, stirring is started and a stream of chlorine gas (Note 9) is passed through at such a rate as to maintain the temperature below 2°. After 1 hour the passage of chlorine is stopped and the greenish yellow solution is transferred to a 1-l. round-bottomed flask which is then connected to an aspirator to remove most of the dissolved chlorine. The light yellow solution thus obtained is stripped of the solvent at 40° under reduced pressure (Note 3). The almost colorless residual liquid is dissolved in 150 ml. of petroleum ether (b.p. 40–60°) and cooled, with scratching, in a dry ice-acetone bath, whereupon a colorless crystalline solid starts separating. The cooling is continued for 30 minutes and the solid is then filtered, washed with 50 ml. of cold petroleum ether (b.p. 40–60°), pressed to remove most of the adhering mother liquor, and dried over a filter paper. The yield of benzohydroxamoyl chloride, m.p. 48–52°, which is pure enough (Note 10) for the next step, is 33.38 g. (51–59%).

C. *Diphenylcarbodiimide* (Note 11). A solution of 15.6 g. (0.1 mole) of benzohydroxamoyl chloride in 300 ml. of anhydrous benzene contained in a 500-ml. wide-mouthed Erlenmeyer flask is cooled to 5°, agitated vigorously, and treated with 10.1 g. (0.1 mole) of freshly distilled triethylamine added in one portion. The mixture is shaken continuously for 3 minutes while being cooled in an ice bath and then filtered rapidly through a Buchner funnel into a filter flask cooled in an ice bath. The residue is washed with 50 ml. of anhydrous benzene, pressed to remove as much of the adhering solution as possible, dried in an oven at 60°, and weighed (Note 12). The yield of the triethylamine hydrochloride, m.p. 254–256°, is 13.4–13.6 g. (97–99%).

The combined filtrates containing benzonitrile oxide are transferred to a 1-l. round-bottomed flask, treated immediately with 13.9 g. (0.1 mole) of N-sulfinylaniline added in one portion, with swirling, and set aside protected from moisture, while the temperature reaches a maximum of 33–34° (usually 15 minutes). The mixture is then heated to reflux, protected from moisture, in a temperature-controlled oil bath for 3–5 hours. Continuous evolution of sulfur dioxide takes place during this period at the end of which the mixture is cooled and evaporated under reduced pressure (Note 3) at 70–80° to remove the solvent. The residual dark brown liquid is transferred to a 50-ml., pear-shaped distilling flask (Note 13) and heated, protected from moisture, at 110° for 30 minutes to complete the decomposition. It is then cooled and distilled under high vacuum (Note 14). Unchanged N-sulfinylaniline (2.0–2.5 g.) distills over at 45–50° (0.1–0.2 mm.). A second fraction (1.2–1.5 g.) is collected until the temperature reaches 112° (Note 15); then diphenyl carbodiimide is collected at 114–117° (0.1–0.2 mm.) as a clear yellow liquid; yield 10.5–10.8 g. (54–56%) (Note 16); n_D^{23} 1.6355; $\nu_{\max}^{\text{CHCl}_3}$ 2140 cm^{-1} (very strong), 2110 cm^{-1} (medium), and 1480 cm^{-1} (medium) (Note 17).

2. Notes

1. This method is essentially that described by Kresze and co-workers² which is a modification of the original procedure of Michaelis.³

2. The yield of the product depends on the purity of the thionyl chloride. Thionyl chloride obtained from Riedel-Haen (Hannover, West Germany) was used as such.

3. A rotary evaporator equipped with a constant-temperature water bath is ideal for this purpose.

4. This method is essentially that of Werner and Buss.⁴

5. The calcium chloride tube is, in turn, attached to a rubber tube which is either led out of a ventilator or connected to a water pump through which water is adjusted to flow gently.

6. Purum grade α -benzaloxime, m.p. 32°, obtained from Fluka AG (Buchs, Switzerland) was used most of the time.

When out of stock, it was prepared in the usual manner and distilled before use.

7. Chloroform distilled over phosphorous pentoxide was used.

8. An ice-salt mixture is not adequate to regulate the temperature, as it rises steeply when chlorine is let in.

9. It is better to lead the gas through a drying tower containing small lumps of calcium chloride before passing it through the reaction mixture.

10. Although it is not necessary, the product can be recrystallized from petroleum ether (b.p. 40–60°) without much loss. The melting point of the recrystallized product is 51–52°.

11. This is a modification of the new general method for the preparation of carbodiimides by the thermolysis of 5-substituted 4-aryl-1,2,3,5-thiaoxadiazole-1-oxides described recently by Rajagopalan and Advani,⁵ whereby the 4,5-diphenyl-1,2,3,5-thiaoxadiazole-1-oxide, which is formed in this reaction, is not isolated but decomposed *in situ*.

12. The drying and weighing of triethylamine hydrochloride should be carried out only after N-sulfinylaniline has been added to the solution of benzonitrile oxide, as otherwise the latter, not being very stable in the free state, would dimerize resulting in the reduction in yield of the carbodiimide.

13. At this point it is best to use the flask that is going to be employed subsequently for the distillation of the carbodiimide to avoid unnecessary loss in transferring from one flask to the other.

14. The temperature of the bath used in this distillation should not exceed 160°. A short-path distillation apparatus should be used.

15. Most of this fraction is comprised of diphenylcarbodiimide.

16. The yield, on the basis of average recovered N-sulfinylaniline, is 64–66%.

17. The infrared spectrum was determined in a Perkin-Elmer Infracord 337 spectrophotometer.

3. Discussion

Diphenylcarbodiimide can be prepared by the removal of the elements of hydrogen sulfide from N,N'-diphenylthiourea by

mercuric oxide,⁶ lead oxide,⁷ sodium hypochlorite,⁸ or phosgene;⁹ by heating phenylisocyanate in a sealed tube¹⁰ or in the presence of catalysts such as phospholenes¹¹ or phosphonates;¹² by the pyrolysis of N,N',N''-triphenylguanidine,¹³ 3-phenyl-4-phenylimino-1,3-thiazetidin-2-one (carbonythiocarbanilide),¹⁴ and 1,5-diphenyl tetrazole;¹⁵ and by heating phenylisocyanide dichloride with aniline hydrochloride in an inert solvent.¹⁶

Although this procedure offers no advantage over that of Hünig, Lehmann, and Grimmer,⁷ it effectively illustrates a new method for the synthesis of symmetrical and unsymmetrical carbodiimides.⁵ The generality of this procedure is limited only by the number of substituted benzohydroxamoyl chlorides that can be made without difficulty, as a variety of N-sulfinylamines is easily accessible.²

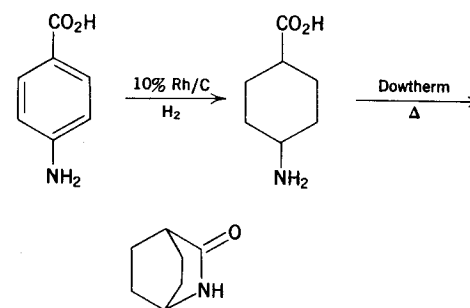
N-Sulfinylaniline, the procedure for the preparation of which is described in Part A, is a versatile intermediate in the synthesis of heterocyclic compounds.^{2, 5, 17} Benzohydroxamoyl chloride, the method for the preparation of which is given in Part B, is the precursor of the highly reactive benzonitrile oxide, the diverse dipolar addition reactions of which have been thoroughly investigated.¹⁸ A wide array of heterocyclic compounds can be prepared starting with benzonitrile oxide.¹⁸

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3-ISOQUINUCLIDONE

(3-Azabicyclo[2.2.2]octan-2-one)



Submitted by W. M. PEARLMAN¹

Checked by PETER CAMPBELL and RONALD BRESLOW

1. Procedure

A. *cis- and trans-4-Aminocyclohexanecarboxylic acid*. A mixture of 27.4 g. (0.20 mole) of *p*-aminobenzoic acid (Note 1), 200 ml. of water, and 2 g. of 10% rhodium-0.1% palladium on carbon catalyst (Note 2) is placed in a pressure bottle and hydrogenated at 50 p.s.i. When 0.6 mole of hydrogen has been absorbed (Note 3), the mixture is filtered and concentrated under reduced pressure until crystals start to form (Note 4). The mixture is diluted with 200 ml. of dimethylformamide and cooled to 5°, filtered, washed with dimethylformamide, then methanol, and dried, giving 19.4–20.3 g. (68–71%) of *cis- and trans-4-aminocyclohexanecarboxylic acid*, m.p. 292–296° (Note 5).

B. *3-Isoquinuclidone*. A mixture of 4.53 g. of *cis- and trans-4-aminocyclohexanecarboxylic acid* and 30 ml. of Dowtherm A (Note 6) is heated as rapidly as possible to reflux temperature.

Heating is continued for 20 minutes during which time the water formed is allowed to distill away; at the end of this time, solution has taken place. The solution is allowed to cool to room temperature and is diluted with 100 ml. of isooctane. The solution is extracted three times with 50-ml. portions of water. The combined water extracts are treated with charcoal, filtered, and concentrated to dryness under reduced pressure. The residue is crystallized from cyclohexane giving 3.20–3.33 g. (81–84%) of 3-isoquinuclidone, m.p. 197–198° (Note 5).

2. Notes

1. Purchased from B. L. Lemke and Co., Inc., 199 Main Street, Lodi, New Jersey. The checkers used material from Eastman Organic Chemicals Department.

2. A mixture of 5.26 g. of rhodium chloride trihydrate, 0.34 g. of palladium chloride, 18 g. of carbon (Darco G-60), and 200 ml. of water is rapidly stirred and heated to 80°. Lithium hydroxide hydrate (2.7 g.) dissolved in 10 ml. of water is added all at once and the heating stopped. The mixture is stirred overnight, filtered, and washed with 100 ml. of 0.5 v/v% aqueous acetic acid. The product is dried under reduced pressure at 65°, giving 20.6–21 g. of the catalyst. One gram of this catalyst consumes 0.0022–0.0028 mole of hydrogen in aqueous suspension.²

3. The checkers found that the reduction requires 4–5 days, whereas the submitter reported the reaction requires 24 hours. Fresh catalyst is added whenever the rate of hydrogen uptake significantly decreases. When fresh catalyst is added to the reaction vessel, it is important that it first be wet with solvent and that the hydrogen be well evacuated. Opening the mixture to the atmosphere without careful evacuation will produce a hydrogen-oxygen mixture which may explode on contact with fresh catalyst.

4. It is necessary to concentrate the solution to one-fifth volume before crystals form.

5. The submitters report the preparation scaled up by fifty-fold with similar yields and purities.

6. Purchased from Dow Chemical Co., Midland, Michigan.

3. Discussion

Ferber and Brückner³ reduced *p*-aminobenzoic acid using Adams catalyst (PtO₂) at atmospheric pressure, and Schneider and Dillman⁴ reduced *p*-aminobenzoic acid using 10% rhodium on carbon at 140 atm. and 70°. 3-Isoquinuclidone has been prepared, by the previously mentioned investigators,^{3, 4} by heating the dry 4-aminocyclohexane carboxylic acid at elevated temperatures.

The described method of preparation of 3-isoquinuclidone has the following advantages: The isolation of the *cis* form of 4-aminocyclohexane carboxylic acid is not required in order to obtain a good yield; the amount of 3-isoquinuclidone that can be prepared at a time is limited only by the size of available equipment; the yield is excellent and the workup is easy and straightforward.

3-Isoquinuclidone has been found to be an excellent substitute for camphor for molecular weight determinations.²

1. Research Laboratories, Parke, Davis & Company, Ann Arbor, Michigan.

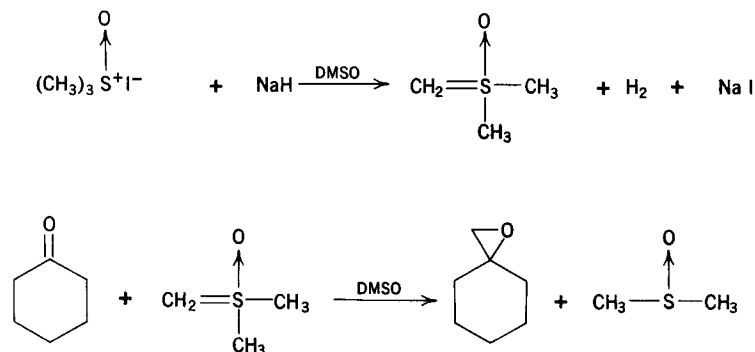
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METHYLENECYCLOHEXANE OXIDE

(Octane, 1-oxaspiro[2.5]-)



Submitted by E. J. COREY¹ and MICHAEL CHAYKOVSKY²
 Checked by WILLIAM WASHBURN and RONALD BRESLOW

1. Procedure

A. *Dimethyloxosulfonium methylide* (Note 1). In a 500-ml., three-necked, round-bottomed flask with a magnetic stirrer (Note 2) are placed 8.8 g. (0.22 mole) of sodium hydride (60% oil dispersion) (Note 3) and 150 ml. of petroleum ether (30–60°). The suspension is stirred, the hydride allowed to settle, the petroleum ether decanted (Note 4), and 250 ml. of dry dimethyl sulfoxide (Note 5) is added. The flask is immediately fitted with an inlet and outlet for nitrogen and a piece of Gooch tubing connected to a 125-ml. Erlenmeyer flask containing 50.6 g. (0.23 mole) of trimethyloxosulfonium iodide (Note 6). A gentle stream of dry nitrogen is then continuously passed through the system. With stirring, the oxosulfonium iodide is added, in portions, over a period of 15 minutes (Note 7) and stirring is then continued for an additional 30 minutes (Note 8).

B. *Methylenecyclohexane oxide*. The Gooch tubing is removed

from the reaction flask and immediately replaced with a sealed, pressure-compensated dropping funnel containing 19.6 g. (0.2 mole) of cyclohexanone (Note 9), which is then added to the reaction mixture over a 5-minute period. After stirring for 15 minutes, the reaction mixture is heated to 55–60° for 30 minutes with an oil bath and then poured into 500 ml. of cold water and extracted with three 100-ml. portions of ether. The combined ether extracts are washed with 100 ml. of water, then with 50 ml. of saturated aqueous salt solution, dried over anhydrous sodium sulfate, and the ether is distilled at atmospheric pressure through a 20-cm. Vigreux column. The almost colorless residue is transferred to a 50-ml. round-bottomed flask and distilled under reduced pressure through a 5-cm. Vigreux column to yield 15–17 g. (67–76%) of the oxide as a colorless liquid, b.p. 61–62° (39 mm.); n_D^{23} 1.4485 (Note 10). The n.m.r. spectrum (CDCl_3 ; $(\text{CH}_3)_4\text{Si}$ internal standard) showed a band at δ 1.58 (10H) and a sharp singlet at δ 2.53 (2H).

2. Notes

1. The reaction should be carried out in a well-ventilated hood because hydrogen is evolved.
2. The submitters used a mechanical stirrer, but the checkers found that the more convenient magnetic stirrer works as well.
3. The submitters used Alfa Inorganics Inc. sodium hydride dispersion.
4. The petroleum ether removes most of the oil from the hydride dispersion.
5. Matheson, Coleman and Bell anhydrous dimethyl sulfoxide was stirred over powdered calcium hydride overnight and then distilled under reduced pressure, b.p. 64–65° (4 mm.). Dimethyl sulfoxide should not be distilled at temperatures above 90° since at these higher temperatures appreciable disproportionation occurs producing dimethyl sulfone and dimethyl sulfide, the latter of which contaminates the distilled solvent.
6. Trimethyloxosulfonium iodide was purchased from Aldrich Chemical Co. and was recrystallized from water, crushed, and dried in a desiccator over phosphorus pentoxide before use. The

salt may be prepared by reaction of dimethyl sulfoxide with excess methyl iodide.³

7. The reaction is only mildly exothermic. No cooling is necessary.

8. After this time the evolution of hydrogen is essentially complete.

9. Eastman Kodak white label cyclohexanone was used without further purification.

10. Reported physical constants are b.p. 62–63° (37 mm.), n_D^{20} 1.4470;⁴ b.p. 66–68° (50 mm.) n_D^{20} 1.4506.⁵

3. Discussion

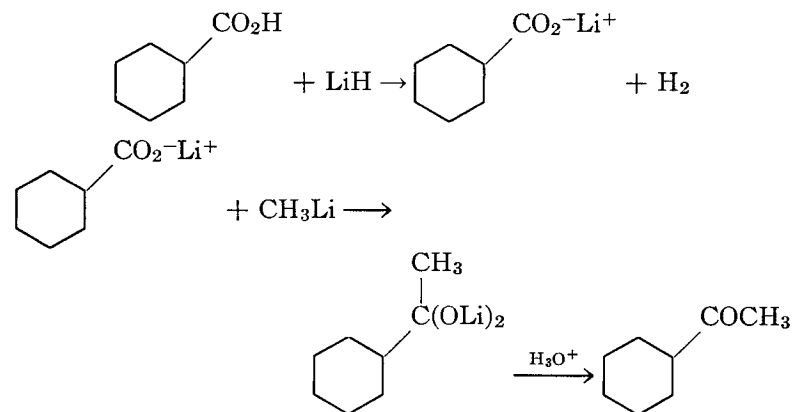
Methylenecyclohexane oxide has been prepared by the oxidation of methylenecyclohexane with benzonitrile-hydrogen peroxide or with peracetic acid;⁵ by treatment of 1-chlorocyclohexylmethanol with aqueous potassium hydroxide;⁶ and by the reaction of dimethylsulfonium methylide with cyclohexanone.⁷

This reaction illustrates a general method for the conversion of ketones and aldehydes⁸ into oxiranes using the methylene-transfer reagent dimethyloxosulfonium methylide. The yields of oxiranes are usually high, and the crude products, in most cases, are of sufficient purity to be used in subsequent reactions (e.g., rearrangement to aldehydes) without further purification.

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METHYL KETONES FROM CARBOXYLIC ACIDS: CYCLOHEXYL METHYL KETONE

(Ketone, cyclohexyl methyl)



Submitted by THOMAS M. BARE and HERBERT O. HOUSE¹
Checked by A. DE MEIJERE and K. B. WIBERG

1. Procedure

Caution! Since hydrogen is liberated in the first step of this reaction, it should be conducted in a hood. A dry, 500-ml., three-necked flask is fitted with a reflux condenser, a pressure-equalizing dropping funnel, a mechanical stirrer, and an inlet tube to maintain a static nitrogen atmosphere in the reaction vessel throughout the reaction. In the flask are placed 1.39 g. (0.174 mole) of powdered lithium hydride (Note 1) and 100 ml. of anhydrous 1,2-dimethoxyethane (Note 2). While this suspension is stirred vigorously, a solution of 19.25 g. (0.150 mole) of cyclohexanecarboxylic acid (Note 3) in 100 ml. of anhydrous 1,2-dimethoxyethane (Note 2) is added dropwise over a 10-minute period. The resulting mixture is heated to reflux with stirring for 2.5 hours, at which time hydrogen evolution and the formation of lithium cyclohexanecarboxylate are complete. After the resulting sus-

pension has been cooled to approximately 10° with an ice bath, it is stirred vigorously while 123 ml. of an ethereal solution containing 0.170 mole of methyllithium (Note 4) is added dropwise over a 30-minute period. After the addition is complete, the ice bath is removed and the resulting suspension is stirred at room temperature for 2 hours. The dropping funnel is removed from the reaction flask and replaced by a rubber septum fitted with a 4-mm. O.D. glass tube of suitable dimensions to permit the reaction mixture to be siphoned from the reaction flask when a slight positive nitrogen pressure is present in the flask.

The fine suspension in the reaction flask is agitated and siphoned into a vigorously stirred mixture of 27 ml. (0.32 mole) (Note 5) of concentrated hydrochloric acid and 400 ml. of water. The reaction flask is rinsed with an additional 100 ml. of ether which is also added to the aqueous solution. After the resulting mixture has been saturated with sodium chloride, the organic phase is separated and the alkaline (Note 5) aqueous phase is extracted with three 150-ml. portions of ether. When the combined organic solutions have been dried over magnesium sulfate, the bulk of the ether is distilled from the mixture through a 40-cm. Vigreux column (Note 6) and then the residual ether and the 1,2-dimethoxyethane are distilled from the mixture through a 10-cm. Vigreux column. Distillation of the residual pale yellow liquid separates 17.1–17.7 g. (91–94%) of the methyl ketone as a colorless liquid, b.p. 57–60° (8 mm.), n_D^{26} 1.4488–1.4489 (Note 7).

2. Notes

1. Lithium hydride of suitable quality may be purchased from Alfa Inorganics, Inc., 8 Congress Street, Beverly, Massachusetts 01915.

2. Commercial 1,2-dimethoxyethane, b.p. 85–86°, purchased from Eastman Organic Chemicals, was distilled from lithium aluminum hydride before use.

3. The cyclohexanecarboxylic acid, m.p. 31–32°, purchased from Aldrich Chemical Company was used without further purification.

4. An ethereal solution which was 1.38M in methyllithium was purchased from Foote Mineral Company. The concentration of methyllithium in ethereal solutions may be conveniently determined by a procedure described elsewhere^{2, 3} in which the lithium reagent is titrated with *sec*-butyl alcohol, utilizing the charge transfer complex formed from bipyridyl or *o*-phenanthroline and the lithium reagent as an indicator.

5. The quantity of hydrochloric acid used is normally insufficient to neutralize all the lithium hydroxide produced when the reaction mixture is quenched in the aqueous solution. As a result, any unchanged cyclohexanecarboxylic acid will be present as its lithium salt and will remain in the aqueous phase.

6. The product is sufficiently volatile that use of a rotary evaporator or an open flask to distill the bulk of the ether and 1,2-dimethoxyethane from this solution may result in loss of a significant fraction of the product.

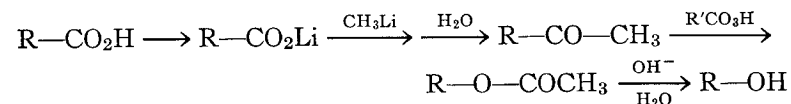
7. The product may be analyzed by use of a gas chromatography column packed with either LAC-728 (diethylene glycol succinate) or Carbowax 20M suspended on Chromosorb P. Using a 2.5-m. LAC-728 column heated to 100°, the submitters found retention times of 9.4 and 13.0 minutes for cyclohexyl methyl ketone and cyclohexyldimethylcarbinol. Less than 1% of the carbinol by-product was present.

3. Discussion

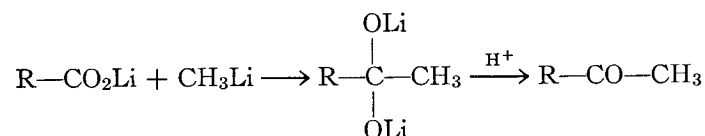
Apart from the reaction of cyclohexanecarboxylic acid with methyllithium,⁴ cyclohexyl methyl ketone has been prepared by the reaction of cyclohexylmagnesium halides with acetyl chloride or acetic anhydride^{5–7} and by the reaction of methylmagnesium iodide with cyclohexanecarboxylic acid chloride.⁸ Other preparative methods include the aluminum chloride-catalyzed acetylation of cyclohexene in the presence of cyclohexane,⁹ the oxidation of cyclohexylmethylcarbinol,^{10, 11} the decarboxylation and rearrangement of the glycidic ester derived from cyclohexanone and *t*-butyl α -chloropropionate,¹² and the catalytic hydrogenation of 1-acetylcyclohexene.^{13, 14}

This preparation illustrates the procedure for reaction of

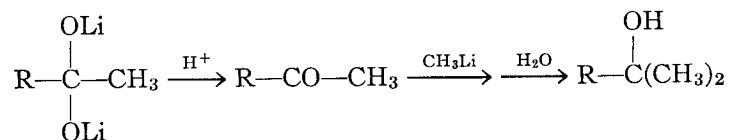
organolithium reagents with the lithium salts of carboxylic acids to form ketones.¹⁵ The reaction is generally applicable to alkyl, vinyl, and aryl organolithium reagents and carboxylic acid salts which do not contain other interfering functional groups. However, the reaction has been most often used with methyl-lithium for the preparation of methyl ketones. The reaction is known to effect the *stereospecific* conversion of a carboxylic acid to methyl ketone and, consequently, is a useful part of the sequence illustrated in the accompanying equations for interrelating the stereochemistry of alcohols and carboxylic acids.^{16, 17}



The reaction is believed to proceed by the indicated conversion of a lithium carboxylate to the dilithium salt¹⁸ which is stable



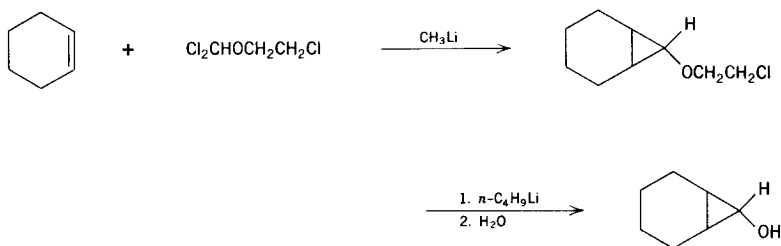
at room temperature in the absence of proton-donating solvents or reactants. However, the rapidity with which this dilithium salt is decomposed to a ketone in the presence of proton donors, accompanied by the rapidity of the subsequent reaction of the ketone with more methyllithium, can lead to a common side reaction in which an alkyldimethyl carbinol is formed. Both of the aforementioned reactions appear to be fast compared with 0.01 second usually required to disperse components with the conventional mixing techniques. This side reaction can be almost entirely avoided by taking precautions to minimize the



possibility that high *local concentrations* of the geminal dialkoxide and the lithium reagent are present when a proton donor is added during either the reaction or the *subsequent quenching*. It

is frequently possible to obtain only relatively small amounts of the alcohol by-product by the dropwise addition *with vigorous mixing* of 2 equivalents of the organolithium reagent *to* a solution of the carboxylic acid. During this procedure it is not uncommon for the lithium carboxylate to separate during the addition of the first mole of organolithium reagent and then to react and redissolve as the second equivalent of organolithium reagent is added. The reverse procedure, adding the acid to a solution of the organolithium reagent, appears always to produce substantial amounts of the alcohol by-product. The procedure used in this preparation illustrates how this mixing problem may be avoided by the initial conversion of the carboxylic acid to its lithium salt with lithium hydride. In all cases it is important not to add a large excess of organolithium reagent and to add the final reaction mixture to the aqueous quenching bath slowly and with vigorous stirring if the formation of substantial amounts of alcohol by-product is to be avoided.

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exo/endo-7-NORCARANOL

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 Checked by WILLIAM G. DAUBEN, MICHAEL H. MCGANN, and
 NOEL VIETMEYER

1. Procedure

A. *exo/endo*-7-(2-Chloroethoxy)bicyclo[4.1.0]heptane. A 2-l., three-necked, round-bottomed flask is equipped with a sealed stirrer, a pressure-equalizing dropping funnel, and a condenser fitted with a nitrogen-inlet tube (Note 1). The flask is flushed with dry nitrogen, and to it are added 500 ml. of cyclohexene (Note 2) and 49.0 g. (0.300 mole) of dichloromethyl 2-chloroethyl ether (Note 3). To the stirred solution at room temperature is added dropwise 430 ml. (0.47 mole) of a 1.1*N* ethereal solution of methyllithium (Note 4) at a rate adequate to maintain gentle reflux of the ether; the addition requires *ca.* 4 hours (Note 5). The reaction mixture is poured into 1.5 l. of ice water, the aqueous layer is separated, and the organic layer is extracted with four 300-ml. portions of water and dried over anhydrous sodium sulfate. The solvents are removed by distillation through a 10-cm. Vigreux column (Note 6), and the residue is distilled under reduced pressure to yield 21–29 g. (40–56%) of *exo/endo*-7-(2-chloroethoxy)bicyclo[4.1.0]heptane, b.p. 98–101° (10 mm.). This material is sufficiently pure for the next step (Note 7).

B. *exo/endo*-7-Norcaranol. A 500-ml. three-necked flask equipped with a magnetic stirrer, a pressure-equalizing dropping

funnel, and a condenser fitted with a nitrogen-inlet tube (Note 1) is flushed with nitrogen, and a solution of 20.0 g. (0.115 mole) of *exo/endo*-7-(2-chloroethoxy)bicyclo[4.1.0]heptane in 150 ml. of dry ether is added. To this solution is added dropwise at room temperature 280 ml. (0.45 mole) of a 1.6*N* solution of *n*-butyllithium in hexane over a 30- to 45-minute period (Note 5). The mixture is poured into 800 ml. of ice-cold, saturated, aqueous sodium bicarbonate, and the aqueous phase is separated and extracted with four 150-ml. portions of ether. The organic solutions are combined and dried over anhydrous sodium sulfate, and the solvents are removed by distillation through a 10-cm. Vigreux column at a maximum bath temperature of 65°. The residue is distilled under reduced pressure to yield 11.6–12.3 g. (90–95%) of *exo/endo*-7-norcaranol, b.p. 80–85° (10 mm.) (Notes 8 and 9).

2. Notes

1. The nitrogen-inlet system described by Johnson and Schneider² is satisfactory.

2. The cyclohexene was dried over potassium hydroxide pellets and distilled from sodium before use.

3. The checkers prepared this ether in the following manner. 2-Ethoxy-1,3-dioxolane was prepared in 82% yield from ethylene glycol and ethyl orthoformate and treated with acetyl chloride to give 2-chloroethyl formate by the procedures of Baganz and Domaschke;³ the overall yield was 56–60%. The formate was converted to dichloromethyl 2-chloroethyl ether with phosphorus pentachloride by the procedure of Gross, Rieche, and Höft,⁴ and the product was distilled through a 10-cm. column containing glass helices; b.p. 107–111° (110 mm.); yield 85%.

4. The methyllithium must be prepared from methyl iodide because the presence of the iodide anion is essential. The submitters prepared methyllithium in the following manner. Methyl iodide (425.7 g., 3.00 moles) was added with stirring to 48 g. (7.0 g. atoms) of lithium in 2.5 l. of ether under nitrogen at a rate adequate to maintain gentle reflux of the ether. After 24 hours the solution of methyllithium was decanted into a storage vessel filled with nitrogen. The concentration was estimated in the

usual way by hydrolysis of an aliquot and titration with 0.1*N* hydrochloric acid.

5. The addition of the organolithium solution is continued until a positive Gilman test ⁵ is obtained.

6. Isopropyl 2-chloroethyl ether, b.p. 118–121°, is formed in variable amounts as a by-product.

7. The *exo/endo* ratio is ~6:1; the *exo* and *endo* isomers show characteristic triplets in their n.m.r. spectra at δ 2.9 and 3.1 p.p.m., respectively.

8. The *exo/endo* ratio is ~8:1; the *exo* and *endo* isomers show characteristic triplets in their n.m.r. spectra at δ 3.0 and 3.25 p.p.m., respectively.

9. In some runs, *exo*-7-norcaranol, m.p. 57–58°, crystallized in the condenser or in the receiver.

3. Discussion

This method for the preparation of *exo/endo*-7-norcaranol is an adaptation of that described by Schöllkopf, Paust, Al-Azrak, and Schumacher.⁶ The method has been used by the submitters for the preparation of the following cyclopropanols: *exo/endo*-6-hydroxybicyclo[3.1.0]hexane, *exo/endo*-8-hydroxybicyclo[5.1.0]octane, *exo/endo*-9-hydroxybicyclo[6.1.0]nonane, 2,2-dimethylcyclopropanol, 2,2,3,3-tetramethylcyclopropanol, *trans*-2,3-dimethylcyclopropanol, *cis*-2,3-dimethyl-*cis/trans*-cyclopropanol, *cis/trans*-2,2,3-trimethylcyclopropanol, and *cis/trans*-2-phenylcyclopropanol.

The principal disadvantage of this procedure is that the olefin must be used in at least three- to fourfold excess in order to obtain reasonable yields. In case of rare olefins, or of olefins containing groups such as the carbonyl group which add organolithium compounds, other methods ^{7, 8} might be more advantageous. The method is also limited to the preparation of secondary cyclopropanols.

The most satisfactory procedure for obtaining cyclopropanol itself is that of Cottle^{7, 9} which is also recommended for the synthesis of 1-arylcyclopropanols.⁷ 1-Alkylcyclopropanols are best prepared via the corresponding acetates which are obtained

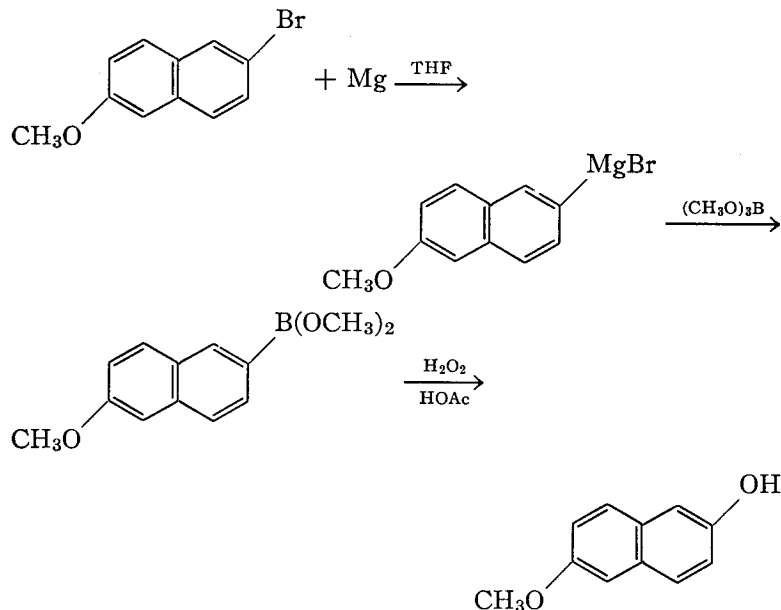
by the method of Freeman¹⁰ that involves thermolysis of a 3-acetoxy-1-pyrazolin. According to DePuy,⁷ cyclopropyl acetates are best cleaved to cyclopropanols by methyllithium. However, the preparation of cyclopropyl acetates is somewhat laborious. It usually involves reactions of an olefin with ethyl diazotate—in this step the olefin must be used in excess, too—followed by a Baeyer-Villiger rearrangement of the corresponding methyl cyclopropyl ketone.⁷

The cyclopropanols, the study of whose chemistry is still in its early stages,^{7, 8} show promise as useful synthetic intermediates. The chemistry of their derivatives should aid in the understanding of the nature of nucleophilic substitution on three-membered rings.^{7, 8, 11}

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PHENOLS: 6-METHOXY-2-NAPHTHOL

(2-Naphthol, 6-methoxy-)



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 Checked by R. E. IRELAND, J. W. TILLEY, and C. KOWALSKI

1. Procedure

A 2-l. three-necked flask equipped with a condenser and containing 27 g. (1.1 mole) of magnesium is flame-dried and the atmosphere replaced with nitrogen. A 200-ml. portion of tetrahydrofuran (Note 1) is added along with several lumps, totaling about 95 g., of 6-bromo-2-methoxynaphthalene (Note 2) and a small crystal of iodine. The mixture is heated to reflux until the boiling becomes spontaneous. An additional 600 ml. of tetrahydrofuran is added with more of the bromide to maintain a vigorous reflux, until 237.4 g. (1 mole) of 6-bromo-2-methoxy-

naphthalene has been added. After the spontaneous reflux has subsided, the dark solution is heated to reflux for 20 minutes.

A 5-l. three-necked flask fitted with a paddle stirrer, a Claisen adapter containing a thermometer well and nitrogen inlet, and a dropping funnel is flame-dried and placed under nitrogen. Into the flask are introduced 125 ml. (1.1 mole) of trimethyl borate (Note 3) and 600 ml. of tetrahydrofuran. This solution is cooled to -10° with an all-encompassing ice-salt bath or a dry ice-carbon tetrachloride bath. The dropping funnel is charged with the Grignard solution which is added over 30 minutes to the borate solution while stirring rapidly and maintaining the temperature between -10° and -5° . A white sludge separates from the solution during the addition. After stirring for an additional 15 minutes, 86 ml. (1.5 mole) of chilled acetic acid (Note 4) is added all at once. This is followed by the addition of a cold solution of 112 ml. (1.1 mole) of 30% hydrogen peroxide in 100 ml. of water, dropwise over 15 minutes, while maintaining the temperature below 0° (Note 5) and stirring vigorously.

The mixture is allowed to warm up over 20 minutes and is poured into a 2-l. separatory funnel. The purplish solution is washed with a saturated ammonium sulfate solution (about 1.5 l.) containing ferrous ammonium sulfate until the rust-brown ferric color is no longer produced. The organic layer is dried over magnesium sulfate and concentrated, leaving a dark solid. Purification of the solid by high-vacuum short path distillation gives 127–142 g. (73–81%) of a pinkish or tan-colored product, b.p. $148-150^{\circ}$ (0.15 mm.), m.p. $145-147^{\circ}$. It may be further purified by sublimation, or recrystallization from benzene-hexane, m.p. $148-149^{\circ}$.

2. Notes

1. Reagent grade tetrahydrofuran (Mallinckrodt) has been used directly. The formation of the Grignard reagent starts readily and no precipitates are formed. Tetrahydrofuran obtained from the Quaker Oats Company in 1-gal. cans has also been used; the reaction, however, is slower to start, a cloudy precipitate is formed, and the yield is slightly lower.

2. This starting material is obtained conveniently from the bromination² and methylation of 2-naphthol. The procedure is modified by not removing the tin salts.

After bromination of 144 g. (1 mole) of 2-naphthol, the hot solution is poured into water and filtered. The dry precipitate is mixed with a solution of 200 ml. of concentrated sulfuric acid in 500 ml. of technical methanol and heated to vigorous reflux for 4 hours. An oily layer separates during the heating period. The hot mixture is poured into 3 l. of ice and water, and the solids are removed by filtration. The moist solid is triturated with 1 l. of hot 5% sodium hydroxide. After chilling the mixture to solidify the oil, it is filtered and the product is washed and dried. The 6-methoxy-2-bromonaphthalene is purified by distillation, b.p. 114–118° (0.2 mm.). After distillation the product is most conveniently handled by remelting and pouring it into a mold to solidify. The overall yield is 173–208 g. (73–88%), m.p. 101.5–103°.

3. Commercial trimethyl borate contains an appreciable amount of methanol. It is removed by adding anhydrous lithium chloride³ to the bottle and allowing the mixture to stand with occasional shaking. The upper layer is decanted off and fractionated, b.p. 68–69°. The product must be protected from moisture.

4. Water added at this point hydrolyzes the arylboronic ester extremely rapidly to 2-methoxynaphthalene.

5. The reaction is exothermic. Except for a darkening of the product, no apparent harm results if occasionally the temperature rises to 10–15°.

3. Discussion

The classic caustic fusion of sulfonic acid salts has been used for preparing 2,6-dinaphthol⁴ and its derivatives. Other more recent procedures have employed the direct hydrolysis of aryl bromides⁵ and the oxidation of aryl Grignard reagents.⁶

The indirect oxidation of an aryl Grignard reagent through a boronic ester nearly doubles the yield of phenol obtained by direct oxidation and decreases the reaction time. Tetrahydro-

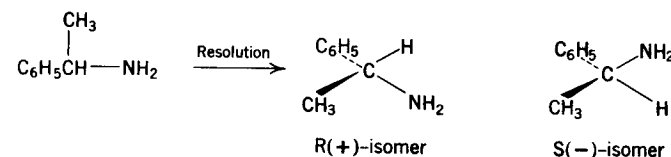
furan is the preferred solvent. It facilitates the dissolution of the bromide, which is relatively insoluble in diethyl ether, solvates the Grignard reagent, and renders the oxidation reaction homogeneous.

The preparation of 6-methoxy-2-naphthol is of particular interest as the starting point in many synthetic sequences. It is readily converted to 6-methoxy-2-tetralone through a Birch reduction.⁷

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R(+)- AND S(-)- α -PHENYLETHYLAMINE

(Benzylamine, α -methyl)



Submitted by ADDISON AULT¹

Checked by MARTIN GALL, ELIA J. RACAH, and
HERBERT O. HOUSE

1. Procedure

A. *S(-)- α -Phenylethylamine*. A mixture of 31.25 g. (0.208 mole) of (+)-tartaric acid and 450 ml. of methanol is placed in a 1 l. Erlenmeyer flask and heated to boiling. To the hot solution is added, cautiously to avoid foaming, 25.0 g. (26.2 ml., 0.206 mole) of racemic α -phenylethylamine (Note 1) and the

resulting solution is allowed to cool. Since crystallization occurs slowly, the solution should be allowed to stand at room temperature for approximately 24 hours. The (–)-amine (+)-hydrogen tartarate salt separates as white prismatic crystals (Note 2). The product (18.1–19.3 g.) should be collected on a filter and washed with a small volume of methanol. The combined mother liquor and methanol washings should be concentrated to a volume of 175 ml. with a rotary evaporator. The resulting mixture is then heated to boiling, and the solution is allowed to cool and stand at room temperature for approximately 24 hours. In this way an additional crop (2.0–3.8 g.) of the (–)-amine (+)-hydrogen tartarate salt may be separated as white prisms (Note 2). The combined methanolic mother liquors and washings from these crystallizations are concentrated to dryness on a rotary evaporator. The crude residual salt is used for the preparation of the (+)-amine.

The combined crops of crude (–)-amine (+)-hydrogen tartarate are pulverized in a mortar and redissolved in 450–500 ml. of boiling methanol. The resulting hot solution is concentrated to 350 ml. (Note 3) and then allowed to cool and stand for 24 hours. After the initial crop (14.3–16.2 g.) of pure (–)-amine (+)-hydrogen tartarate has been collected as white prisms (Note 2) (m.p. 179–182° dec.), the mother liquors and washings are concentrated to 75 ml. and again allowed to stand for 24 hours. In this way a second crop (2.9–3.6 g.) of the pure (–)-amine salt is obtained. The total yield of the pure (–)-amine salt is 17.9–19.1 g. (64–68%).

A mixture of the pure (–)-amine salt (17.9–19.1 g.) and 90 ml. of water is treated with 15 ml. of aqueous 50% sodium hydroxide and the resulting mixture is extracted with four 75-ml. portions of ether. After the combined ether extracts have been washed with 50 ml. of saturated aqueous sodium chloride and dried over magnesium sulfate, the bulk of the ether is distilled from the mixture through a 30-cm. Vigreux column and the residual liquid is distilled under reduced pressure. The (–)-amine is collected as 6.9–7.2 g. (55–58%) of colorless liquid, b.p. 94–95° (28 mm.), n_D^{25} 1.5241–1.5244, $[\alpha]_D^{25}$ –39.4° (neat) (Notes 4, 5).

B. *R*(+)- α -Phenylethylamine. The residual salts (approx-

mately 35 g.) obtained by concentration of the methanolic mother liquors from the initial crystallization of the (–)-amine (+)-hydrogen tartarate are treated successively with 160 ml. of water and 25 ml. of aqueous 50% sodium hydroxide. After the resulting mixture has been extracted with ether, the extract is dried, concentrated, and distilled as previously described. The recovered amine amounts to 12.5–14.1 g. of colorless liquid, b.p. 79–80° (18 mm.), $[\alpha]_D^{28}$ +23.8 to +24.7° (neat). From the weight and specific rotation data for this amine sample and the reported² specific rotation, $[\alpha]_D^{25}$ +40.6° (neat), for the pure (+)-amine, the amount of excess (+)-amine present in the recovered amine sample is calculated. Typical values range from 0.06 to 0.07 mole of excess (+)-amine. A solution of this partially resolved amine in 90 ml. of 95% ethanol is heated to boiling and then treated with 180 ml. of an ethanolic solution containing a sufficient amount (0.03–0.035 mole) of concentrated sulfuric acid to convert the excess (+)-amine to its neutral sulfate salt (Note 6). The hot solution is allowed to cool to room temperature, and the crude (+)-amine sulfate which separates as white needles (7.8–9.3 g.) is collected on a filter and washed with 95% ethanol. The combined ethanolic mother liquors and washings are concentrated and allowed to cool to separate a second crop (1.2–1.4 g.) of the crude (+)-amine sulfate. The combined crops of (+)-amine sulfate are dissolved in a minimum volume (about 45 ml. of hot water), and the resulting hot solution is diluted with acetone until it is just saturated at the boiling point. After the solution has been allowed to cool to room temperature, the pure (+)-amine sulfate which separates as white needles, m.p. 240–265° dec. (5.0–6.1 g.) is collected on a filter and washed with cold 95% ethanol. The combined mother liquors and washings are concentrated to dryness, and the residual solid is recrystallized from aqueous acetone to separate additional crops (2.6–2.8 g.) of the pure (+)-amine sulfate. The total yield of the pure amine sulfate is 7.8–8.9 g. (45–51% on the basis of the starting α -phenylethylamine).

A mixture of the pure (+)-amine sulfate (7.8–8.9 g.) and 40 ml. of water is treated with 6.0 ml. of aqueous 50% sodium hydroxide and the resulting mixture is extracted with four 75 ml.

portions of ether. The combined ether extracts are washed with 50 ml. of saturated aqueous sodium chloride, dried over magnesium sulfate, and concentrated by distillation of the ether through a 30-cm. Vigreux column. The residual liquid is distilled under reduced pressure to separate 5.1–5.5 g. (41–44%) of the (+)-amine as a colorless liquid, b.p. 85–86° (21 mm.), n_D^{25} 1.5243–1.5248, $[\alpha]_D^{29} + 39.7^\circ$ (neat) (Note 7).

2. Notes

1. A practical grade of racemic α -phenylethylamine supplied by Eastman Organic Chemicals is satisfactory. However, if the racemic amine is highly discolored, distillation before use is recommended.

2. Sometimes a salt separates in the form of white needles. The (–)-amine recovered from these needlelike crystals is not optically pure; $[\alpha]_D^{25} -19^\circ$ to -21° (neat). If the product separates either partially or completely as needlelike crystals during the crystallization, the mixture should be warmed until all the needlelike crystals have dissolved, and then the solution should be allowed to cool slowly. If possible, the solution should be seeded with the prismatic crystals. Separation of the prismatic and needlelike crystals can also be effected by taking advantage of the fact that the needles dissolve more rapidly than the prisms in warm methanol.

3. Because of the low rate of solution of the amine salt, the desired solution is obtained most rapidly by dissolving the salt in excess solvent and then concentrating the solution.

4. The literature value (d_4^{25} 0.9528)² for the density of α -phenylethylamine was used to calculate the specific rotation.

5. From the reported specific rotation value, $[\alpha]_D^{25} -40.14^\circ$ (neat),³ $[\alpha]_D^{22} -40.3^\circ$ (neat),⁴ the optical purity of this preparation is estimated to be 98%. The boiling point of this amine at atmospheric pressure is 186–187°.

6. For example, a 14.1-g. (0.116 mole) sample of amine, $[\alpha]_D^{28} +23.8^\circ$ (neat), was estimated to contain 0.0676 mole of excess (+)-amine. Therefore 3.52 g. (0.0345 mole) of concentrated sulfuric acid was added.

7. From the reported specific rotation value, $[\alpha]_D^{25} +40.6^\circ$ (neat),² the optical purity of this preparation is estimated to be 98%. The boiling point of this amine at atmospheric pressure is 186–187°.

3. Discussion

The method presented is based on the procedure of Theilacker and Winkler.⁴ It makes use of (+)-tartaric acid, an inexpensive and readily available material, as the resolving agent and provides optically pure samples of both enantiomers of α -phenylethylamine.

Some other methods of resolution include the use of *l*-malic acid [(+)-form],⁵ *l*- and *dl*-malic acids [(+)- and (–)-forms],⁶ *l*-malic acid and *d*-tartaric acids [(+)- and (–)-forms],⁷ *d*- α -bromocamphor- π -sulfonic acid [(–)-form],⁸ *l*-quinic and *d*-tartaric acids [(+)- and (–)-forms],⁹ 2,3,4,6-tetraacetyl-*D*-glucose [(+)-form],¹⁰ and barium (–)-bornyl sulfate [(+)- and (–)-forms].¹¹

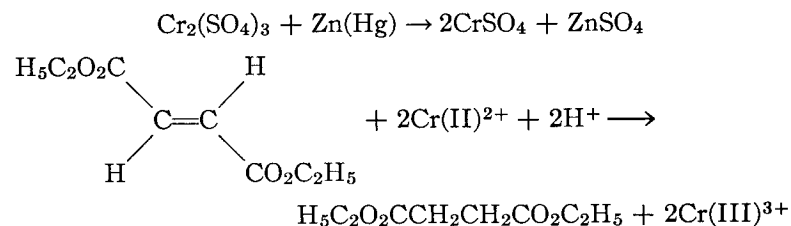
The enantiomers of this amine are useful resolving agents. Some of the compounds which have been resolved with one of the optically active forms of α -phenylethylamine are: mandelic acid,¹² α -methylmandelic acid,¹³ α -ethylmandelic acid,¹⁴ 2-phenylpropionic acid,¹⁵ 2-(*p*-nitrophenyl)propionic acid,¹⁶ 2,3-dichloro-2-methylpropionic acid,¹⁷ 2-phenylbutyric acid,¹⁵ 2-phenylvaleric acid,¹⁸ 2-phenylcaproic acid,¹⁸ α -methylhydrocinnamic acid,¹⁹ β -methylhydrocinnamic acid,²⁰ benzylsuccinic acid,²¹ N-formyl-phenylalanine,²² N-acetyl-3,5-dibromotyrosine,²³ N-acetyltryptophan,²⁴ 6,6'-dinitrodiphenic acid,²⁵ and 3-methylcyclohexanone and β -methylcinnamaldehyde, via the amine bisulfite complexes.²⁶

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REDUCTION OF CONJUGATED ALKENES WITH CHROMIUM(II) SULFATE: DIETHYL SUCCINATE

(Succinic acid, diethyl ester)



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Checked by FREDERICK J. SAUTER and HERBERT O. HOUSE

1. Procedure

A. Chromium(II) sulfate solution. A 3-l., three-necked flask fitted with a gastight mechanical stirrer and nitrogen inlet and outlet stopcocks is charged with 300 g. (ca. 0.55 mole) of hydrated

chromium(III) sulfate (Note 1), 2 l. of distilled water, 75 g. (1.15 g. atoms) of mossy zinc (Note 2), and 4.0 ml. (54 g., 0.27 g. atom) of mercury (Note 3). After the flask has been flushed with nitrogen for 30 minutes, the mixture is warmed in a water bath to about 80° (Note 4) with stirring for 30 minutes under a nitrogen atmosphere to initiate reaction. Then the mixture is stirred at room temperature under a nitrogen atmosphere for an additional 30 hours, at which time the originally green reaction mixture has been converted to a clear, deep blue solution. While a nitrogen atmosphere is maintained over the reaction solution, the mechanical stirrer is removed and replaced with a nitrogen outlet (Note 5). The third neck of the reaction flask is fitted with a short adapter closed with a rubber septum (Note 6).

The solution is standardized by withdrawing 5.0-ml. aliquots into a hypodermic syringe (Note 6) fitted with a relatively wide-bore needle and flushed with nitrogen before use. The aliquots are quenched by injecting them into 10 ml. of aqueous 1*M* ferric chloride solution in an Erlenmeyer flask under a nitrogen atmosphere. After 2 minutes the flow of nitrogen is stopped, and the resulting solution is diluted with 50 ml. of water and titrated with 0.1*N* ceric sulfate to the ferrous ion-phenanthroline end point (Note 7). Solutions prepared in this fashion are usually 0.55*M* in chromium(II) species (Note 8) and are stable for years, if they are protected from reaction with oxygen.

B. Reduction of diethyl fumarate. A 1-l. three-necked flask is equipped with a magnetic stirring bar, an addition funnel with a pressure-equalizing tube, a stopcock connected to a mercury trap, and a rubber septum (Note 9). The addition funnel is charged with a solution of 13.87 g. (0.080 mole) of diethyl fumarate (Note 10) in 137 ml. of dimethylformamide (Note 11). A nitrogen line is connected to the top of the addition funnel and the system is thoroughly flushed with nitrogen (Note 12). With a hypodermic syringe, 318 ml. (0.175 mole) of the previously described 0.55*M* chromium(II) sulfate solution (0.175 mole) is added to the reaction flask through the rubber septum. After the stirrer has been started, the diethyl fumarate solution is added rapidly. The solution immediately turns green and the reduction is complete in 10 minutes (Note 13). The resulting

solution is diluted with 100 ml. of water and 30 g. of ammonium sulfate is added. The mixture is extracted with four 150-ml. portions of ether, and the combined ether extracts are washed with three 50-ml. portions of water and then dried over magnesium sulfate. After the ether has been removed by distillation through a 60-cm. Vigreux column, the residual liquid is distilled through a short Vigreux column to separate 12.4–13.2 g. (88–94%) of diethyl succinate (Note 14); b.p. 129° (44 mm), n_{D}^{23} 1.4194.

2. Notes

1. Mallinckrodt analytical reagent, chromium(III) sulfate crystals, $\text{Cr}_2(\text{SO}_4)_3(\text{H}_2\text{O})_x$, were employed. Repeated preparations with this substance have indicated its average formula weight to be 542.

2. Either Baker and Adamson or Mallinckrodt reagent grades of mossy zinc have been used interchangeably.

3. Distilled mercury was employed.

4. Warming is not always essential, but a more rapid reduction occurs routinely if the reaction is initiated by warming. In some cases a longer heating period may be required.

5. In order to maintain an oxygen-free atmosphere over the solution, it is essential that all standard taper joints be adequately lubricated and that the various joints be held together with rubber bands, wire, or springs.

6. Transfers are conveniently made by maintaining a slightly positive nitrogen pressure in the reaction vessel before the aliquots are removed and using an adapter consisting of a standard taper joint sealed to a wide-bore stopcock. The short length of glass tubing above the stopcock is fitted with a securely fastened rubber septum. The rubber septum above the stopcock is pierced with the hypodermic syringe, and then the stopcock is opened to place a slightly positive nitrogen pressure in the small septum-capped chamber. This procedure forces the plunger of the syringe out and sweeps any remaining oxygen from the syringe. The syringe plunger is replaced and the syringe needle is pushed below the surface of the solution. The internal nitrogen pressure forces

liquid into the syringe until slightly more than the desired amount is obtained. The syringe is then withdrawn and inverted and the excess solution is expelled into an absorbent paper. Finally, the syringe containing the desired volume of solution is emptied into a reaction vessel under a nitrogen atmosphere.

7. The preparation of the indicator solution is described by Kolthoff and Sandell.² The red-brown to green end point is easily observed.

8. Solutions of higher or lower concentrations can be prepared by adjusting the amounts of reagents.

9. Though unnecessary for this reduction, it is more usually convenient for chromium(II) sulfate reductions to fit the rubber septum to a stopcock adapter of the type described in Note 6.

10. Diethyl fumarate was purchased from either Eastman Organic Chemicals, Inc., or Aldrich Chemical Company and used without purification.

11. Baker reagent grade dimethylformamide was used without further purification.

12. The submitters recommend that the system be flushed with a slow stream of nitrogen for 30 minutes.

13. The kinetics of this reduction have been reported.³ The reaction is easily followed by withdrawing aliquots and analyzing them for chromium(II) content.

14. Diethyl succinate is the sole product of the reduction. The yield reflects the efficiency of the workup. The distilled product gives a single sharp peak on gas chromatography employing a column packed with Carbowax 20M suspended on Chromosorb P. On this column the checkers found the retention times of diethyl fumarate and diethyl succinate to be 38.8 minutes and 43.6 minutes, respectively.

3. Discussion

Aqueous solutions of chromium(II) sulfate have been prepared from chromium(III) sulfate by reduction with zinc powder³ and from potassium dichromate by reduction with amalgamated zinc and sulfuric acid.⁴ Solid chromium(II) sulfate pentahydrate can be obtained from the reaction of highly purified chromium metal

with concentrated sulfuric acid.⁵ The present procedure is especially simple since it avoids filtration of zinc powder and avoids the acid present in the dichromate reduction.

Chromium(II) sulfate is a versatile reagent for the mild reduction of a variety of bonds. Thus aqueous dimethylformamide solutions of this reagent at room temperature couple benzylic halides,^{3, 6} reduce aliphatic monohalides to alkanes,⁶ convert vicinal dihalides to olefins,⁷ convert geminal halides to carbenoids,⁸ reduce acetylenes to *trans*-olefins,⁹ and reduce α,β -unsaturated esters, acids, and nitriles to the corresponding saturated derivatives.¹⁰ These conditions also reduce aldehydes to alcohols.⁷

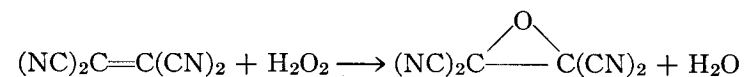
The reduction of diethyl fumarate described in this preparation illustrates the mildness of the reaction conditions for the reduction of acetylenes and α,β -unsaturated esters, acids, and nitriles.

The reduction of diethyl fumarate to diethyl succinate has also been effected with diethyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate¹¹ and by catalytic hydrogenation.

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TETRACYANOETHYLENE OXIDE

(Ethanetetracarbonitrile, 1,2-epoxy-)



Submitted by W. J. LINN¹

Checked by A. ESCHENMOSER, W. LUSUARDI,
and R. SCHEFFOLD

1. Procedure

Caution! Both tetracyanoethylene and tetracyanoethylene oxide slowly evolve hydrogen cyanide when exposed to water. Therefore all operations should be conducted in an efficient hood and contact with the skin should be avoided.

In a 500-ml. Erlenmeyer flask fitted with an efficient stirrer and thermometer are placed 25.6 g. (0.2 mole) of tetracyanoethylene (Note 1) and 150 ml. of acetonitrile (Note 2). The flask is surrounded by an ice-salt bath and the stirrer is started. When the temperature is about -4° , 21 ml. of 30% hydrogen peroxide is added from a buret at the rate of 3–5 ml. per minute. The rate is adjusted to keep the temperature at 10 – 12° (Note 3). Near the end of the addition, the color of the reaction mixture changes from dark amber to pale yellow. When all the peroxide has been added, the reaction mixture is stirred with efficient cooling for 3–4 minutes. Without delay the solution is then poured slowly, with very rapid stirring, into a mixture of 500 ml. of water and approximately 250 g. of crushed ice contained in 2-l. beaker (Note 4). The solid is filtered rapidly by suction through a coarse, sintered-glass funnel and washed with 200 ml. of ice water. For best results the product is dried on the funnel with continuous suction for 3–4 hours and recrystallized from 1,2-dichloroethane (10 ml. per g.) (Note 5). The yield of nearly colorless needles melting at 177 – 178° (sealed capillary) is 17.1

19.6 g. (59–68%) (Note 6). The infrared spectrum of the oxide (Nujol mull) is simple and useful in product identification. In addition to the strong $\text{—C}\equiv\text{N}$ absorption at 4.38μ , there are bands at 7.68 , 8.47 , 8.66 , 10.54 , and 11.23μ .

2. Notes

1. Tetracyanoethylene may be purchased from the Columbia Organic Chemicals Co., the Eastman Kodak Co., or prepared by the method of Carboni.² This procedure has been simplified in this laboratory as follows.³

To 450 ml. of cold water in the apparatus of Part A² there is added 99 g. (1.5 moles) of molten malononitrile followed by 250 g. of ice and 158 ml. (3.05 moles at 25°) of bromine. The bromine is added during 5–10 minutes, and during the addition enough ice (about 200 g.) is added to maintain the temperature at 10 – 15° . The mixture is stirred at 20° for 1 hour. A heavy layer of dibromomalononitrile is separated, and the aqueous layer is extracted with two 50-ml. portions of 1,2-dichloroethane. The dibromomalononitrile and the extracts are combined, dried over magnesium sulfate, and added to 750 ml. of dry 1,2-dichloroethane in the flask of Part B. Twenty grams of copper powder is added, and the mixture is heated to gentle reflux with stirring. An exothermic reaction generally occurs; when it subsides, or after about 10 minutes, a second 20-g. portion is added, and this process is continued until 120 g. has been added. The mixture is allowed to reflux a total of 4–6 hours. The solids are separated from the hot mixture using a fluted filter paper, which is washed with a little hot 1,2-dichloroethane. The filtrate is stored overnight at 0 – 5° . Nearly colorless tetracyanoethylene crystallizes out. It is separated on a Buchner funnel, washed with a little 1,2-dichloroethane, and dried in a vacuum desiccator; weight 29–38 g. (30–40%). The purity of the product is over 98% as judged by the ϵ_{max} [pure tetracyanoethylene has $\lambda_{\text{max.}}^{\text{CH}_2\text{Cl}_2}$ $277\text{ m}\mu$ (ϵ 12,050) $267\text{ m}\mu$ (ϵ 13,600)]. It is pure enough for most purposes including synthesis of the epoxide. If very pure material is needed, tetracyanoethylene can be recrystallized from 1,2-dichloroethane (15 ml. per g.) or sublimed at 130 – 140° at 1 mm.

2. Eastman Kodak Co. practical grade is sufficiently pure for the reaction.

3. The rate of addition of hydrogen peroxide is fairly fast initially but is slowed to maintain the indicated temperature. It is important to get the reaction over in a short time (5–7 minutes) for the best yield.

4. It is wise to use a mechanical or magnetic stirrer in order to induce rapid crystallization of the product. Prolonged contact of the product with water at this stage diminishes the yield markedly. The presence of anions, *e.g.*, chloride, can lead to more rapid decomposition of the product, and it is best to use distilled water and ice prepared from distilled water at this point. If the oil cannot be induced to crystallize rapidly, more ice water should be added.

5. If it is necessary to interrupt the preparation before recrystallization, the product should be stored in a desiccator with continuous evacuation until it is absolutely dry.

6. This preparation has been carried out on a 4.2-mole scale using essentially the same procedure with only a slight diminution in yield. In larger runs the crude product may be more efficiently washed by rapidly resuspending the filter cake in fresh ice water, filtering, and drying. The only problem is that of drying the product rapidly. The drying can be hastened on a large scale by heating the mass on the funnel slightly with an infrared lamp.

3. Discussion

The usual method for epoxidation of an olefin with a peracid fails when the double bond is substituted with an electron-withdrawing group.⁴ This difficulty has been circumvented in certain cases by the use of a very strong peracid; *i.e.*, peroxytrifluoroacetic acid, in the presence of a buffer⁵ or by the use of alkaline hydrogen peroxide.⁶ In the latter case, the attack is by the hydroperoxide anion.⁷ This method is normally not applicable to the synthesis of epoxynitriles because of the simultaneous conversion of the nitrile to an amide group.⁸ However, the four nitrile groups of tetracyanoethylene so diminish the electron

density at the double bond that it is attacked by hydrogen peroxide in the absence of any added base. There is no significant attack on the nitrile groups when the reaction is carried out rapidly in a mutual solvent for the olefin and peroxide.⁹ Olefins that are somewhat less electrophilic, *e.g.*, phenyltricyanoethylene and diethyl 1,2-dicyanoethylene-1,2-dicarboxylate, can be epoxidized by essentially the same procedure using a catalytic amount of a mild base such as pyridine.¹⁰

Slight variations in the procedure described above have been used to prepare tetracyanoethylene oxide. Hydrogen peroxide in ether or *t*-butyl hydroperoxide in benzene¹¹ gives the epoxide in higher yield than the present method but requires large amounts of organic solvents and is not readily adaptable to large-scale preparations. An apparent contradiction of the opening statement above is the observation that tetracyanoethylene *can* be epoxidized with a peracid.¹² This is undoubtedly due to *nucleophilic* attack by the peracid or its anion on the electron-deficient double bond, a mechanism which cannot operate with olefins containing only one or two electronegative substituents. An example of this type of epoxidation is the preparation of 1,1-dicyano-2,2-bis(trifluoromethyl)ethylene oxide.¹³

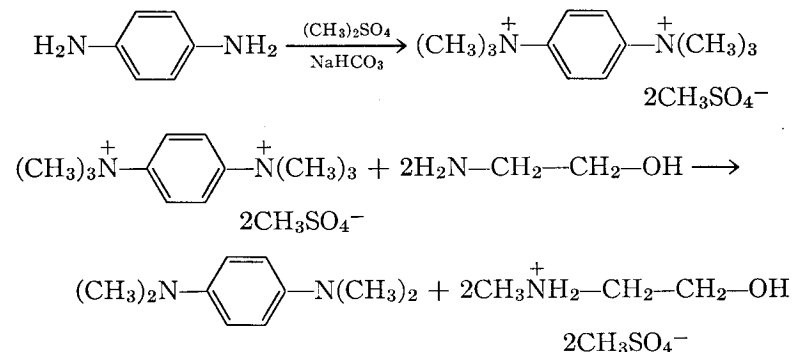
Tetracyanoethylene oxide does not undergo reactions typical of epoxides of simple hydrocarbon olefins. Entirely new types of reactions are observed; *e.g.*, cleavage by nucleophilic reagents into the elements of dicyanomethylene and carbonyl cyanide¹⁰ and cleavage of the carbon-carbon bond, followed by addition to a wide variety of olefins, acetylenes, and aromatic compounds.¹⁴ For example, tetracyanoethylene oxide adds thermally to adjacent positions on the benzene ring to give 1,1,3,3-tetracyano-1,3,3a,7a-tetrahydroisobenzofuran.

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TETRAMETHYL-*p*-PHENYLENEDIAMINE

(*p*-Phenylenediamine, N,N,N',N'-tetramethyl)



Submitted by S. HÜNIG, H. QUAST, W. BRENNINGER,
and E. FRANKENFELD¹

Checked by R. A. SCHWARTZ and K. B. WIBERG

1. Procedure

In a 2-l. three-necked flask fitted with a stirrer, thermometer, and pressure-compensated dropping funnel are placed 54 g. (0.5 mole) of powdered *p*-phenylenediamine (Note 1), 310 g. (3.7 mole) of sodium bicarbonate, and 250 ml. of water. The temperature of the solution is maintained at 18–22° using an ice bath while 320 ml. (3.4 mole) of dimethyl sulfate (Note 2) is added with stirring over a 30- to 50-minute period. Carbon dioxide is evolved vigorously and a transient purple color is developed; it changes to a brown tinge later on.

When the addition of dimethyl sulfate is complete, stirring is continued for 1 hour at 20–25°. Then the temperature is raised to 60–65° during 10 minutes (Note 3) and is kept at this value

until the evolution of carbon dioxide ceases. After the addition of 250 ml. of cold water, the reaction flask is cooled rapidly in an ice bath and 100 ml. of ethanolamine (Note 4) is added. The resultant crystalline slurry is removed from the flask, and the apparatus is rearranged as indicated in Note 5, using an upright condenser between the dropping funnel (Note 6) and the receiving flask.

To the reaction flask is added 200 ml. of ethanolamine, and it is heated to 140° with stirring. The slurry above is added in moderate portions over a 40- to 50-minute period (Note 7). When the heating bath is maintained at 230–240°, the addition of the slurry should provide an inner temperature at 120–140° as the water and oily product distill. After the addition is complete, the dropping funnel is rinsed with 100–150 ml. of water. As soon as the inner temperature has reached 160°, 50 ml. of ethanolamine is added and the temperature is maintained at 160–170° for 20 minutes. Water (50 ml.) is added through the dropping funnel to initiate a rapid steam distillation. Steam distillation is continued by the addition of 50-ml. portions of water at an inner temperature of 120–140° and a bath temperature of 230–240° until no more oil appears in the distillate (Note 8).

The oily product solidifies on cooling to about 20°, forming white lumps. After filtration by suction, the lumps are crushed, filtered, and washed four times with 50-ml. portions of ice water. Drying over silica gel in a vacuum gives 62–72 g. (82–88%) of white glistening scales, m.p. 51°.

2. Notes

1. A technical grade of *p*-phenylenediamine was used.
2. Dimethyl sulfate was distilled, b.p. 73–75° (13 mm.).
3. At this temperature the excess of dimethyl sulfate is destroyed.
4. Ethanolamine was distilled, b.p. 74–75° (13 mm.).
5. The apparatus shown in Fig. 1 is suitable for this step. It is essential that the condenser be very effective since the steam distillation is very rapid. If vapor is lost from the top of an

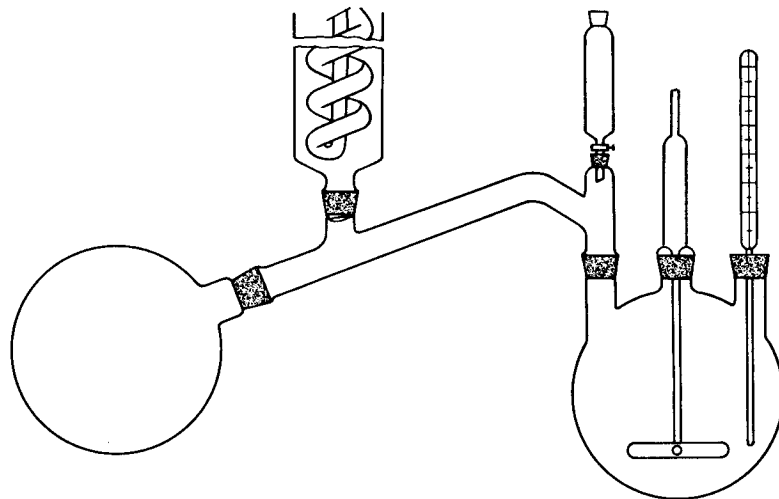


Fig. 1

internal coil condenser, cold towels placed on the outside of the condenser will provide additional cooling.

6. The dropping funnel should have a stopcock bore as large as possible.

7. Stirring and addition of only 40–50 ml. of the slurry into the dropping funnel should avoid obstruction of the stopcock. The use of a thin metal wire is sometimes helpful.

8. Transient blue colors in the distillate result from autooxidation. They do not, however, affect the purity of the final product.

3. Discussion

Tetramethyl-*p*-phenylenediamine has been obtained in low yield by the reaction of *p*-phenylenediamine with various alkylating agents such as methyl iodide,² methanol in the presence of hydrochloric acid at 170–200°,³ or formaldehyde and formic acid.⁴ In addition it has been prepared by methylating *p*-dimethylaminoaniline using methanol in the presence of hydrochloric acid at 170–200°,^{5, 6} followed by treatment of the resulting salts with aqueous ammonia at 180–190°. In the most recent procedure, *p*-phenylenediamine was alkylated with sodium chloro-

acetate. Decarboxylation of the *p*-phenylenediaminetetraacetic acid at 180° gave 28% of tetramethyl-*p*-phenylenediamine based on the starting diamine.⁷

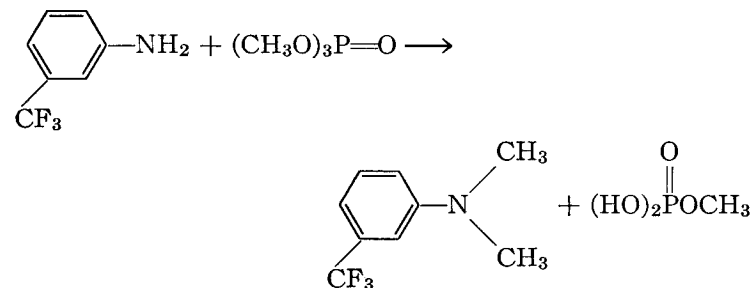
The present procedure combines two general methods described earlier.^{8, 9} It is conveniently carried out and gives a substantially higher yield than previous methods. Dimethyl sulfate in the presence of aqueous sodium bicarbonate selectively methylates aromatic amines under mild conditions to give quaternary salts without affecting phenolic hydroxy groups present in the molecule. If the quaternization step is sterically hindered, the reaction stops at the tertiary amine stage.⁸ Heterocyclic compounds may also be converted to quaternary salts in high yield, two or more methyl groups being introduced in one step.¹⁰ The rate of reaction may conveniently be followed by observing the carbon dioxide evolution.

Dealkylation of quaternary ammonium salts using ethanolamine is more convenient than the use of aqueous ammonia in sealed tubes at high temperatures.⁹ Ethanolamine may be replaced by other ethanolamines.¹¹ The reaction leads to preferential removal of methyl groups.

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m-TRIFLUOROMETHYL-N,N-DIMETHYLANILINE

(*m*-Toluidine, α,α,α -trifluoro-N,N-dimethyl-)



Submitted by WILLIAM A. SHEPPARD¹

Checked by G. B. BENNETT and K. B. WIBERG

1. Procedure

A solution of 16.1 g. (0.100 mole) of *m*-trifluoromethylaniline (Note 1) and 14.3 g. (0.102 mole) of trimethyl phosphate (Note 2) is added to a 300-ml. round-bottomed flask with a side arm. The flask is equipped with a thermometer, magnetic stirrer, and air condenser topped by a water condenser under a nitrogen atmosphere. The stirred reaction mixture is gradually heated by an oil bath to approximately 150° over 30–60 minutes; at this point there is a mild exothermic reaction such that the temperature of the reaction reaches 160–170° and reflux starts (Note 3). After 2 hours at reflux (reaction temperature 145–150°) with oil-bath temperature maintained at 180–200°, the reaction mixture is cooled to room temperature.

A solution of 15 g. of sodium hydroxide in 100 ml. of water is added, and the mixture is stirred vigorously for 1.5 hours to hydrolyze the phosphate ester. The hydrolysis is initially mildly exothermic, and the reaction temperature increases to 50–70°. An additional 200 ml. of water is added. The product, which separates as an oil, is extracted with two 150-ml. portions of

ether (Note 4). The combined ether extracts are dried for at least several hours over a mixture of anhydrous magnesium sulfate and sodium hydroxide pellets, filtered, and concentrated by distillation of the ether through a Vigreux column. The residue is distilled at reduced pressure. *m*-Trifluoromethyl-N,N-dimethylaniline is collected at 66–67° (4.5 mm.) and weighs 10.4–11.0 g. (55–58%); n_D^{24} 1.4834–1.4828 (Notes 5, 6).

2. Notes

1. *m*-Trifluoromethylaniline (under the name *m*-aminobenzo-trifluoride) obtained from Columbia Organic Chemicals Co., Inc., Columbia, South Carolina, was employed. The aniline is also available from Eastman Kodak under the name α,α,α -trifluoro-*m*-toluidine.

2. Trimethyl phosphate obtained from Columbia Organic Chemicals was employed. Although the phosphate ester is reported to be nontoxic under normal handling conditions,³ use of a hood is recommended.

3. Separation of the reaction mixture into two phases can be observed if the stirrer is stopped for a short period at this point and is also noted on cooling after completion of reflux.

4. The phosphate salts sometimes precipitate before or during the extraction and should be removed by suction filtration to facilitate the extraction. Precipitation may be avoided by addition of larger volumes of water before extraction.

5. A very small forecut is discarded, and only a small amount of tarry residue remains in the pot after the distillation is complete. A spinning-band distillation column was employed by the submitter, but a simple Claisen head is considered adequate because of lack of by-products.

6. The product is free from secondary aniline product on the basis of infrared and n.m.r. proton analysis. If equimolar amounts of aniline and phosphate are employed, the product is obtained in a higher yield (12.3 g., 65%), but it contains a trace of *m*-trifluoromethyl-N-methylaniline as detected by infrared analysis. This secondary aniline is readily removed by heating the product to reflux with 1 ml. of acetic anhydride followed by

redistillation. Use of a larger molar excess of trimethyl phosphate does not affect the purity but does decrease the yield significantly.

3. Discussion

The described method of dialkylation of anilines is essentially that of Billman and co-workers.^{2,3} It has not previously been applied to *m*-trifluoromethylaniline. *m*-Trifluoromethyl-N,N-dimethylaniline has been prepared in 29% yield by alkylating *m*-trifluoromethylaniline with methyl iodide.⁴

The use of trialkyl phosphates for dialkylation of anilines has been found applicable to naphthylamines³ and to a large number of anilines substituted in the ortho, meta, or para position by groups such as chloro, methoxy, and methyl² and in the meta position by fluoroalkyl (author's laboratory). The reaction has been used to introduce ethyl and *n*-butyl as well as methyl groups by employing the appropriate phosphate esters. The reported yields range from 50% to 95%.

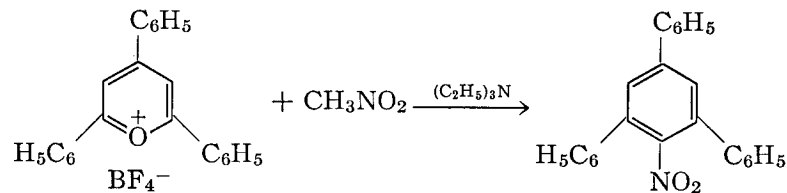
This method has two major advantages over other alkylation procedures: much less manipulation and higher yields; and no troublesome by-products, such as monoalkylated or quaternary products. The Eschweiler-Clarke procedure⁵ for alkylation of amines (formaldehyde-formic acid) also has these synthetic advantages for the aliphatic series but gives high molecular weight condensation products with anilines (anilines highly substituted in the ortho-para position may be employed successfully, but *m*-trifluoromethylaniline gives only a resin).

The phosphate method has not been synthetically useful for alkylation of anilines of low basicity such as *p*-nitro-³ or *p*-trifluoroaniline. Only monoalkylation occurs in introducing branched-chain alkyl groups such as isopropyl.³ Use of this method for alkylation of aliphatic amines has not been reported.

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2,4,6-TRIPHENYLNITROBENZENE

(Benzene, 2-nitro-1,3,5-triphenyl-)



Submitted by K. DIMROTH, A. BERNDT, and C. REICHARDT¹
 Checked by SAUL CHERKOFKY and RICHARD E. BENSON

1. Procedure

In a 1-l. three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel are placed 119 g. (0.30 mole) of 2,4,6-triphenylpyrylium tetrafluoroborate (Note 1), 21 ml. (24 g., 0.39 mole) of nitromethane (Note 2), and 350 ml. of absolute ethanol (Note 3). Triethylamine (70 ml., 51 g.) (Note 4) is added rapidly from the dropping funnel to the well-stirred suspension. The reaction mixture becomes reddish brown immediately, and the solid dissolves. After all the triethylamine has been added, the mixture is heated under reflux for 3 hours, cooled, and allowed to stand overnight in a refrigerator. The crystalline product that separates is collected on a Buchner funnel and washed with two 50-ml. portions of ice-cold methanol. The product (75–80 g.; m.p. 142–144°) is recrystallized from 200–250 ml. of glacial acetic acid to yield 70–75 g. (67–71%) of 2,4,6-triphenylnitrobenzene as slightly yellow crystals, m.p. 144–145° (Note 5).

2. Notes

1. The preparation of 2,4,6-triphenylpyrylium tetrafluoroborate is described on p. 121.

2. Nitromethane is dried over anhydrous calcium sulfate (Drierite) or calcium chloride for 1 day and distilled; the fraction with b.p. 101.5–102.5° is used.

3. Commercial absolute ethanol is used without additional drying.

4. Triethylamine is dried over sodium hydroxide pellets and distilled; the fraction with b.p. 89.5–90° is used.

5. The n.m.r. spectrum (CDCl₃) shows singlets at 7.45 p.p.m. (15 H) and 7.65 p.p.m. (2 H) (downfield from internal tetramethylsilane reference).

3. Discussion

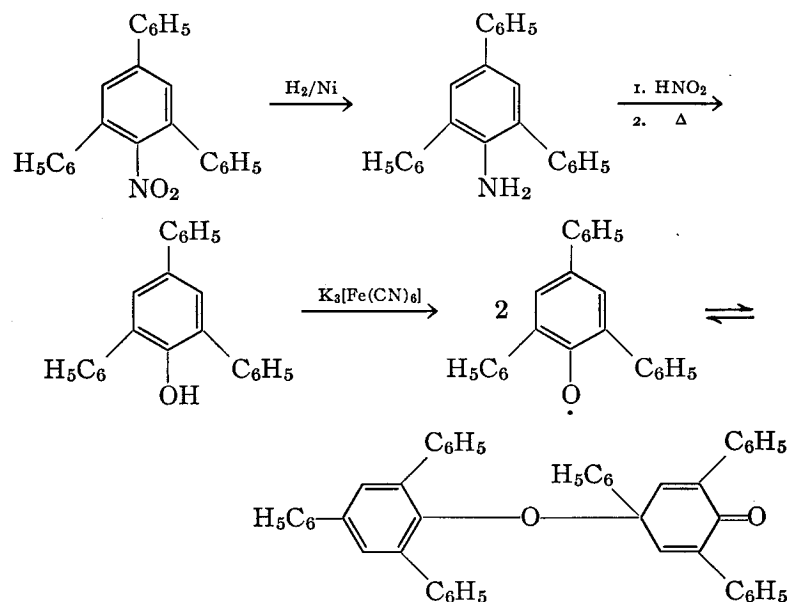
2,4,6-Triphenylnitrobenzene may be prepared by direct nitration of 1,3,5-triphenylbenzene²⁻⁴ and by the reaction of 2,4,6-triphenylpyrylium tetrafluoroborate with nitromethane.⁵ The present procedure is an adaptation of the latter method.

This procedure illustrates a general method for converting substituted pyrylium salts to nitrobenzene derivatives. The reaction has been the subject of several reviews.⁶⁻⁸ The yields are generally high, and under these conditions only a single product is formed, in contrast to the nitration of 1,3,5-triphenylbenzene. The preparation of 2,4,6-triphenylnitrobenzene from the corresponding pyrylium salt eliminates isomer separation problems, which are encountered when the direct nitration procedure is used. Also, labeled compounds can readily be prepared by this method.⁹

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2,4,6-TRIPHENYLPHENOXYL

(Phenoxy, 2,4,6-triphenyl)

Submitted by K. DIMROTH, A. BERNDT, H. PERST
and C. REICHARDT¹

Checked by E. K. W. WAT and R. E. BENSON

1. Procedure

A. *2,4,6-Triphenylaniline*. To a filtered solution of 70 g. (0.20 mole) of 2,4,6-triphenylnitrobenzene (Note 1) in 500 ml. of dioxane (total volume *ca.* 540 ml.) in a 1-l. pressure vessel equipped with a magnetic stirrer is added 10 g. of Raney nickel catalyst (Note 2) that has been previously rinsed with absolute ethanol. The head and fittings are attached, and the vessel is connected to a hydrogen cylinder. The system is alternately

evacuated to 40–50 mm. and pressured with hydrogen to 30–40 p.s.i. three times (Note 3). After a final evacuation, hydrogen is introduced into the vessel until the pressure reaches 1000 p.s.i. (*ca.* 70 atm.). The reaction is allowed to proceed overnight (*ca.* 25 hours) (Note 4), during which time 0.6 mole (13.5 l.) of hydrogen is absorbed. The vessel is vented and the catalyst is removed by filtration from the reaction mixture and is washed with 30 ml. of dioxane. The filtrates are combined, and the solvent is removed by distillation under reduced pressure using a rotary evaporator at 40–50° (50 mm.) to leave an oil which solidifies on trituration with a small portion of methanol. The product is collected on a Buchner funnel and washed twice with 40-ml. portions of ice-cold methanol. The remaining light yellow 2,4,6-triphenylaniline (m.p. 135–136°) weighs 60–63 g. (94–98%) (Note 5).

B. *2,4,6-Triphenylphenol*. To a 2-l. three-necked flask equipped with a mechanical stirrer, a dropping funnel, and a thermometer are added 32 g. (0.10 mole) of 2,4,6-triphenylaniline and 300 ml. of glacial acetic acid. Stirring is begun and the contents of the flask are brought into solution by heating to 70°. Concentrated sulfuric acid (90 ml., *d* 1.84) is added dropwise while the temperature is lowered concurrently from 70° to 20° by cooling. After the addition is completed, the mixture is cooled to 0° with an ice-salt bath, and a solution of 9 g. (0.13 mole) of sodium nitrite in 50 ml. of water is added over a period of 20–30 minutes with stirring, the reaction temperature being kept at 0–5°. The stirring is continued for 20 minutes after the sodium nitrite solution has been added, then 300 ml. of ice-cold water and 3 g. of urea or amidosulphonic acid are added in small portions. The yellow diazonium salt solution is filtered with suction into an ice-cold flask and is kept cold (at 0°) while the next step is carried out.

To a 2-l. three-necked flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel is added a mixture of 600 ml. of water and 150 ml. of concentrated sulfuric acid (*d* 1.84). The acid solution is vigorously stirred and heated to boiling, and the cold diazonium salt solution is added at such a rate that the boiling is not interrupted (Note 6). The time required for this addition should not exceed 30 minutes. After the addition is

completed, boiling is continued for 10 minutes and then the mixture is allowed to cool to room temperature with stirring. The product is collected on a Buchner funnel, washed with water, and dried in a vacuum desiccator containing phosphorus pentoxide to give 28–32 g. of crude 2,4,6-triphenylphenol. After drying, the product is dissolved in *ca.* 200 ml. of benzene and filtered through a layer of 300 g. of alumina packed in a 30-mm. x 75-cm. chromatography column (Note 7). The product is eluted with benzene until about 500 ml. of eluate has been collected. The collected eluate is concentrated under reduced pressure using a rotary evaporator at 50 mm. pressure and 50° to yield light yellow crystals, which are recrystallized from glacial acetic acid (10 g. of 2,4,6-triphenylphenol requires *ca.* 30–35 ml. of acetic acid). The pure, nearly colorless product (13–15 g., 39–47%) melts at 149–150°.

C. *2,4,6-Triphenylphenoxyl*. In a 1-l. separatory funnel is placed a filtered solution of 10 g. (31 mmoles) of 2,4,6-triphenylphenol in 300 ml. of ether. To this solution is added 60 ml. of a filtered, saturated solution of potassium hexacyanoferrate(III) in 2N sodium hydroxide solution (Note 8), and the resulting mixture is vigorously shaken for about 10 minutes. After a few minutes the dimer of 2,4,6-triphenylphenoxyl begins to separate in the form of pink crystals. The crystals are isolated by filtration, washed with several portions of water (Note 9) and twice with ether. After drying in a vacuum desiccator over phosphorus pentoxide while protecting from light, the product weighs 8–9 g. (81–91%) and melts at 145–150° to a red liquid (Note 10). The purity of the 2,4,6-triphenylphenoxyl dimer (which in solution attains a rapid equilibrium with its red monomer) is established by titration with a solution of hydroquinone in acetone (Note 11). The radical titer of a freshly prepared solution of the dimer in benzene or acetone should be 98–99%.

2. Notes

1. The preparation of 2,4,6-triphenylnitrobenzene is described in *Organic Syntheses*, this volume, p. 114.

2. The submitters used Raney nickel catalyst from the

Badische Anilin- & Sodafabrik AG, Ludwigshafen (Rhein), Germany.

3. The checkers used a stainless steel pressure vessel that was cooled to –60° and then evacuated to 1 mm. The cold system was purged with hydrogen three times, evacuated, and placed in the rocker assembly before pressuring it to 1000 p.s.i. with hydrogen.

4. The checkers used a rocking-motion autoclave and the reduction required 48 hours to complete.

5. The 2,4,6-triphenylaniline resulting from this procedure is sufficiently pure for use in the preparation of 2,4,6-triphenylphenol, but it may be recrystallized from 100 ml. of glacial acetic acid to give 50–55 g. (78–86%) of pure 2,4,6-triphenylaniline, m.p. 136–137°. On occasions a product with initial m.p. 121–122° is obtained which solidifies on further heating and then melts at 136–137°.

6. Contact of the diazonium salt solution with the hot wall of the flask before decomposition in the solution should be avoided in order to prevent the formation of a brown resin.

7. The submitters used Aluminiumoxid WOELM neutral, Aktivitätsstufe I.

8. A saturated solution requires *ca.* 35 g. (110 mmoles) of potassium hexacyanoferrate(III) per 100 ml. of 2N sodium hydroxide solution at room temperature.

9. The final wash water must be free of potassium hexacyanoferrate(III). The checkers washed the product until the filtrates were colorless.

10. The product obtained is analytically pure: Calcd. for $C_{24}H_{17}O$: C, 89.69; H, 5.33; O, 4.98. Found: C, 89.94; H, 5.27; O, 5.00. The product is stable for several months when stored in the dark. The 2,4,6-triphenylphenoxyl dimer is piezochromic; rubbing in a mortar produces a red color. Solutions of the colorless dimer in organic solvents are red owing to dissociation to the monomer radical.

11. The radical solution is titrated with 0.01M solution of analytically pure hydroquinone in pure acetone. The end point of the titration is marked by disappearance of the red color of the phenoxyl radical: 1 ml. of 0.01M hydroquinone solution is equivalent to 6.428 mg. of 2,4,6-triphenylphenoxyl dimer.

3. Discussion

The procedure for preparing 2,4,6-triphenylphenoxyl is based on the method described by Dimroth and co-workers.² This method represents the commonly used preparation of aroxyl radicals by oxidation of the corresponding phenol.³ The chemistry of stable phenoxyl radicals has been reviewed.⁴

In solution the colorless 2,4,6-triphenylphenoxyl dimer attains a rapid equilibrium with its red monomer radical (dissociation constant in benzene 4×10^{-5} at 20°). The radical is surprisingly stable toward oxygen and can be stored in solution for a long time when it is protected from light. The stability of the 2,4,6-triphenylphenoxyl radical is ascribed to steric and mesomeric effects.^{2,5} The e.s.r. spectrum⁵ and an ENDOR-spectrum⁶ of the radical are described.

The dimer belongs to the rare group of compounds which are piezochromic. Rubbing in a mortar produces a red color due to mechanical bond-breaking and dissociation into the red-colored monomer. The *p*-quinol structure of the 2,4,6-triphenylphenoxyl dimer has been confirmed by infrared studies of ¹⁸O-labeled material⁷ and by X-ray analysis of 3-bromo derivative.⁸

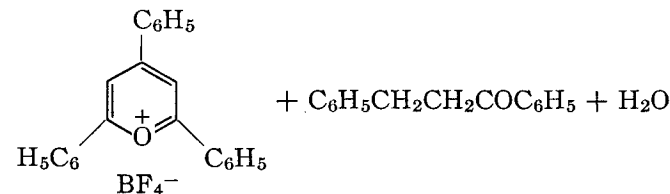
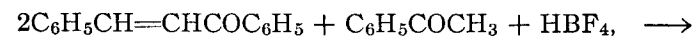
Other aroxyl radicals, especially those with *t*-butyl groups at the phenyl ring, are described by Cook⁹ and by Müller.¹⁰

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2,4,6-TRIPHENYLPYRYLIUM TETRAFLUOROBORATE

(Pyrilium tetrafluoroborate, 2,4,6-triphenyl-)



Submitted by K. DIMROTH, C. REICHARDT, and K. VOGEL¹
 Checked by SAUL CHERKOFKY and RICHARD E. BENSON

1. Procedure

In a 1-l. four-necked flask (or a three-necked flask with a Y-tube connector) equipped with a mechanical stirrer, a reflux condenser, a dropping funnel, and a thermometer are placed 208 g. (1.00 mole) of benzalacetophenone (Note 1), 60 g. (58.5 ml., 0.50 mole) of acetophenone, and 350 ml. of 1,2-dichloroethane. The contents of the flask are warmed to 70–75°, and 160 ml. of a 52% ethereal solution of fluoboric acid (Note 2) is added from the funnel with stirring during 30 minutes. With the first addition the mixture becomes orange; subsequently the color changes to brownish yellow. After the addition is completed, the mixture is stirred and heated under reflux for 1 hour (Note 3). The fluorescent mixture is allowed to stand overnight in a refrigerator. The crystalline product that separates is collected on a Buchner funnel and washed well with ether. By addition of 250 ml. of ether (Note 4) to the mother liquor an additional quantity of 2,4,6-triphenylpyrylium tetrafluoroborate is obtained. A total yield of 125–135 g. (63–68%) of yellow crystals

results; m.p. 218–225° (Note 5). The product can be recrystallized from 650–700 ml. of 1,2-dichloroethane, when it separates in the form of yellow needles, m.p. 251–257° (Note 6). The yield of product dried at 80° (10 mm.) for 3 hours is 102.5–107 g. (52–54%) (Note 6).

2. Notes

1. The preparation of benzalacetophenone is described in *Org. Syntheses*, Coll. Vol. 1, 78 (1941).

2. Ethereal fluoboric acid can be prepared as follows: 19 ml. (19 g., 0.95 mole) of anhydrous hydrofluoric acid, b.p. 19.4° (760 mm.) [*Caution! Hydrofluoric acid in contact with the skin produces extremely painful burns. It is therefore necessary to use every precaution to protect exposed parts of the body, especially the hands and eyes. Cf. Org. Syntheses, Coll. Vol. 2, 295 (1943), Note 3; Org. Syntheses, 46, 10 (1966), Note 1*] is added in small portions with shaking or stirring to 126 ml. (142 g., 1.00 mole) of distilled boron trifluoride etherate, b.p. 126° (760 mm.), contained in a 500-ml. polyethylene flask that is cooled in an ice bath to 0°. The concentration of the resulting yellowish solution of fluoboric acid in ether is about 52% by weight (*ca.* 6.6 moles per l.).

3. Some boron trifluoride is evolved during the first part of the refluxing; it may be disposed of by absorption in water in a gas trap [*cf. Org. Syntheses, Coll. Vol. 2, 3 (1943)*].

4. The ether used for washing the product may be added to the filtrate.

5. The 2,4,6-triphenylpyrylium tetrafluoroborate resulting from this procedure is sufficiently pure for use in the preparation of 2,4,6-triphenylnitrobenzene.²

6. It is necessary to dry under reduced pressure in order to remove that portion of the solvent that is tightly held. *Anal.* Calcd. for C₂₃H₁₇BF₄O: C, 69.73; H, 4.33; B, 2.73; F, 19.18. Found: C, 69.38; H, 4.47; B, 3.07; F, 19.51. The n.m.r. spectrum (acetone-d₆) shows a singlet at 9.1 p.p.m. (2 H) and multiplets at 8.6 p.p.m. and 7.9 p.p.m. (15 H) (downfield from internal tetramethylsilane reference).

3. Discussion

The present procedure is an improved modification of that described by Balaban³ for the corresponding perchlorate. 2,4,6-Triphenylpyrylium tetrafluoroborate has also been prepared from the corresponding tetrachloroferrate^{4, 5} with fluoboric acid,⁵ from acetophenone and boron trifluoride,⁶ and from acetophenone, benzaldehyde, and boron trifluoride etherate.⁷ Additional methods for the preparation of pyrylium salts have been reviewed.^{5, 8–13}

2,4,6-Triphenylpyrylium tetrafluoroborate is a versatile and useful stable starting material. Its reaction with nitromethane under basic conditions has made 2,4,6-triphenylnitrobenzene easily available.^{2, 14} In addition, pyrylium salts are readily converted to a variety of pyridine derivatives^{15, 16, 20} including alkyl- and arylpyridinium salts,^{16, 20} to thiopyrylium salts,¹⁷ and to substituted azulenes.¹⁸

The chemistry and transformation of pyrylium salts have been reviewed.^{5, 8–11, 19}

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SUBJECT INDEX

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Names in small capital letters refer to the titles of individual preparations. A number in ordinary boldface type denotes the volume. A page number in boldface italics indicates that the detailed preparative directions are given or referred to; entries so treated include principal products and major by-products, special reagents or intermediates (which may or may not be isolated), compounds mentioned in the text or Notes as having been prepared by the method given, and apparatus described in detail or illustrated by a figure. Page numbers in ordinary type indicate pages on which a compound or subject is mentioned in connection with other preparations.

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ORGANIC SYNTHESIS

AN ANNUAL PUBLICATION OF SATISFACTORY
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