Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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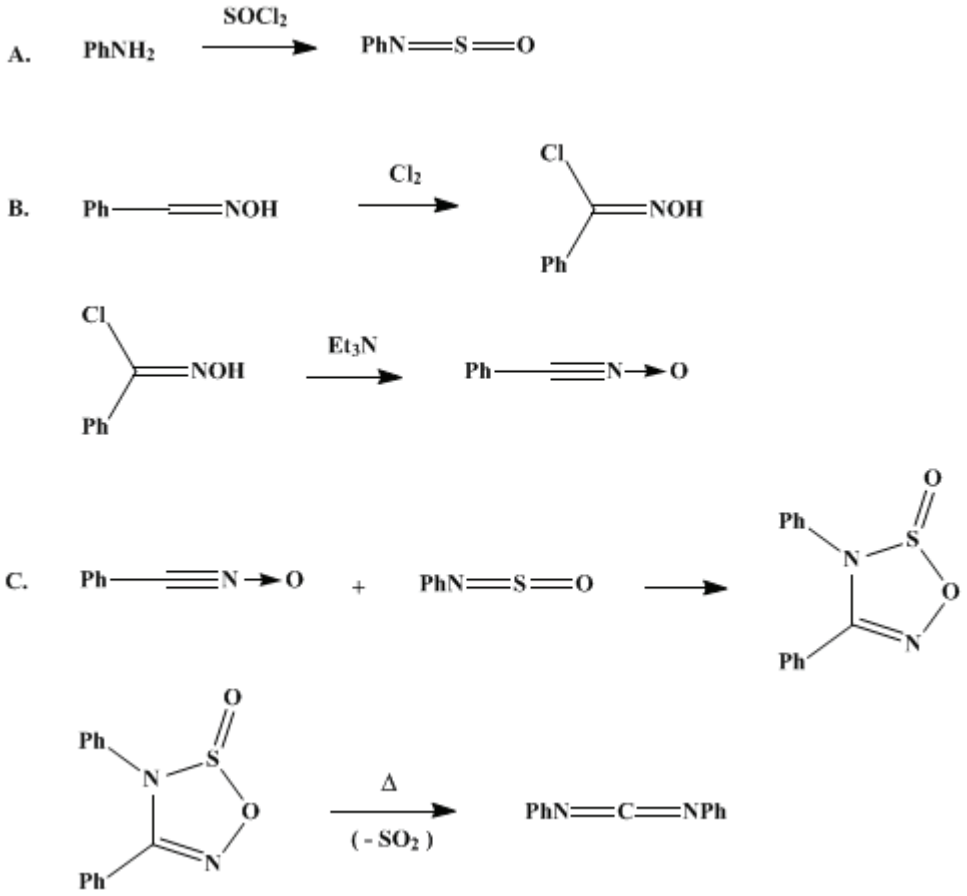
DIPHENYLCARBODIIMIDE

[Carbodiimide, diphenyl
Method II]



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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^{21}D 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 benzaldoxime (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^{23}D 1.6355; $\nu_{max.}^{CHCl_3}$ 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-workers[2] 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-benzaldoxime, 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 phosphorus 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 tube[10] or in the presence of catalysts such as phospholenes[11] 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]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 787

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

petroleum ether

Benzohydroxamoyl chloride

phospholenes

N,N',N''-triphenylguanidine

carbonythiocarbanilide

benzohydroxamoyl chlorides

N-sulfinylamines

calcium chloride (10043-52-4)

Benzene (71-43-2)

aniline (62-53-3)

thionyl chloride (7719-09-7)

chloroform (67-66-3)

lead oxide

hydrogen sulfide (7783-06-4)

sulfur dioxide (7446-09-5)

aniline hydrochloride (142-04-1)

mercuric oxide (21908-53-2)

chlorine (7782-50-5)

phosgene (75-44-5)

Triethylamine hydrochloride (554-68-7)

sodium hypochlorite (7681-52-9)

N,N'-diphenylthiourea (102-08-9)

phenylisocyanate (103-71-9)

triethylamine (121-44-8)

carbodiimide

Diphenylcarbodiimide,
Carbodiimide, diphenyl,
diphenyl carbodiimide (622-16-2)

N-Sulfinylaniline (1122-83-4)

benzaldoxime,
α-benzaldoxime

benzonitrile oxide (873-67-6)

4,5-diphenyl-1,2,3,5-thiaoxadiazole-1-oxide

3-phenyl-4-phenylimino-1,3-thiazetidin-2-one

1,5-diphenyl tetrazole (7477-73-8)

phenylisocyanide dichloride

phosphorus pentoxide (1314-56-3)