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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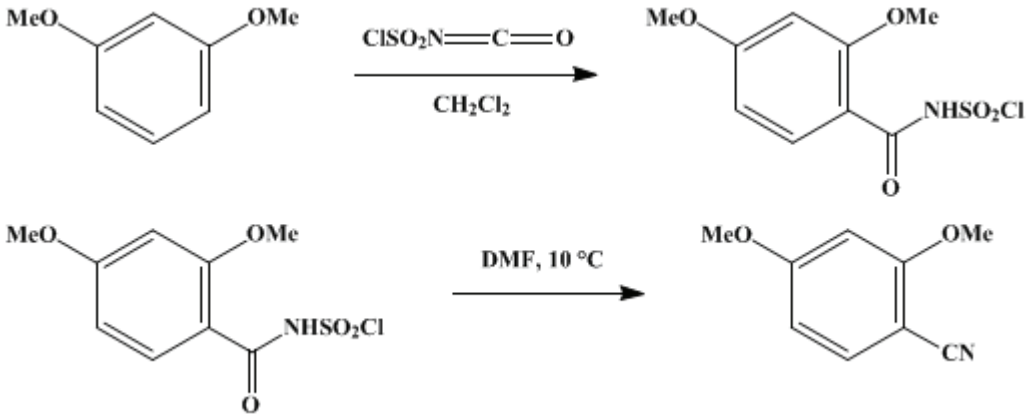
Organic Syntheses, Coll. Vol. 6, p.465 (1988); Vol. 50, p.52 (1970).

2,4-DIMETHOXYBENZONITRILE

[Benzonitrile, 2,4-dimethoxy-]



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Checked by Jurgen K. Weise and Richard E. Benson.

1. Procedure

Caution! Chlorosulfonyl isocyanate is a highly corrosive, irritating compound. This reaction should be carried out in an efficient hood.

A 1-l., round-bottomed flask equipped with a stirrer, a thermometer, a dropping funnel, and a reflux condenser to which is attached a drying tube containing calcium chloride, is charged with 138 g. (131 ml., 1.00 mole) of resorcinol dimethyl ether and 200 ml. of dichloromethane. The solution is stirred, and a solution of 150 g. (1.06 moles) of chlorosulfonyl isocyanate (Note 1) in 100 ml. of dichloromethane is added with stirring at 15–20° over a 25-minute period. The amide *N*-sulfonyl chloride separates as a crystalline solid, and the mixture is stirred for an hour at room temperature. The resulting mixture is cooled to 10–12° (Note 2) and 154 g. (2.1 moles) of *N,N*-dimethylformamide (Note 3) is added over a period of 5 minutes. The cooling bath is removed and the temperature gradually rises to about 30°, then falls. After 1 hour the crystals dissolve and the reaction mixture is poured onto 200 g. of ice. After the ice has melted, dichloromethane (150 ml.) is added, the mixture is shaken, and the organic layer is separated. The aqueous layer is extracted with 100 ml. of dichloromethane, and the organic phases are combined and washed with 100 ml. of water. The dichloromethane is removed by distillation, giving a white solid that is triturated with 250 ml. of cold water, recovered by filtration, and dried, yielding 155–157 g. (95–96%) of 2,4-dimethoxybenzonitrile, m.p. 91°. GC using a Chromosorb W column with 10% butadiene sulfone as the stationary phase indicates that the product has a purity of 98%. The IR spectrum shows absorption at 2220 $cm.^{-1}$ attributable to the cyano group.

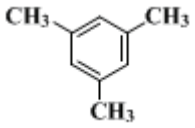
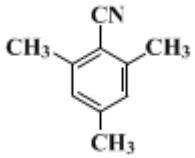
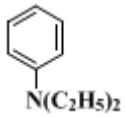
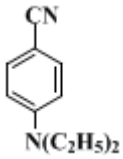
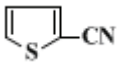
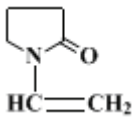
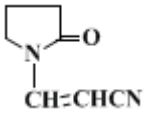
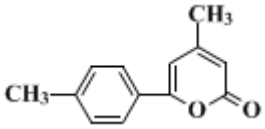
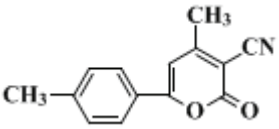
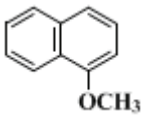
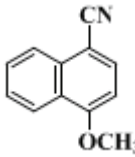
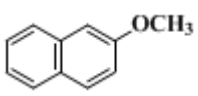
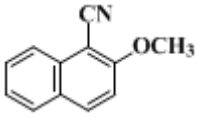
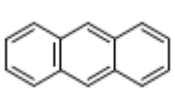
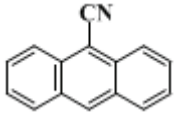
2. Notes

1. Chlorosulfonyl isocyanate may be prepared as described in *Org. Synth.*, **Coll. Vol. 5**, 226 (1973); it is available from Farbwerke Hoechst AG. The checkers found it necessary to distill the product before use.
2. A less pure product is obtained if the temperature is allowed to rise at this phase of the reaction.
3. Other amides also can be used, but *N,N*-dimethylformamide generally is preferred, especially because of its low molecular weight, high solvent power, and miscibility with water. In addition, it is readily available.

3. Discussion

This procedure[2] is an example of a broadly applicable, simple method for introducing the cyano substituent into compounds that readily undergo electrophilic substitution. The method is characterized by mild reaction conditions, a simple workup procedure, and, in most cases, good yields. Although the method has two steps, the reaction generally can be carried out without isolation of the intermediate chlorosulfonamide. An indication of its scope is given in Table I.[2] Additional examples of the substitution reaction of chlorosulfonyl isocyanate with aromatic and heterocyclic compounds and with olefins, yielding carboxylic acid amide *N*-sulfonyl chlorides are reported.[2,3,4,5,6]

TABLE I
NITRILES[2] PREPARED FROM $ClSO_2NCO$

Reactant	Product	Yield, %
		67
		20
		66
		86
		84
		81
		95
		89

Other procedures for the preparation of 2,4-dimethoxybenzonitrile include the reaction of 2,4-dimethoxybenzamide with thionyl chloride,[3] the action of acetic anhydride on 2,4-dimethoxybenzaldoxime,[7] the reaction of diazotized 2,4-dimethoxyaniline with potassium copper

cyanide,[8] and the action of cyanogen bromide on resorcinol dimethyl ether in the presence of aluminum chloride.[9]

References and Notes

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7. H. Baganz and I. Paproth, *Naturwissenschaften*, **40**, 341 (1953).
8. E. Späth, K. Klager, and C. Schlösser, *Ber. Dtsch. Chem. Ges.*, **64**, 2203 (1931).
9. P. Karrer, A. Rebmann, and E. Zeller, *Helv. Chim. Acta*, **3**, 261 (1920).

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

butadiene sulfone

acetic anhydride (108-24-7)

thionyl chloride (7719-09-7)

aluminum chloride (3495-54-3)

dichloromethane (75-09-2)

Cyanogen bromide (506-68-3)

N,N-dimethylformamide (68-12-2)

CHLOROSULFONYL ISOCYANATE (1189-71-5)

2,4-DIMETHOXYBENZONITRILE,
Benzonitrile, 2,4-dimethoxy- (4107-65-7)

resorcinol dimethyl ether (151-10-0)

2,4-dimethoxybenzamide

2,4-dimethoxybenzaldoxime

2,4-dimethoxyaniline (2735-04-8)

potassium copper cyanide