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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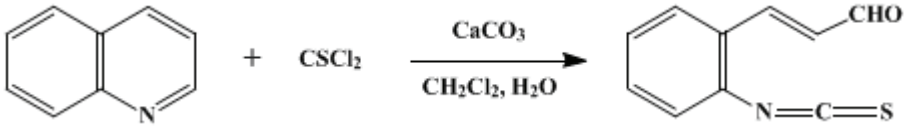
o-ISOTHIOCYANATO-(*E*)-CINNAMALDEHYDE

[2-Propenal, 3-(2-isothiocyanatophenyl)-, (*E*)-]



Submitted by R. Farrand and R. Hull[1].
Checked by K. E. Fahrenholtz and G. Saucy.

1. Procedure

Caution! This reaction should be carried out in a good hood because of the toxicity of thiophosgene.

A 1000-mL (Note 1), multinecked flask is provided with an efficient stirrer, vented outlet, thermometer, and 250-mL dropping funnel. The flask is surrounded by an ice–water bath and charged with 62.5 mL (68.4 g, 0.53 mol) of quinoline, 250 mL of dichloromethane, 55 g (0.55 mol) of finely powdered calcium carbonate, and 250 mL of water. The mixture is stirred vigorously, cooled to 10°C, and maintained at 10–15°C as a solution of 37.5 mL (56.5 g, 0.49 mol) of thiophosgene (Note 2) in 120 mL of dichloromethane is added over 15 min. There is very little exotherm or foaming. The cooling bath is removed and the reaction mixture is stirred vigorously at ambient temperature overnight. The reaction is then filtered through a bed of filter aid. The layers are separated and the aqueous layer is extracted with 50 mL of dichloromethane. The combined organic layers are washed twice with 150 mL of 2 *N* hydrochloric acid (Note 3), then with 150 mL of water, and dried over anhydrous magnesium sulfate. Concentration under reduced pressure gives 95–103 g of crude material (Note 4). This is dissolved with heating in 400 mL of cyclohexane, decolorizing carbon is added, and the mixture is filtered through a bed of filter aid. The filtrate is heated under reflux for 2 hr (Note 5) and allowed to cool with stirring (Note 6). The resulting solid is isolated by filtration, washed with cyclohexane, and dried in a vacuum oven at 40°C to give 78–83 g (84–89%) of *o*-isothiocyanato-(*E*)-cinnamaldehyde as cream crystals, mp 77–79°C (Note 7).

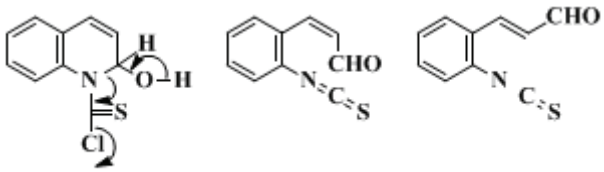
2. Notes

1. The reaction has been carried out on 10 times these quantities with no difficulty.
2. The checkers used an older bottle of thiophosgene and obtained an 84% yield (based on thiophosgene). A subsequent run was carried out with Aldrich "85% in CCl_4" thiophosgene found by analysis to contain 63% thiophosgene (therefore 89.4 g was used) and an 89% yield was obtained. A subsequent run on an unanalyzed bottle of the same lot number using 89.4 g gave a 100% yield (92% based on quinoline). It is suggested that thiophosgene be analyzed before use (Note 8).
3. These two washes remove unreacted quinoline.
4. The crude material consists of a mixture of *Z* and *E* isomers, with *Z* predominating. If workup of the reaction is delayed, more of the less soluble *E* isomer is formed, complicating subsequent filtration.
5. This additional heating completes the isomerization of the *Z* to the *E* isomer.
6. Subsequent breakup and filtration of the solid are facilitated if this solution is transferred and allowed to cool with stirring in a large-mouth container such as a beaker.
7. Melting points were taken in open capillaries on a Thomas-Hoover melting point apparatus. The crude material can be purified by dissolving it in dichloromethane, passing the solution over a plug of silica gel, and concentrating the solution with the addition of ether. The recrystallized material has essentially the same melting point and is colorless. The spectral properties of *o*-isothiocyanato-(*E*)-cinnamaldehyde are as follows: IR (Nujol) cm^{-1}: 2075 (NCS) and 1670 (conjugated CHO); ^1H NMR ($CDCl_3$) δ: 6.75 (d of d, 1 H, *J* = 16 and 7.5, CH=C*H*CHO), 7.4 (m, 4 H, aromatic H), 7.8 (d, 1 H, *J* = 16, ArC*H*=CH), 9.78 (d, 1 H, *J* = 7.5, C*H*O).

8. Thiophosgene mixed with CCl_4 can be analyzed as follows: a 0.5-mL aliquot of the reagent is mixed with a warm mixture of 15 mL of 30% hydrogen peroxide and 15 mL of 1 *N* sodium hydroxide. The mixture is shaken occasionally during 20 min (overnight gives the same titer) and diluted to 200 mL with water. Liberated Cl^- is then titrated with mercuric nitrate.

3. Discussion

This procedure is an example of a simple fission reaction of *N*-heterocyclic compounds by thiophosgene and base[2] wherein the dihydro intermediate **1** undergoes ring fission to yield the *Z*-isothiocyanate **2**, which isomerizes in situ to the *E*-isomer **3**. The reaction may be applied to certain substituted quinolines,[3,4] isoquinoline,[2] pyridine,[5] benzoxazole,[6] benzimidazole,[6,7] and oxazole[8] derivatives, but not to benzothiazole.[6]



1 2 3

The ortho-substituted isothiocyanates are valuable intermediates for the preparation of a variety of heterocyclic compounds; for example, *o*-isothiocyanato-(*E*)-cinnamaldehyde with sodio diethyl malonate undergoes facile cyclization to 3-formylquinoline-2(1*H*)-thione,[9] which in turn may be used for the preparation of tricyclic[9,10] and large ring heterocyclic compounds.[11]

References and Notes

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

silica gel

hydrochloric acid (7647-01-0)

ether (60-29-7)

sodium hydroxide (1310-73-2)

CCl_4 (56-23-5)

cyclohexane (110-82-7)

calcium carbonate (471-34-1)

decolorizing carbon (7782-42-5)

hydrogen peroxide (7722-84-1)

Thiophosgene (463-71-8)

Quinoline (91-22-5)

sodio diethyl malonate

dichloromethane (75-09-2)

mercuric nitrate

magnesium sulfate (7487-88-9)

benzothiazole (95-16-9)

o-Isothiocyanato-(E)-cinnamaldehyde,
2-Propenal, 3-(2-isothiocyanatophenyl)-, (E)- (19908-01-1)

3-formylquinoline-2(1H)-thione