



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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.

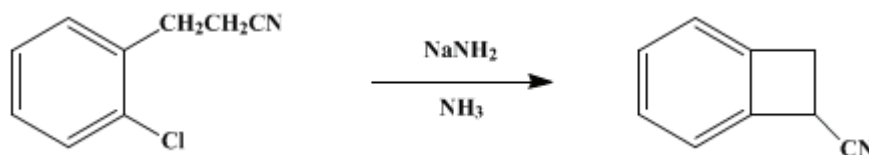
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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1-CYANOBENZOCYCLOBUTENE

[Bicyclo[4.2.0]octa-1,3,5-triene-7-carbonitrile]



Submitted by J. A. Skorcz and F. E. Kaminski¹.

Checked by V. Z. Williams and K. B. Wiberg.

1. Procedure

A 2-l. three-necked flask is thoroughly dried and fitted with a large dry-ice condenser, a mechanical stirrer, a nitrogen inlet, and a powder funnel in an efficient hood. With nitrogen flowing through the system, 62.5 g. (1.60 moles) of commercial sodium amide (Note 1) is added rapidly. (*Caution! Sodium amide is corrosive and readily decomposes in the presence of moisture.*) The funnel is replaced by a gas-inlet tube, the condenser is filled with a mixture of dry ice and acetone, and ca. 400 ml. of liquid ammonia is introduced from a cylinder. The gas-inlet tube is replaced by an addition funnel, stirring is commenced, and 66.3 g. (0.400 mole) of *o*-chlorohydrocinnamionitrile (Note 2) is added over a 10-minute period. The last traces of the nitrile are washed into the flask with small amounts of anhydrous ether.

The dark green reaction mixture is stirred vigorously for 3 hours and then is treated carefully with 96 g. (1.2 moles) of solid ammonium nitrate (Note 3). All the fittings are removed from the flask, and the ammonia is allowed to evaporate (Note 4). Water (300 ml.) is added cautiously to the residue. (*Caution! Traces of undecomposed sodium amide may adhere to the upper walls of the flask.*) The organic layer is taken up in two 160-ml. portions of chloroform, and the solutions are combined and washed twice with 100 ml. of 5% hydrochloric acid and once with 100 ml. of water. (*Caution! The extraction procedure and subsequent chloroform distillation should be conducted in a hood because some hydrogen cyanide is usually evolved.*) The chloroform solution is dried over anhydrous sodium sulfate, and the chloroform is removed by distillation. The residual liquid is distilled under reduced pressure through an insulated, 5-in. Vigreux column. The forerun, b.p. 95–100° (3 mm.), weighs ca. 1 g.; the product boils at 100–101° (3 mm.); n_D^{25} 1.5451. The yield of 1-cyanobenzocyclobutene is 33–34 g. (64–66%) (Note 5) and (Note 6).

2. Notes

1. The sodium amide was obtained from Farchan Research Laboratories and was approximately 90% pure.
2. The submitters prepared *o*-chlorohydrocinnamionitrile by the following procedure. Ethyl cyanoacetate (3040 g., 27 moles) was added to a solution of 140 g. (6.1 g. atoms) of sodium in 4 l. of absolute ethanol, followed by 970 g. (6 moles) of *o*- α -dichlorotoluene (Eastman Organic Chemicals), to afford 890 g. (63%) of ethyl 2-(*o*-chlorobenzyl)cyanoacetate,² b.p. 117–123° (0.03 mm.). Hydrolysis of this material in 2 l. of 10% aqueous sodium hydroxide at room temperature gave a quantitative yield (790 g.) of 2-(*o*-chlorobenzyl)cyanoacetic acid, m.p. 129–132° without recrystallization. Decarboxylation of 750 g. of the acid in 750 ml. of refluxing dimethylformamide gave 550 g. (93%) of *o*-chlorohydrocinnamionitrile,³ b.p. 82–85° (0.3 mm.), n_D^{25} 1.5362. The checkers carried out this preparation starting with 8 moles of ethyl cyanoacetate and obtained comparable yields.
3. Other ammonium salts, such as ammonium chloride, are equally satisfactory.
4. Overnight evaporation at room temperature is convenient.
5. The submitters carried out the reaction on 1-molar and 3-molar scales and obtained yields of 62–64% and 67%, respectively.

6. This procedure has also been used to obtain 1-cyano-5-methoxybenzocyclobutene from 2-bromo-4-methoxyhydrocinnamionitrile.⁴

3. Discussion

1-Cyanobenzocyclobutene has been prepared from sodium cyanide and 1-bromobenzocyclobutene,⁵ formed by reaction of benzocyclobutene with N-bromosuccinimide,⁶ and by ring closure of *o*-chlorohydrocinnamionitrile with potassium amide in liquid ammonia.⁷ The present procedure is a modification of the latter method and was previously described by one of the submitters.⁸

4. Merits of the Preparation

Cyclization by addition of a side-chain carbanion to an aryne bond has been proposed as the method of choice for synthesis of the versatile 1-substituted benzocyclobutene system.⁷ This general procedure now has been modified to permit convenient large-scale preparations utilizing a commercially available base, a minimum amount of liquid ammonia, and distillation for isolation of the product.

References and Notes

1. Lakeside Laboratories, Division of Colgate-Palmolive Company, Milwaukee, Wisconsin 53201.
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 3. A. D. Grebenyuk and I. P. Tsukervanik, *Zh. Obshch. Khim.*, **25**, 286 (1955); *J. Gen. Chem. USSR (Engl. Transl.)*, **25**, 269 (1955).
 4. J. A. Skorcz and J. E. Robertson, *J. Med. Chem.*, **8**, 255 (1965).
 5. M. P. Cava, R. L. Litle, and D. R. Napier, *J. Am. Chem. Soc.*, **80**, 2257 (1958).
 6. M. P. Cava and D. R. Napier, *J. Am. Chem. Soc.*, **80**, 2255 (1958).
 7. J. F. Bunnett and J. A. Skorcz, *J. Org. Chem.*, **27**, 3836 (1962).
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Appendix Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium cyanide (143-33-9)

hydrogen cyanide (74-90-8)

sodium sulfate (7757-82-6)

nitrogen (7727-37-9)

acetone (67-64-1)

sodium (13966-32-0)

Ethyl cyanoacetate (105-56-6)

ammonium nitrate

sodium amide (7782-92-5)

dimethylformamide (68-12-2)

N-bromosuccinimide (128-08-5)

potassium amide

1-Cyanobenzocyclobutene

Bicyclo[4.2.0]octa-1,3,5-triene-7-carbonitrile (6809-91-2)

o- α -dichlorotoluene (611-19-8)

1-cyano-5-methoxybenzocyclobutene

2-bromo-4-methoxyhydrocinnamonitrile

1-bromobenzocyclobutene

benzocyclobutene

o-chlorohydrocinnamonitrile (7315-17-5)

ethyl 2-(o-chlorobenzyl)cyanoacetate

2-(o-chlorobenzyl)cyanoacetic acid