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.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

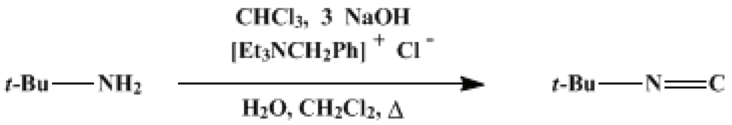
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.055.0096

Organic Syntheses, Coll. Vol. 6, p.232 (1988); Vol. 55, p.96 (1976).

PHASE-TRANSFER HOFMANN CARBYLAMINE REACTION: *tert*-BUTYL ISOCYANIDE

[Propane, 2-isocyano-2-methyl-]



Submitted by George W. Gokel[1] [2], Ronald P. Widera, and William P. Weber[1].
Checked by F. A. Souto-Bachiller, S. Masamune, Charles J. Talkowski, and William A. Sheppard.

1. Procedure

Caution! This preparation should be conducted in an efficient hood because of the evolution of carbon monoxide and the obnoxious odor of the isocyanide.[3]

A 2-l., round-bottomed flask equipped with a magnetic stirring bar, a reflux condenser, and a pressure-equalizing dropping funnel is charged with 300 ml. of water. Stirring is begun and 300 g. (7.50 moles) of sodium hydroxide are added in portions in order to maintain efficient stirring (Note 1). A mixture of 141.5 g. (203.3 ml., 1.938 moles) of *tert*-butylamine, 117.5 g. (78.86 ml., 0.9833 mole) of chloroform (Note 2), and 2 g. (0.009 mole) of benzyltriethylammonium chloride (Note 3) in 300 ml. of dichloromethane is added dropwise to the stirred, warm (*ca.* 45°) solution over a 30-minute period. The reaction mixture begins to reflux immediately (Note 4) and subsides within 2 hours; stirring is continued for an additional hour (Note 5). After the reaction mixture is diluted with 800 ml. of ice and water, the organic layer is separated and retained, and the aqueous layer is extracted with 100 ml. of dichloromethane. The dichloromethane solutions are combined and washed successively with 100 ml. of water and 100 ml. of aqueous 5% sodium chloride, and dried over anhydrous magnesium sulfate.

The drying agent is removed by filtration, and the filtrate is distilled under nitrogen through a spinning band column (Note 6) and (Note 7). The fraction, boiling at 92–93° (725 mm.), is collected, yielding 54.2–60.0 g. (66–73%, based on chloroform) of *tert*-butyl isocyanide (Note 8) and (Note 9).

2. Notes

1. Efficient stirring is required. A solution of 225 g. (5.62 moles) of sodium hydroxide in 225 ml. of water can be added to the stirred mixture of the organic substrates in dichloromethane if a more efficient mechanical stirrer is used. In the original procedure, the submitters noted an induction period of about 20 minutes which was found to vary somewhat with the stirring rate, stirring-bar size, and relative amount of phase-transfer catalyst. Three moles of base are required for the reaction: one to generate the carbene and two to react with the additional two moles of hydrochloric acid lost by the amine–carbene adduct in the isonitrile formation step. If less base is used, the excess hydrochloric acid reacts with the isonitrile by α-addition, and the yield is substantially reduced.
2. Chloroform, commercially available, normally contains 0.75% ethanol and was used as supplied.
3. Benzyltriethylammonium chloride is available from Eastman Organic Chemicals. The checkers prepared the salt in a state of high purity by a modification of a reported procedure.[4] A solution of 33.7 g. (0.334 mole) of triethylamine and 50.0 g. (0.395 mole) of benzyl chloride (both from Eastman Organic Chemicals) in 60 ml. of absolute ethanol was refluxed for 64 hours, cooled to room temperature, and treated with 300 ml. of ether. The precipitated ammonium salt was removed by filtration, redissolved in the minimum amount of hot acetone, and reprecipitated with ether.
4. The volatilities of both *tert*-butylamine and dichloromethane necessitate the use of an efficient condenser as a precaution, although the rate of reflux is generally not vigorous. In preparations where

higher boiling amines are used, this precaution is less critical.

5. The submitters noted that a longer stirring period did not seem to affect the yield appreciably.

6. The bulk of the residual *tert*-butylamine is recovered.

7. A 60-cm., annular, Teflon®, spinning band, distillation column is recommended to achieve clean separation of solvent and unreacted reagent from product rather than a column packed with glass helices. For higher boiling isocyanides, separation of solvent and unreacted reagents may be effected by the use of a rotary evaporator, although the thermal instability of the isocyanides should be taken into consideration.

8. Yields higher than about 70% for any of these isonitrile preparations generally indicate incomplete fractionation. The purity of the product may be conveniently checked by ^1H NMR ($CDCl_3$) spectroscopy. The characteristic 1:1:1 triplet for β-hydrogen: ^{14}N coupling in *tert*-butyl isocyanide appears at δ 1.45. A small upfield peak usually indicates the presence of unreacted amine. Other common contaminants are dichloromethane and chlorofrom. The purity may be determined more accurately by GC analysis on a 230 cm. by 0.6 cm. column packed with 10% SE-30 on Chromosorb G, 60–80 mesh, at 80°.

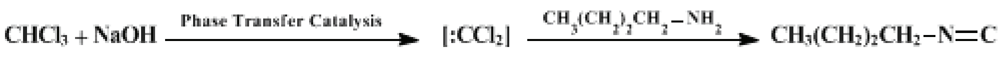
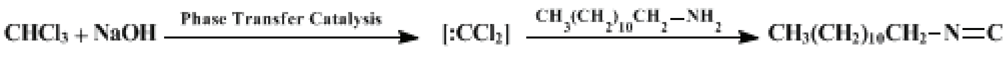
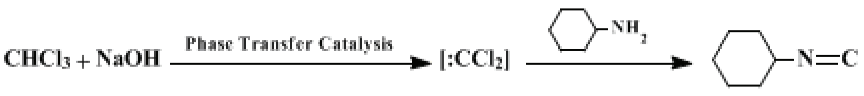
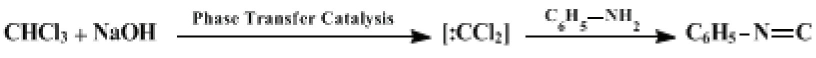
9. Glassware may be freed from the isocyanide odor by rinsing with a 1:10 mixture of concentrated hydrochloric acid and methanol.

3. Discussion

The present method utilizes dichlorocarbene generated by the phase-transfer method of Makosza[5] and Starks.[6] The submitters have routinely realized yields of pure distilled isocyanides in excess of 40%.[7] With less sterically hindered primary amines a 1:1 ratio of amine to chloroform gives satisfactory results. Furthermore, by modifying the procedure, methyl and ethyl isocyanides may be prepared directly from the corresponding aqueous amine solutions and bromoform.[8] These results are summarized in Table I.

TABLE I

PREPARATION OF ISOCYANIDES (RN=C) BY THE CARBYLAMINE REACTION[a]

 R	>Yi (%	
 $CH_3(CH_2)_2CH_2$-	60	40–42° (11 mm.)
 $C_6H_5CH_2$-	45	92–93° (11 mm.)
 $CH_3(CH_2)_{10}CH_2$-	41	115–118° (0.1 mm.)
 cyclo-C_6H_{11}-	48	67–72° (13 mm.)
 C_6H_5-	57	50–52° (11 mm.)
		59–60°

 CH_3-[b]		24	(760 mm.)
 CH_3CH_2-[b]		47	78–79° (760 mm.)

[a]Prepared by the phase-transfer method using chloroform and aqueous sodium hydroxide with the corresponding amines.[7]

[b]Bromoform substituted for chloroform for ease of fractionation.[8]

Various synthetic routes to isocyanides have been reported since their identification over 100 years ago.[9] Until now,[9,10] the useful synthetic procedures required a dehydration reaction.[11,10,12] Although the carbylamine reaction involving the dichlorocarbene intermediate is one of the early methods,[9] it had not been preparatively useful until the innovation of phase-transfer catalysis (PTC).[5,6]

The phase-transfer catalysis method has also been utilized effectively for addition of dichlorocarbene to olefins,[5] as well as for substitution and elimination reactions, oxidations, and reductions.[13] A later procedure in this volume is another example.[14]

This preparation is referenced from:

- Org. Syn. Coll. Vol. 6, 897
- Org. Syn. Coll. Vol. 6, 940
- Org. Syn. Coll. Vol. 6, 954
- Org. Syn. Coll. Vol. 7, 27

References and Notes

1. Department of Chemistry, University of Southern California, University Park, Los Angeles, California 90007. This work was supported in part by a grant from the National Science Foundation, grant number GP 40331X.
2. Present address: Department of Chemistry, University of Maryland, College Park, Maryland 20742.
3. Many isocyanides are reported to exhibit no appreciable toxicity to mammals. See J. A. Green II and P. T. Hoffmann in "Isonitrile Chemistry," I. Ugi, Ed., Academic Press, New York, 1971, p. 2. However, since certain isocyanides are highly toxic (*e.g.*, 1,4-diisocyanobutane), the checkers recommend that all isocyanides be handled with due caution.
4. R. A. Moss and W. L. Sunshine, *J. Org. Chem.*, **35**, 3581 (1970).
5. M. Makosza and M. Wawrzyniewicz, *Tetrahedron Lett.*, 4659 (1969).
6. C. M. Starks, *J. Am. Chem. Soc.*, **93**, 195 (1971).
7. W. P. Weber and G. W. Gokel, *Tetrahedron Lett.*, 1637 (1972).
8. W. P. Weber, G. W. Gokel, and I. Ugi, *Angew. Chem. Int. Ed. Engl.*, **11**, 530 (1972).
9. For a review, see P. T. Hoffmann, G. Gokel, D. Marquarding, and I. Ugi in "Isonitrile Chemistry," I. Ugi, Ed., Academic Press, New York, 1971, Chapter II.
10. G. E. Niznik, W. H. Morrison III, and H. M. Walborsky, *Org. Synth.*, **Coll. Vol. 6**, 751 (1988).
11. I. Ugi, R. Meyr, M. Lipinski, F. Bodesheim, and F. Rosendahl, *Org. Synth.*, **Coll. Vol. 5**, 300 (1973); I. Ugi and R. Meyr, *Org. Synth.*, **Coll. Vol. 5**, 1060 (1973).
12. R. E. Schuster, J. E. Scott, and J. Casanova, Jr., *Org. Synth.*, **Coll. Vol. 5**, 772 (1973).
13. J. Dockx, *Synthesis*, 441 (1973); E. V. Dehmlow, *Angew. Chem. Int. Ed. Engl.*, **13**, 170 (1974); A. W. Herriott and D. Picker, *Tetrahedron Lett.*, 1511 (1974).
14. M. Makosza and A. Jónczyk, *Org. Synth.*, **Coll. Vol. 6**, 897 (1988).

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

chlorofrom

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

methanol (67-56-1)

ether (60-29-7)

sodium hydroxide (1310-73-2)

carbon monoxide (630-08-0)

chloroform (67-66-3)

sodium chloride (7647-14-5)

nitrogen (7727-37-9)

acetone (67-64-1)

benzyl chloride (100-44-7)

bromoform (75-25-2)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

triethylamine (121-44-8)

dichlorocarbene

Propane, 2-isocyano-2-methyl-,
tert-Butyl isocyanide (7188-38-7)

1,4-diisocyanobutane

benzyltriethylammonium chloride (56-37-1)

tert-Butylamine (75-64-9)