



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](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.

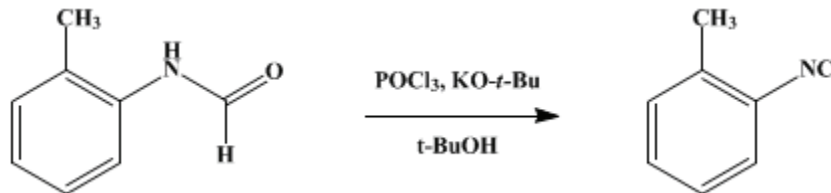
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The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures 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.*

*Organic Syntheses, Coll. Vol. 5, p.1060 (1973); Vol. 41, p.101 (1961).*

## ***o*-TOLYL ISOCYANIDE**



Submitted by Ivar Ugi and Rudolf Meyr<sup>1</sup>.  
Checked by B. C. McKusick and O. W. Webster.

### 1. Procedure

*Caution! Isocyanides should be prepared in a hood since they have pungent odors and some are known to be toxic.*

The reaction is conducted in a 2-l. round-bottomed flask equipped with a dropping funnel, Hershberg stirrer, thermometer, and reflux condenser. A T-tube attached to a cylinder of dry nitrogen is inserted in the top of the condenser in order to keep the reaction mixture blanketed with nitrogen.

A suspension of potassium *tert*-butoxide is prepared by a slight modification of the procedure of Johnson and Schneider,<sup>2</sup> *particular attention being paid to the precautions they recommend for safe handling of potassium*. Dry *tert*-butyl alcohol (1250 ml.) is distilled directly into the reaction flask under nitrogen. One hundred grams (2.6 g. atoms) of potassium cut into about ten pieces is added. The stirred mixture spontaneously warms to the melting point of potassium (62°) in the course of 15–60 minutes, whereupon the metal disperses into droplets. As the potassium gradually dissolves, the temperature of the mixture rises to the boiling point of *tert*-butyl alcohol. The rate of solution of the potassium should be such that the *tert*-butyl alcohol refluxes gently, and this rate is regulated by the speed of stirring. If the boiling becomes too vigorous, the stirring is stopped completely, and if necessary the reaction vessel is cooled by immersion in a bath of cold oil kept in readiness for this purpose. Potassium *tert*-butoxide gradually precipitates, and the mixture is a thick suspension when all the potassium has reacted (Note 1).

*N*-*o*-Tolylformamide (135 g., 1.00 mole) (Note 2) is added to the hot stirred suspension, which becomes a clear solution within a few minutes. The solution is cooled to 10–20° by means of an ice bath and maintained at this temperature while 92 g. (0.60 mole) of phosphorus oxychloride is added to it with stirring over the course of 30–40 minutes. The reaction mixture is stirred at 30–35° for 1 hour and poured into an ice-cold stirred solution of 50 g. of sodium bicarbonate in 5 l. of water (Note 3). *o*-Tolyl isocyanide precipitates as an oil. It is taken up in 300 ml. of petroleum ether (b.p. 40–60°), and the organic phase is separated in a separatory funnel. The aqueous phase is extracted with three 200-ml. portions of petroleum ether. The combined extracts are washed with 50 ml. of 5% sodium bicarbonate solution, dried over 50 g. of powdered potassium hydroxide, and distilled through a 30-cm. vacuum-jacketed Vigreux column. *o*-Tolyl isocyanide is collected as a colorless, vile-smelling liquid at 61–63°/10 mm.;  $n_D^{25}$  1.5212–1.5222; weight 74–85 g. (63–73%) (Note 4).

### 2. Notes

- In order to keep down the volume of the reaction mixture, less *tert*-butyl alcohol is used than is necessary to dissolve the potassium *tert*-butoxide.
- The checkers prepared *N*-*o*-tolylformamide<sup>3</sup> as follows. A solution of 100 g. (0.94 mole) of *o*-toluidine and 82 ml. (100 g., 2.13 moles) of 98% formic acid in 300 ml. of toluene is refluxed under a condenser attached to a water separator.<sup>4</sup> After water stops collecting in the separator (about 3 hours), toluene and excess formic acid are removed by distillation under reduced pressure. The crude *N*-*o*-

tolylformamide that remains is recrystallized from toluene to give 95–101 g. (75–80%) of *N*-*o*-tolylformamide, m.p. 60/61°. If a formamide that melts above the boiling point of *tert*-butyl alcohol is to be converted to an isocyanide by the present procedure, it should be finely pulverized.

3. *o*-Tolyl isocyanide is rather unstable, and in order to get a good yield one should work up the reaction mixture as quickly as possible and avoid unnecessary heating of the crude isocyanide. If the isocyanide is to be stored for a long time, it should be kept at the temperature of Dry Ice.

4. The equipment used in this preparation can be freed of the disagreeable odor of *o*-tolyl isocyanide by being washed with 5% methanolic sulfuric acid.

### 3. Discussion

*o*-Tolyl isocyanide has been prepared in 20% yield by the action of chloroform and potassium hydroxide on *o*-toluidine.<sup>5</sup> It has also been prepared by the dehydration of *N*-*o*-tolylformamide using the phosgene/tertiary amine system in good yield.<sup>6</sup> The present procedure is better than the carbylamine reaction<sup>5</sup> in terms of yield.

Although the use of phosgene/tertiary amine systems is superior to the present procedure for production of isonitriles, the toxicity of phosgene and the difficulty with which it is handled by the inexperienced worker make it less convenient than the present procedure. For most purposes, this procedure illustrates the best way to prepare aryl isocyanides. It is quite general, having been used by Ugi and Meyr<sup>7</sup> to make the following isocyanides from the corresponding formamides: phenyl (56%), *p*-tolyl (66%), 2,6-dimethylphenyl (88%), mesityl (80%), *o*-chlorophenyl (43%), *p*-chlorophenyl (54%), 2-chloro-6-methylphenyl (87%), *p*-methoxyphenyl (64%), *p*-diethylaminophenyl (75%), *p*-nitrophenyl (41%), and 2-naphthyl (50%). Aliphatic isonitriles are generally best prepared by a simpler procedure involving the action of phosphorus oxychloride on an *N*-alkylformamide in the presence of pyridine.<sup>8</sup>

This preparation is referenced from:

- Org. Syn. Coll. Vol. 5, 300
- Org. Syn. Coll. Vol. 5, 772
- Org. Syn. Coll. Vol. 6, 232

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### References and Notes

1. Institute of Organic Chemistry, University of Munich, Munich, Germany.
2. W. S. Johnson and W. P. Schneider, *Org. Syntheses*, Coll. Vol. 4, 134 (1963).
3. A. Ladenburg, *Ber.*, **10**, 1123 (1877).
4. S. Natelson and S. Gottfried, *Org. Syntheses*, Coll. Vol. 3, 381 (1955).
5. J. U. Nef, *Ann.*, **270**, 309 (1892).
6. P. Hoffmann, G. Gokel, D. Marquarding, and I. Ugi, in I. Ugi, "Isonitrile Chemistry," Academic Press, New York, 1971, p. 9.
7. I. Ugi and R. Meyr, *Ber.*, **93**, 247 (1960).
8. I. Ugi, R. Meyr, M. Lipinski, F. Bodesheim, and F. Rosendahl, this volume, p. 300; R. E. Schuster, J. E. Scott, and J. Casanova, Jr., this volume, p. 772.

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### Appendix

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

petroleum ether

sulfuric acid (7664-93-9)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

formic acid (64-18-6)

nitrogen (7727-37-9)

Phosphorus Oxychloride (21295-50-1)

pyridine (110-86-1)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

phosgene (75-44-5)

potassium (7440-09-7)

tert-butyl alcohol (75-65-0)

o-toluidine (95-53-4)

potassium tert-butoxide (865-47-4)

N-o-Tolylformamide (94-69-9)

o-Tolyl isocyanide (10468-64-1)