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.

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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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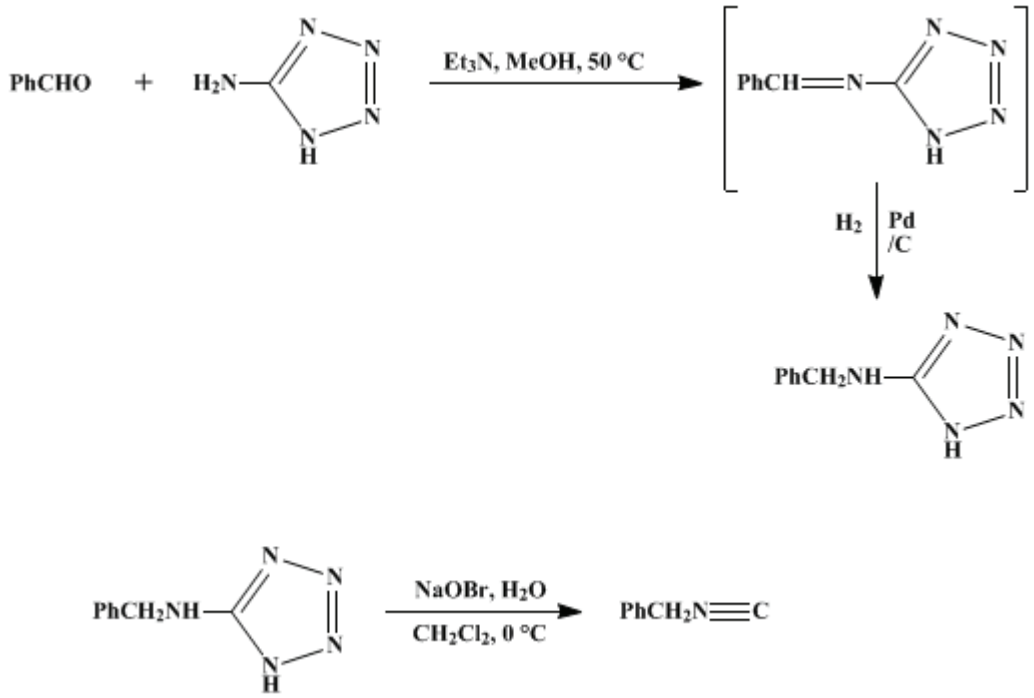
OXIDATION OF 5-AMINOTETRAZOLES: BENZYL ISOCYANIDE

[Benzene, isocyanomethyl]



Submitted by Gerhard Höfle and Bernd Lange[1].
Checked by Orville L. Chapman and Thomas C. Hess.

1. Procedure

Caution! This preparation should be conducted in an efficient hood because of the obnoxious odor of the isocyanide.

A. *5-Benzylaminotetrazole*. Freshly distilled benzaldehyde (21.2 g, 0.2 mol) is added in one portion to a warm (50°C) solution of 5-aminotetrazole (17.2 g, 0.2 mol) (Note 1) and triethylamine (20.2 g, 0.2 mol) in 100 mL of absolute methanol. After 15 min the reaction mixture is cooled to room temperature, transferred to an autoclave, and hydrogenated with agitation at room temperature over Pd (10%) on carbon (1 g) for 18 hr at 500 psi (pounds per square inch) of hydrogen. The catalyst is removed by filtration and all volatile material is removed at 60°C under aspirator pressure. The gummy tan solid is triturated with 250 mL of hot water. Aqueous 20% HCl is added until pH 3 is reached. The mixture is cooled to room temperature and the solid collected, washed with water, and dried over-night at room temperature under reduced pressure (100 μ); yield: 27.5 g (80%), mp 183.5–185°C (lit.[2] mp 183°C).

B. *Benzyl isocyanide*. In a 500-mL, round-bottomed flask equipped with a magnetic stirring bar and a pressure-equalizing funnel are placed 5-benzylaminotetrazole (10.5 g, 60 mmol), 100 mL of 10% sodium hydroxide solution, and 70 mL of dichloromethane. The mixture is cooled to 0°C and a solution of NaOBr in water (165 mL, 65 mmol) (Note 2) is added with vigorous stirring over a 15-min period (Note 3). The dichloromethane layer is separated and the aqueous phase extracted with five 50-mL portions of dichloromethane. The combined dichloromethane extracts are dried over anhydrous $MgSO_4$, the drying agent is removed by filtration, and the dichloromethane is removed by simple distillation. The pressure is then reduced to ~20 mm with an aspirator and benzyl isocyanide is distilled at 98–100° C; yield: 5.91 g (84%) (Note 4) and (Note 5).

2. Notes

1. 5-Aminotetrazole monohydrate is available from Aldrich Chemical Company, Inc.; it was dehydrated by heating over P_2O_5 at 100°C under reduced pressure (100 μ) for 4 hr.
2. The NaOBr solution was prepared according to a procedure described in *Organic Syntheses*.[3] Bromine [12.6 g (4 mL, 79 mmol)] was added dropwise with vigorous stirring to 150 mL of a 10% NaOH solution at −10°C. Enough 10% NaOH solution was added to the yellow solution to give 200 mL of reagent.
3. During addition of the NaOBr solution the mixture warms to 20°C. The reaction is virtually instantaneous and can be monitored by the liberated nitrogen.
4. The product was pure by IR and NMR spectroscopy. The IR spectrum showed a very strong band at 2150 cm^{-1}, the NMR spectrum a distorted triplet at δ 4.5 (2 H) and a broad singlet at δ 7.3 (5 H).
5. Glassware can be freed from the odor of isocyanide by rinsing with a 1 : 10 mixture of concentrated hydrochloric acid and methanol.

3. Discussion

By this method high yields of isocyanides are obtained by an oxidation process. Since this oxidation can also be performed anodically or with bromine or lead tetraacetate and triethylamine in the absence of water (see Table I),[4] it represents a valuable alternative to other procedures: dehydration reactions,[5,6,7] the alkylation of silver cyanide[8,9] or the carbylamine (isocyanide) reaction.[10] The starting materials, 5-aminotetrazoles, can be readily obtained by reductive alkylation of 5-aminotetrazole[2] or from monosubstituted thioureas and sodium azide.[11] A limitation of the reaction is that the substituent R must be stable toward oxidation. From a mechanistic point of view the oxidation of 5-aminotetrazoles is a two step process with a pentaazafulvene as an unstable, undetectable intermediate.

TABLE I
PREPARATION OF ISOCYANIDES (R-N=C) BY OXIDATION OF 5-AMINOTETRAZOLES

R	Yield (%) NaOBr[a]	$Pb(OAc)_4/NEt_3$[b]	Br_2/NEt_3[b]	Anodic Oxidation[a]
C_6H_5	92	70	43	39
C_4H_9	75			
$C_6H_5CH_2$	84			48

[a] In 2*N* sodium hydroxide solution.
[b] In dichloromethane.

Benzyl isocyanide is a useful precursor of compounds containing the α-benzylamino moiety. Substituted styrenes, vinyl isocyanides, 2-oxazolines, 1-pyrrolines, imidazoles, and α-amino acids and ketones can be obtained by metalation of isocyanides with butyllithium[12] or copper salts,[13] and subsequent reaction with various electrophiles.[12]

References and Notes

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

Pd

hydrochloric acid,
HCl (7647-01-0)

methanol (67-56-1)

hydrogen (1333-74-0)

sodium hydroxide,
NaOH (1310-73-2)

bromine (7726-95-6)

nitrogen (7727-37-9)

benzaldehyde (100-52-7)

carbon (7782-42-5)

Benzyl isocyanide,
Benzene, isocyanomethyl (10340-91-7)

sodium azide (26628-22-8)

dichloromethane (75-09-2)

NaOBr

magnesium sulfate (7487-88-9)

butyllithium (109-72-8)

silver cyanide (506-64-9)

triethylamine (121-44-8)

5-aminotetrazole (4418-61-5)

5-Benzylaminotetrazole (14832-58-7)

5-Aminotetrazole monohydrate

pentaazafulvene

phosphorus pentoxide (1314-56-3)

lead tetraacetate (546-67-8)