Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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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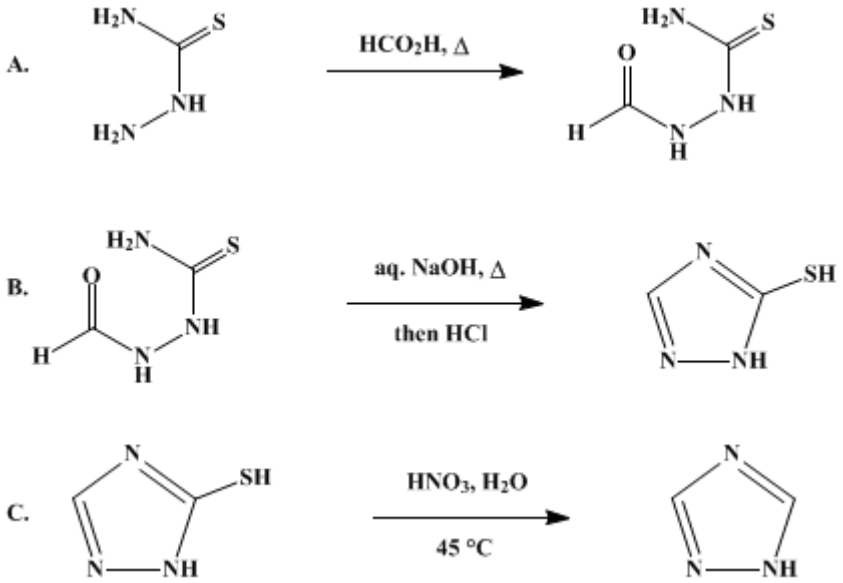
1,2,4-TRIAZOLE

[1H-1,2,4-Triazole]



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1. Procedure

(Note 1)

A. *1-Formyl-3-thiosemicarbazide*. Four hundred milliliters of 90% formic acid contained in a 2-l. round-bottomed flask is heated on a steam bath for 15 minutes, and then 182 g. (2 moles) of colorless thiosemicarbazide (Note 2) is added. The mixture is swirled until the thiosemicarbazide dissolves. The heating is continued for 30 minutes, during which time crystalline 1-formyl-3-thiosemicarbazide usually separates. Boiling water (600 ml.) is added, and the milky solution that results is filtered through a fluted filter paper. After standing for 1 hour, the filtrate is cooled in an ice bath for 2 hours, and the 1-formyl-3-thiosemicarbazide that separates is collected by suction filtration and air-dried overnight. It weighs 170–192 g. (71–81%) and melts at 177–178° with decomposition.

B. *1,2,4-Triazole-3(5)-thiol*. A solution of 178.5 g. (1.5 moles) of 1-formyl-3-thiosemicarbazide and 60 g. (1.5 moles) of sodium hydroxide in 300 ml. of water in a 2-l. round-bottomed flask is heated on a steam bath for 1 hour. The solution is cooled for 30 minutes in an ice bath and then is treated with 150 ml. of concentrated hydrochloric acid. The reaction mixture is cooled in an ice bath for 2 hours, and the 1,2,4-triazole-3(5)-thiol that precipitates is collected by suction filtration. The thiol is dissolved in 300 ml. of boiling water and the solution is filtered through a fluted filter paper. The filtrate is cooled in an ice bath for 1 hour, and the thiol is collected by suction filtration and air-dried overnight. The 1,2,4-triazole-3(5)-thiol weighs 108–123 g. (72–81%) and melts at 220–222°.

C. *1,2,4-Triazole*. *Caution! This preparation should be carried out in a ventilated hood to avoid exposure to noxious fumes.*

A mixture of 300 ml. of water, 150 ml. of concentrated nitric acid, and 0.2 g. of sodium nitrite (Note 3) is placed in a 2-l. three-necked flask equipped with a stirrer and a thermometer. The stirred mixture is warmed to 45°, and 2 g. of 1,2,4-triazole-3(5)-thiol is added. When oxidation starts, as indicated by the evolution of brown fumes of nitrogen dioxide and a rise in temperature, a bath of cold water is placed under the reaction flask to provide cooling and an additional 99 g. (total, 101 g.; 1 mole) of 1,2,4-

triazole-3(5)-thiol is added in small portions over the course of 30–60 minutes. The rate of addition and the extent of cooling by the water bath are so regulated as to keep the temperature close to 45–47° all during the addition. The water bath is kept cold by the occasional addition of ice.

When the addition is completed, the bath is removed and stirring is continued for 1 hour while the reaction mixture gradually cools to room temperature. Sodium carbonate (100 g.) is added in portions, followed by the cautious addition of 60 g. of sodium bicarbonate (Note 4). The water is removed from the slightly basic solution by heating the solution in a 3-l. round-bottomed flask under reduced pressure on a steam bath. To aid in removing the last traces of water, 250 ml. of ethanol is added to the residue and the mixture is heated under reduced pressure on a steam bath until it appears dry (Note 5).

The residue is extracted twice with 600 ml. of boiling ethanol to separate the triazole from a large amount of inorganic salts. This extract is evaporated to dryness on a steam bath under reduced pressure, and the resulting residue is extracted with two 500-ml. portions of boiling ethyl acetate. The ethyl acetate extract is evaporated to dryness on a steam bath under reduced pressure. The crude 1,2,4-triazole remaining in the flask is dissolved by heating it with 50 ml. of absolute ethanol, and then 1 l. of benzene is added. The mixture is heated under reflux for 15 minutes, and the hot solution is filtered through a fluted filter paper. This extraction procedure is repeated. The two extracts are combined, cooled in an ice bath for 30 minutes, and filtered to remove colorless crystals of 1,2,4-triazole (m.p. 120–121°), weighing 28–30 g. after being dried in air. About 300 ml. of the filtrate is removed by slow distillation through a Claisen still-head to remove the bulk of the ethanol. The residual solution is cooled in an ice bath for 30 minutes and filtered to separate an additional 8–10 g. of colorless 1,2,4-triazole, m.p. 119–120°. The total weight of 1,2,4-triazole is 36–40 g. (52–58% yield).

2. Notes

1. This procedure is no longer regarded as the best available for the preparation of 1,2,4-triazole. See Discussion section.
2. The thiosemicarbazide must be of good quality or the yield and quality of 1-formyl-3-thiosemicarbazide will suffer. The thiosemicarbazide supplied by Olin Mathieson Chemical Corporation, obtained as a colorless free-flowing powder, can be used without purification.
3. The use of sodium nitrite helps to avoid an induction period.
4. A large flask is used to contain the vigorous effervescence that occurs upon the addition of carbonate. The final pH should be near 7.5, and it is reached after the addition of bicarbonate no longer causes bubbling.
5. Prolonged heating under reduced pressure should be avoided, since 1,2,4-triazole tends to sublime.

3. Discussion

1-Formyl-3-thiosemicarbazide has been prepared by the reaction of thiosemicarbazide and formic acid.[2]

1,2,4-Triazole-3(5)-thiol has been prepared by heating thiosemicarbazide and formic acid,[3] by heating 1-formyl-3-thiosemicarbazide,[3] and by heating 1,3,5-triazine and thiosemicarbazide.[4] The ring closure of 1-formyl-3-thiosemicarbazide using aqueous base was suggested by L. F. Audrieth and F. Hersman.

1,2,4-Triazole has been prepared by the oxidation of substituted 1,2,4-triazoles,[5] by the treatment of urazole with phosphorus pentasulfide,[6] by heating equimolar quantities of formylhydrazine and formamide,[7] by removal of the amino function of 4-amino-1,2,4-triazole,[8] by oxidation of 1,2,4-triazole-3(5)-thiol with hydrogen peroxide,[3] by decarboxylation of 1,2,4-triazole-3(5)-carboxylic acid,[9] by heating hydrazine salts with formamide,[10] by rapidly distilling hydrazine hydrate mixed with two molar equivalents of formamide,[11] by heating N,N'-diformylhydrazine with excess ammonia in an autoclave at 200° for 24 hours,[11] by the reaction of 1,3,5-triazine and hydrazine monohydrochloride,[12] and by the deamination of 3-amino-1,2,4-triazole with hypophosphorous acid.[13] In view of the availability of 3-amino-1,2,4-triazole in several grades and from several commercial sources, the last-cited procedure, that of Henry and Finnegan,[13] is considered to be preferable to that described here for the preparation of 1,2,4-triazole itself.[14] The Henry and Finnegan procedure has been found to be useful for the

deamination of a wide variety of heteroaromatic amines.[15]

Modifications of the present procedure for the preparation of 1,2,4-triazole have been used to prepared 3-aryl-1,2,4-triazoles[16] and 3-alkyl-1,2,4-triazoles.[17]

References and Notes

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

hypophosphorous acid

1,2,4-Triazole-3(5)-thiol

1,2,4-triazole-3(5)-carboxylic acid

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ammonia (7664-41-7)

Benzene (71-43-2)

ethyl acetate (141-78-6)

formamide (75-12-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

nitric acid (7697-37-2)

sodium carbonate (497-19-8)

formic acid (64-18-6)

sodium nitrite (7632-00-0)

hydrogen peroxide (7722-84-1)

nitrogen dioxide (10102-44-0)

hydrazine hydrate (7803-57-8)

phosphorus pentasulfide

3-amino-1,2,4-triazole (61-82-5)

4-Amino-1,2,4-triazole (584-13-4)

formylhydrazine (624-84-0)

1,2,4-Triazole,
1H-1,2,4-Triazole (288-88-0)

thiosemicarbazide (79-19-6)

1-Formyl-3-thiosemicarbazide (2302-84-3)

1,3,5-triazine (290-87-9)

urazole (3232-84-6)

hydrazine monohydrochloride (2644-70-4)

N,N'-diformylhydrazine