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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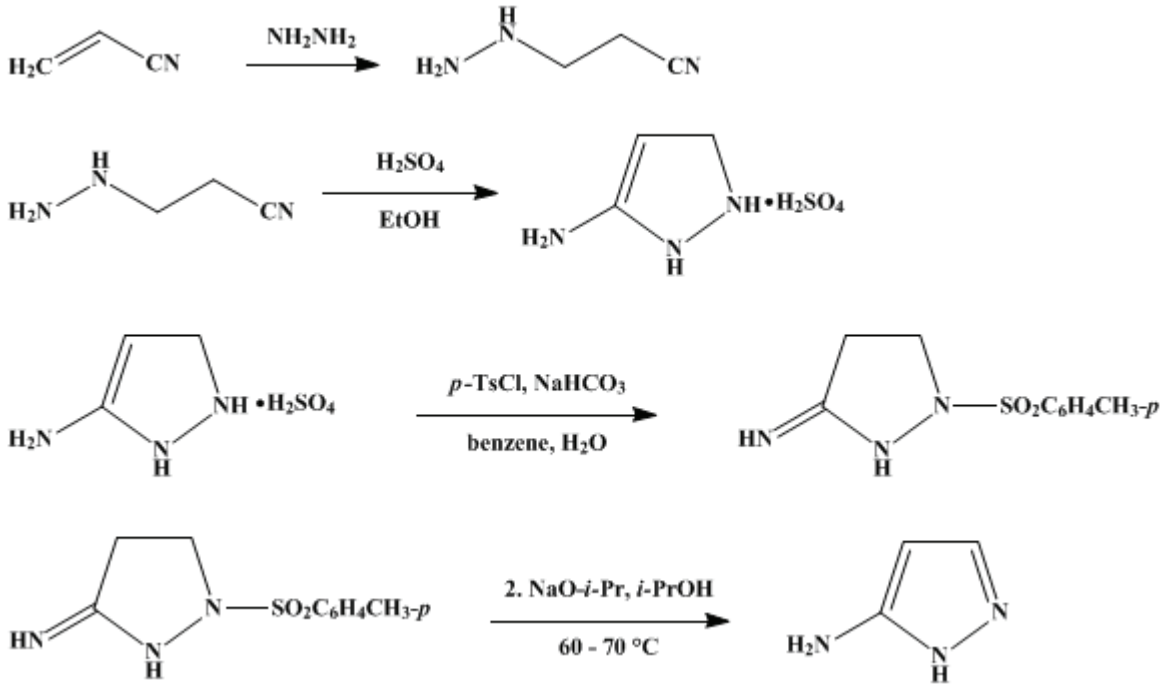
3(5)-AMINOPYRAZOLE

[Pyrazole, 3(or 5)-amino-]



Submitted by H. Dorn and A. Zubek[1].
Checked by L. G. Vaughan and R. E. Benson.

1. Procedure

A. *β-Cyanoethylhydrazine*. To a 2-l. two-necked flask fitted with a thermometer and a pressure-equalizing funnel are added a large magnetic stirring bar and 417 g. (6.00 moles of $N_2H_4 \cdot H_2O$) of 72% aqueous hydrazine hydrate. Acrylonitrile (318 g., 6.00 moles) is gradually added with stirring during 2 hours. The internal temperature is kept at 30–35° by occasional cooling of the flask. The funnel is replaced by a distillation condenser. Removal of water by distillation at 40 mm. at a bath temperature of 45–50° gives 490–511 g. (96–100%) of β-cyanoethylhydrazine as a yellow oil that is suitable for use in the next step. This product can be purified by distillation; b.p. 76–79° (0.5 mm.).

B. *3-Amino-3-pyrazoline sulfate*. In a 2-l. four-necked flask equipped with a reflux condenser, a dropping funnel, a thermometer, and a mechanical stirrer with four blades (Note 1) is placed 308 g. (169 ml., 3.0 moles) of 95% sulfuric acid (sp. gr. 1.834). Absolute ethanol (450 ml.) is added dropwise over 20–30 minutes. The internal temperature is maintained at 35° by cooling. A solution of 85.1 g. (1.00 mole) of β-cyanoethylhydrazine in 50 ml. of absolute ethanol is added with vigorous stirring over 1–2 minutes without further cooling (Note 1). The mixture warms spontaneously to 88–90° and is kept at this temperature for 3 minutes until the product begins to crystallize. The temperature of the stirred mixture is gradually lowered during the next hour to 25° by cooling with water, and the mixture is then allowed to stand at room temperature for 15–20 hours. The crystals are collected by filtration and washed three times with 80 ml. of absolute ethanol and finally with 80 ml. of ether. After being dried at 80° the product weighs 177–183 g. (97–100%), m.p. 143–144° (Note 2). The product is sufficiently pure for use in the following step; it may be recrystallized from methanol to give white needles, m.p. 144–145° (Note 2).

C. *3-Imino-1-(p-tolylsulfonyl)Pyrazolidine*. To a 3-l. four-necked flask fitted with a condenser, a thermometer, a wide-mouthed funnel, and a high-speed mechanical stirrer having five pairs of blades

are added 183 g. (1.00 mole) of 3-amino-3-pyrazoline sulfate and 1 l. of water. Sodium bicarbonate (210 g., 2.5 moles) is gradually added during 10 minutes with stirring. The rate of stirring is increased to 5000–6000 r.p.m., and a solution of 229 g. (1.20 moles) of *p*-toluenesulfonyl chloride in 400 ml. of benzene containing 0.5 g. of sodium dodecylbenzenesulfonate (Note 3) is added at one time. Three further portions of sodium bicarbonate are added sequentially: 25.2 g. (0.30 mole) after 15 minutes; 16.8 g. (0.20 mole) after 30 minutes; 16.8 g. (0.20 mole) after 55 minutes. The mixture is stirred for 5 hours at 18–25°, occasional cooling being required. Sodium bicarbonate (8.4 g., 0.10 mole) is added, then 200 ml. of ether, and stirring is continued for another hour. The colorless product is collected by filtration on a sintered-glass funnel, washed with three 50-ml. portions of ether followed by 50 ml. of water and dried at 90°. The yield is 139–180 g. (58–75%); m.p. 183–185° (Note 4). The product is used directly in the next step.

D. *3(5)-Aminopyrazole* (Note 5). *(Caution! Because hydrogen gas is evolved, this reaction should be conducted in an efficient hood in the absence of an ignition source.)* A solution of sodium isopropoxide is prepared from 18.4 g. (0.80 g. atom) of sodium and 500 ml. of isopropyl alcohol in a 2-l. four-necked flask fitted with a mechanical stirrer, a thermometer, a reflux condenser, and a stopper. The reflux condenser is fitted with a nitrogen-inlet line attached to a bubbler device to maintain an anhydrous atmosphere. After all the sodium has dissolved, the temperature is adjusted to 60–70°, the stopper is replaced by a wide-mouthed funnel, and 191 g. (0.80 mole) of 3-imino-1-(*p*-tolylsulfonyl)-pyrazolidine is added gradually over 10 minutes to the hot solution under a blanket of nitrogen. The funnel is replaced by the stopper, and the mixture is stirred vigorously and then refluxed briefly. Stirring is continued, and the mixture is allowed to cool to room temperature during 2 hours. The precipitated sodium *p*-toluenesulfinate (140–142 g.) is removed by filtration and washed with a total of 100 ml. of isopropyl alcohol in several portions. The filtrate is treated twice with 4-g. portions of Norit activated carbon. The solvent is removed by distillation, the final trace being removed at a bath temperature of 50° (20 mm.) to give 62–66 g. (93–99%) of 3(5)-aminopyrazole as a light yellow oil. This is purified by distillation to give the product as a yellow oil, b.p. 100–102° (0.01 mm.), in 74–84% recovery (Note 6). The product crystallizes on cooling; m.p. 37–39° (Note 7). Its n.m.r. spectrum (60 MHz, dimethyl sulfoxide-d_6) shows two one-proton doublets at δ 7.33 and 5.52 p.p.m. (J = 2 Hz) and a broad three-proton singlet at δ 7.05 p.p.m. that is absent after addition of D_2O.

2. Notes

1. A stirrer with large blades operating at high speed is essential. Inadequate stirring results in solidification of the reaction mixture and makes proper washing of the product very difficult.
2. The checkers found melting points of 138–141° and 140–142°. After three recrystallizations from methanol the product has a melting point of 139.7–140°. The product appeared to be unstable to prolonged heating in methanol.
3. This salt serves as an emulsifying agent.
4. A sample, m.p. 184–185°, prepared by recrystallization of the product from nitromethane, gives satisfactory elemental analytical data. Its n.m.r. spectrum (60 MHz, dimethyl sulfoxide-d_6) reveals that the compound exists in the iminopyrazolidine form under these conditions; signals at δ 7.72 p.p.m. (doublet, J = 8.4 Hz), 7.40 p.p.m. (doublet, J = 8.4 Hz), 6.1 p.p.m. (broad singlet; absent after addition of D_2O), 3.4 p.p.m. (triplet, J = 9.0 Hz), and 2.4 p.p.m. (sharp singlet superimposed on triplet) with relative intensities of 2:2:2:2:5. The signals at 7.72 and 7.40 p.p.m. are assigned to the four aromatic protons, that at 6.1 p.p.m. to the two N-H protons, that at 3.4 p.p.m. to one pair of methylene protons, and that at 2.4 p.p.m. to the second pair of methylene protons plus the protons of the methyl group.
5. 3(5)-Aminopyrazole may also be obtained by hydrolysis of 3-imino-1-(*p*-tolylsulfonyl)pyrazolidine with aqueous alkali. In this case the pyrazolidine (239 g., 1.00 mole) is added to a solution of 40 g. (1.0 mole) of sodium hydroxide in 250 ml. of water at 75°, the resulting solution is stirred briefly, and the water is removed at reduced pressure. 3(5)-Aminopyrazole is separated from the sodium *p*-toluenesulfinate by several extractions with isopropyl alcohol.
6. In order to obtain maximum recovery the submitters conducted the distillation of 120 g. of crude product for 7–10 hours.
7. The checkers observed b.p. 119–121° (1.0 mm.) and m.p. 34–37°.

3. Discussion

3(5)-Aminopyrazole has been prepared by a Curtius degradation of pyrazole-3(5)-carboxylic acid hydrazide,[2,3] by saponification and decarboxylation of ethyl 3-aminopyrazole-4-carboxylate[4] obtained from ethyl ethoxymethylenecyanoacetate and hydrazine, and by the present procedure.[5,6]

4. Merits of the Preparation

This procedure represents the most convenient synthesis of 3(5)-aminopyrazole. It employs readily available starting materials and gives excellent yields in all steps.[5,6] *p*-Toluenesulfonyl chloride can be replaced by other arenesulfonyl chlorides. 3-Imino-1-arylsulfonylpyrazolidines can be alkylated with dimethyl sulfate or with alkyl *p*-toluenesulfonates in dimethylformamide to give salts of 1-alkyl-2-arylsulfonyl-5-amino-4-pyrazolines from which arenesulfinate can be eliminated as described in procedure D. In this fashion 1-alkyl-5-aminopyrazoles can be easily prepared.[6]

References and Notes

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

D_2O

3(5)-Aminopyrazole

Pyrazole, 3(or 5)-amino-

ethanol (64-17-5)

sulfuric acid (7664-93-9)

Benzene (71-43-2)

methanol (67-56-1)

ether (60-29-7)

hydrogen (1333-74-0)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

nitrogen (7727-37-9)

dimethyl sulfate (77-78-1)

Norit activated carbon (7782-42-5)

sodium (13966-32-0)

isopropyl alcohol (67-63-0)

sodium isopropoxide (683-60-3)

hydrazine hydrate (7803-57-8)

methylene (2465-56-7)

hydrazine (302-01-2)

Nitromethane (75-52-5)

acrylonitrile (107-13-1)

dimethylformamide (68-12-2)

ethyl ethoxymethylenecyanoacetate

β-Cyanoethylhydrazine (353-07-1)

3-Amino-3-pyrazoline sulfate (29574-26-3)

sodium dodecylbenzenesulfonate (2211-98-5)

pyrazolidine (504-70-1)

ethyl 3-aminopyrazole-4-carboxylate (6994-25-8)

p-Toluenesulfonyl chloride (98-59-9)

Sodium p-toluenesulfinate

3-imino-1-(p-tolylsulfonyl)pyrazolidine,
3-imino-1-(p-tolylsulfonyl)-pyrazolidine (1018-36-6)