A Facile Synthesis of 3(5)-Aminopyrazoles

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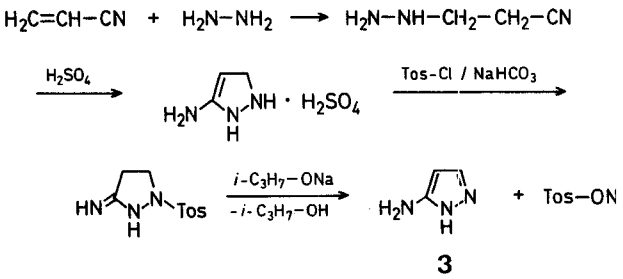
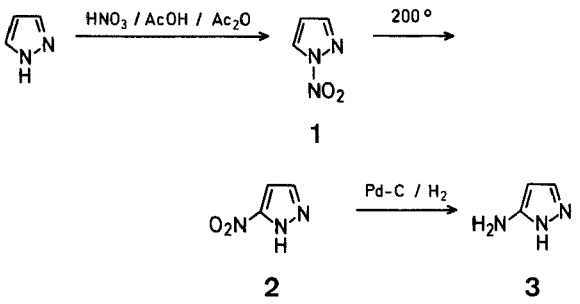
3(5)-Aminopyrazole (**3**) has been prepared in a number of ways[1-5] of which the most recent one[4] is based on the following reaction sequence:



3

In general, reduction of aromatic nitro compounds provides the most simple route to aromatic amines. However, the synthesis first reported for 3(5)-nitropyrazole used 3(5)-aminopyrazole as starting material. Studies in our laboratory[6,7] showed that 3(5)-nitropyrazole can be prepared very easily by N-nitration of pyrazole followed by thermal isomerization of N-nitropyrazole (**1**) to 3(5)-nitropyrazole (**2**). We found that reduction of 3(5)-nitropyrazole with hydrogen and a palladium-on-carbon catalyst affords 3(5)-aminopyrazole (**3**) in high yield.



1 2 3

The scale and the yield of the N-nitration reaction, first described by Hüttel et al.[8], were improved by carefully keeping the temperature of the reaction mixture below 30° and by neutralizing the acetic acid with potassium carbonate in the work-up procedure. The thermal isomerization of N-nitro- to 3(5)-nitropyrazole was carried out by refluxing a 5–10% solution of N-nitropyrazole in benzonitrile according to the general procedure developed by Janssen et al. for the synthesis of 3(5)-nitropyrazoles[7]. The simplicity of the reaction steps makes the present route the most convenient and facile preparation of 3(5)-aminopyrazole. In addition, this route promises to be a general method for the synthesis of 3(5)-aminopyrazoles.

N-Nitropyrazole (1):
Nitric acid (17.5 ml, d = 1.5) was added slowly to a solution of pyrazole (25 g) in acetic acid (75 ml) while stirring vigorously. During this procedure, the mixture was cooled with an ice/salt bath in order to keep the temperature below 30°. Acetic anhydride (50 ml) was added with stirring and the suspension stirred at room temperature until a clear solution was obtained (2–3 hr). This solution was poured onto ice (500 g), and potassium carbonate was added in small portions. The precipitate was isolated by filtration and dried at room temperature; yield: 31.5–35 g (76–84%); m.p. 92–93° (Ref.[8], m.p. 93°).

^{1}H-N.M.R. (DMSO-d_6): δ = 8.63 (d, 5-H), 7.80 (s, 3-H), 6.70 (m, 4-H).
A second crop was obtained by extracting the mother liquor with ether; yield: 3.5–4 g (8.5–9.5%); total yield: 84–93%.

3(5)-Nitropyrazole (2):
A solution of N-nitropyrazole (20 g) in benzonitrile (200 ml) was heated under reflux for 2 hr. The solution was then cooled to room temperature and poured into hexane (2 l). The resultant precipitate was isolated by filtration and recrystallized from benzene in order to prevent contamination of the 3(5)-aminopyrazole with benzylamine in the next step; yield: 16.7–17.2 g (83–86%); m.p. 174–175° (Ref.[6,7], m.p. 174–175°).

^{1}H-N.M.R. (DMSO-d_6): δ = 7.93 [d, 5(3)-H, J = 2.0 Hz], 7.01 (d, 4-H, J = 2.0 Hz).

3(5)-Aminopyrazole (3):
A suspension of 3(5)-nitropyrazole (10 g) and 5% palladium-on-carbon catalyst (5 g) in 70% acetic acid (75 ml) was reduced in a Parr apparatus with hydrogen at a pressure of 3 atm. The catalyst was filtered off and the solvent was evaporated at reduced pressure. The residue was made alkaline with a solution of potassium carbonate in water and the resultant solution was extracted continuously with dichloromethane for 16 hr. The extract was dried with magnesium sulfate and filtered. The solvent was removed by evaporation and the residue distilled in vacuo; yield: 5.9–6.0 g (80–82%); b.p. 160–165°/12 torr (Ref.[4], b.p. 100–103°/0.02 torr, b.p. 119–121°/1.0 torr).

^{1}H-N.M.R. (DMSO-d_6): δ = 7.21 [d, 5(3)-H, J = 2.0 Hz], 5.42 (d, 4-H, J = 2.0 Hz).

The mass- and I.R. spectra were identical with those of 3(5)-aminopyrazole prepared according to Dorn et al.[4].

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