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Practical and Scalable Process for the Preparation of 4-Amino-1,3-dimethylpyrazole Hydrochloride

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Abstract:

A practical and scalable process for the preparation of 4-amino-1,3-dimethylpyrazole hydrochloride 1 is described. Compound 1 is a useful starting material; its preparation is achieved *via* a three-step sequence from methyl hydrazine and technical grade acetaldehyde dimethylacetal. The target molecule is isolated in high chemical and isomeric purity (>99.0% with respect to 4-amino-1,5-dimethylpyrazole).

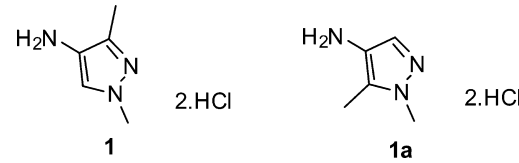
Introduction

The ability to rapidly prepare multikilogram quantities of starting material, 4-amino-1,3-dimethylpyrazole hydrochloride, **1**, would be advantageous. In order to achieve this, we have developed a safe, robust and scalable synthesis. While the material is commercially available, it is expensive, available in only gram quantities, and although processes have been reported, none are convenient to carry out on a large scale. Herein we report development of a robust, practical and scalable process for the preparation of **1**.

Results and Discussion

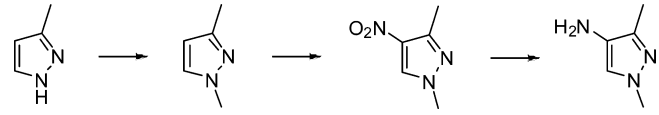
Initial attempts toward preparation of **1** were based on methylation[1] of the commercially available 3-methylpyrazole (Figure 2). Although the desired regioisomer was formed, the synthesis was unsuitable for the following reasons: (1) Reactions failed to go to completion; (2) large proportions of regioisomer were produced; (3) several byproduct were generated over the course of the reaction.

Given the lack of success encountered using this route, we turned our attention to methodology that would construct the pyrazole ring. Previous reports[2] indicated that reaction of methyl hydrazine and acetylacetaldehyde dimethylacetal (AADMA) gives a mixture of regioisomers. However, isolation of the required 1,3 isomer was achieved *via* crystallisation of the picrate salt. Due to the inherent stability issues surrounding picrates, an alternative mode of purification was necessary.



1 **1a**

Figure 1. **4-Amino-1,3-dimethylpyrazole hydrochloride, 1, and regioisomer 4-amino-1,5-dimethylpyrazole, 1a.**



2 **3** **1**

Figure 2. **Selective alkylation approach to 4-amino-1,3-dimethylpyrazole.**

Adopting the AADMA approach towards preparation of **1**, we successfully generated a mixture of 1,3- and 1,5-dimethylpyrazole, **2** and **2a**, largely free of byproduct. The ratio of 1,3- to 1,5- regioisomers was 2.5:1 (^{1}H NMR analysis).[3] Having isolated the crude reaction mixture and demonstrated through user trial that the crude mixture of isomers did not lead to isolation of **1** in the required isomeric purity, we turned our attention toward purification strategies. The reported boiling points[4] of 1,3-dimethylpyrazole and 1,5-dimethylpyrazole indicated that fractional distillation of the desired isomer might be possible. Although enrichment of the desired regioisomer was observed, isolation of isomerically pure material was not possible in our hands by distillation alone. Nevertheless, distillation of the crude reaction mixture under reduced pressure (50−60 °C @ 45 mmHg) allowed efficient separation of a mixture of 1,3- and 1,5-dimethylpyrazoles, free from residual starting materials and water. The ratio of this purified pyrazole fraction (1,3- to 1,5-) was found to be 2.8:1.0. Subsequent distillation of the purified mixture of pyrazoles at ambient pressure (138−143 °C @ 760 mmHg), through a packed bed allowed significant enrichment of the mixture to an isomeric purity level of >95% (^{1}H NMR analysis). Processing of the enriched isomeric mixture through user trial of the subsequent nitration step gave rise to crystalline material which afforded the possibility of further regioisomeric upgrade *via* recrystallisation (4:1, methyl *tert*-butyl ether/heptanes) to >99.0%. Further investigations revealed that isomeric purity of the pyrazole mixture must be >85% to allow isolation of >99.0% (GC analysis) isomerically pure nitro compound, **3**. During development of a nitration procedure suitable for preparation

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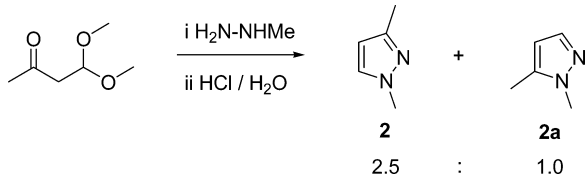
Scheme 1. **AADMA approach towards dimethylpyrazoles 2 and 2a**



of **3**, thermal hazard evaluation was performed and indicated that a feed-controlled reaction could be safely carried out below 70 °C, with no evidence of accumulation. In the subsequent reduction of **3** by heterogeneous catalysis it was found convenient to have hydrochloric acid in the reaction mixture to allow *in situ* formation of **1**. All attempts to isolate the free base of **1** were unsuccessful.

Conclusion

An efficient, practical and scaleable process for the controlled production of 4-amino-1,3-dimethylpyrazole *bis*-hydrochloride, **1**, has been demonstrated. By adopting a procedurally simple distillation/crystallization sequence the use of picrate salts is avoided. The described process allows the target molecule to be isolated in high chemical purity and isomeric purity. The route has proven itself reliable and convenient for the preparation of multimolar quantities of **1**. We acknowledge that scale-up to significantly larger quantities would require further optimization.

Experimental Section

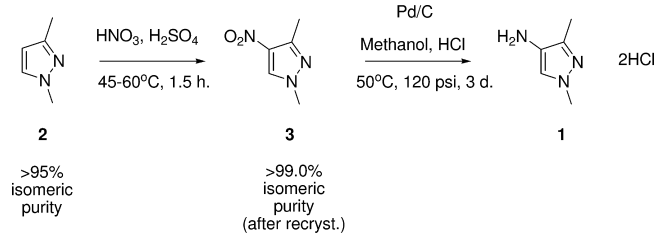
General. All reagents and solvents were used directly as purchased from commercial suppliers. All reactions were conducted under nitrogen unless otherwise stated. NMR spectra were obtained on a Bruker Avance-400 spectrometer.

1,3-Dimethylpyrazole (2). Methyl hydrazine (497.4 g, 10.79 mol) was added to acetylacetaldehyde dimethylacetal (AADMA) (1425.0 g, 10.78 mol) at 90 °C over 1 h (an exotherm to 106 °C was observed). The mixture was stirred at 90 °C for 1.5 h. The reaction mixture was cooled to room temperature. The resultant solution of crude hydrazone was added to 3 N hydrochloric acid (2.87 L) at 68 °C over 30 min (an exotherm to 96 °C was observed). The resulting solution was stirred at 70 °C for 1 h. The mixture was cooled to 30 °C and basified (pH 14) by addition of sodium hydroxide solution (1070 g, 50% aq.) The mixture was extracted with methyl *tert*-butyl ether (3 × 1.5 L), and the combined extracts were dried ($MgSO_4$). The mixture was filtered and the solvent removed under reduced pressure to give the crude mixture of pyrazoles (crude mass 1241 g).

Distillations. The crude mixture of dimethylpyrazoles was distilled under reduced pressure (50−60 °C, @ 45 mmHg), typical wt/wt (with respect to crude mass of **2**) recovery for distillations was in the region of 60%. The mixture from reduced pressure distillation was redistilled through a packed column (Fenske helices) (bp 138−143 °C @ 760 mmHg) to furnish 1,3-dimethylpyrazole **2**. Typical overall yield of **2** was in the region of 40%.

1,3-Dimethyl-4-nitropyrazole (3). A solution of **2** (190 g, 2.0 mol) in concentrated sulfuric acid (190 mL, 3.55 mol) was added dropwise to a mixture of nitric acid (190 mL, 4.50 mol) and sulfuric acid (190 mL, 3.55 mol), maintaining the temperature between 50−60 °C. The reaction mixture was stirred at 60 °C for 1.5 h. The mixture was cooled to room temperature and quenched into water (1.9 L). The aqueous mixture was basified (pH 14) by addition of potassium hydroxide solution (40%, 2.0 kg). The aqueous mixture was extracted with methyl *tert*-butyl ether (3 × 1 L). The combined organics were dried ($MgSO_4$), filtered, partially concentrated until a thick slurry was observed. The resultant mixture was diluted with heptanes (1 L) and partially concentrated again. The slurry was filtered to give the crude product as a white solid (240 g). The crude material was recrystallised from methyl *tert*-butyl ether/heptanes (5 vol, 4:1) to give **3** (158.2 g, 69%, LC purity 99.8% a/a). The mother liquors were reprocessed *via* concentration and solvent switched to heptanes, and the solids were recrystallised from methyl *tert*-butyl ether/heptanes (5 vol, 4:1) to give a second crop of **3** (40.7 g, 15%, LC purity 99.6% a/a).

Scheme 2. **Preparation of 1 from 1,3-dimethylpyrazole 2**



4-Amino-1,3-dimethylpyrazole Hydrochloride (1). A mixture of **3** (76.7 g, 540 mmol), Pd/C (7.7 g, 10% loading, 50% wet) and hydrochloric acid (100 mL, 37%) in methanol (760 mL) was stirred under hydrogen (120 psi) at 50 °C. After 3 days a process test (NMR) showed a 4:1 mixture of product: intermediate. A further portion of Pd/C (3.8 g) was charged to the vessel and the mixture stirred overnight under hydrogen (120 psi) at 50 °C. After a further 24 h, analysis (NMR) showed no intermediate. The mixture was filtered (Whatman GF/F) and the solvent switched for industrial methylated spirit (3 × 500 mL) (some precipitation occurred). The resultant mixture was solvent switched to isopropyl acetate (3 × 500 mL), and the solids were isolated by filtration and dried to constant weight *in vacuo* to give **1** (88.5 g, 88%, NMR purity 98% w/w).

Acknowledgment

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Supporting Information Available

^{1}H NMR spectra for all stages, GC data for stage 1, HPLC data for stages 2 and 3, hazard evaluation data and distillation data for compound **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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