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Efficient and environmentally friendly synthesis of 2-amino-imidazole

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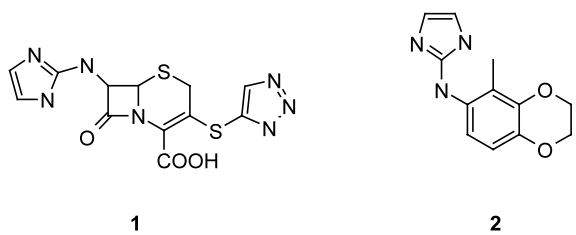
Abstract—A new and efficient method for the preparation of 2-amino-imidazole **3** was developed. Starting from cheap commodities *O*-methyl-iso-urea sulphate and 2-aminoacetaldehyde-acetales the desired product is isolated through a very simple work-up in a good yield. This new procedure overcomes several technical and environmental problems of the traditional approaches to this molecule and is therefore very attractive for large-scale preparation.

2-Amino-imidazoles are a very interesting class of heterocyclic compounds as they are found in many pharmacologically active substances, e.g. cephalosporin **1**[1] or α_2-receptor agonist **2**,[2] (Scheme 1) and also in some natural products like the marine alkaloids Isonaamine A, Dorimidazole A and Preclathridine A.[3] Due to these interesting biological properties, several methods for the preparation of unsubstituted 2-amino-imidazole **3** have been described in the literature.

Preparation of 2-amino-imidazole is a tedious task as it is not only highly prone to oxidation by air, brown oils are often produced during the reaction but it is also very soluble in water. The latter fact makes the work-up, isolation and purification of this compound extremely difficult.

The oldest method was described as early as 1919 by Pyman et al.[4] who used the reduction of 2-arylazo-imidazoles to 2-amino-imidazoles. Unfortunately, this procedure was not viable for us as we had to find a procedure for the preparation of larger amounts of 2-amino-imidazole in the pilot plant. Due to large waste streams and tedious work-up conditions this procedure was not acceptable for large-scale manufacture.



1

2

Scheme 1.

Another procedure which is often cited in the literature is the reaction between cyanamide **4** and 2-amino-acetaldehyde-acetales **5** followed by an acid catalysed cyclisation which was found by Lawson.[5] From a technical point of view this method also faces several problems as the guanidine derivative **6** which is formed as an intermediate is obtained as a gum which has to be triturated with diethyl ether and acetone to purify the material (Scheme 2). In our hands yields and purity of the product produced by this method tended to be low.

A standard procedure for the synthesis of substituted guanidines is the transformation of *S*-methyl-isothiourea derivatives with amines. This method was used by Storey, Sullivan and Moyer for the preparation of 2-amino-imidazole-sulfate by reacting *S*-methyl-isothiourea with 2-amino-acetaldehyde-diethylacetal.[6] The following acid catalysed cyclisation gave the desired product. However, the release of equimolar amounts of badly smelling methyl mercaptan during the course of the reaction gives rise to significant environmental and safety problems which make additional technical measures necessary and therefore adds to the costs of such a manufacturing process. A similar method was also described in a Japanese patent by T. Yamamoto.[7]

As all of the described literature procedures have several drawbacks we tried to find a new and improved method for the large-scale preparation of 2-amino-imidazole. Back in 1954, Fearing and Fox had demon-

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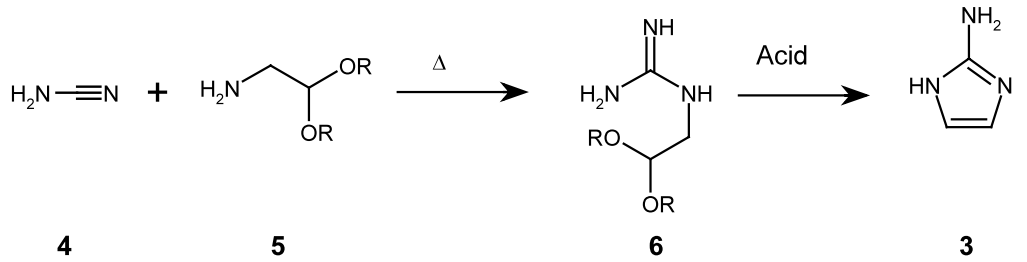
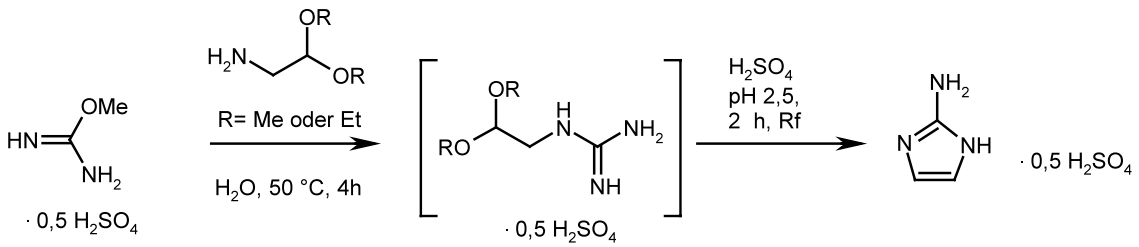


Scheme 2.



Scheme 3.

strated that amines can be reacted with *O*-methyl-isourea-sulfate for the preparation of monosubstituted guanidines.[8] However, to the best of our knowledge, 2-amino-acetaldehyde-acetals have not been used so far. Surprisingly, we found that at 50°C in an aqueous solution after 4 h a complete transformation to the guanidine derivative is achieved (Scheme 3).

The reaction can be performed with 2-amino-acetaldehyde diethylacetal as well as with 2-amino-acetaldehyde dimethylacetal. As the latter is cheaper, we preferred the dimethylacetal. Both the 2-amino-acetaldehyde-dimethylacetal and the *O*-methyl-isourea are cheap commodities and therefore this process has economic advantages and is environmentally more friendly as only methanol is released as a by-product during the reaction.

Unfortunately, our attempts to isolate the guanidine derivative were not successful. Therefore, we developed a one-pot procedure. The transformation of *O*-methyl-isourea to the guanidine is followed immediately by the sulphuric acid-catalysed cyclisation to 2-amino-imidazole-hemisulfate. A pH of 2.5 was found to be optimal as no deterioration or polymerisation occurred under these conditions. After 2 h at 100°C a complete transformation was reached. Due to the extremely good solubility of 2-amino-imidazole in water as a salt or free base, it was impossible to isolate the product from the reaction mixture by the usual extraction with organic solvents. On the other hand, removal of the water through distillation resulted in partial deterioration of the product. It was possible to isolate the product by freeze-drying but, from a technical point of view, this was not an economical method for isolation. Concentration of the solution and crystallisation attempts were also unsuccessful.

Experiments to precipitate the salt from the aqueous solution by adding water-miscible organic solvents like THF or DMF were not successful. To our great surprise we then found that by slowly (over 1 h) dropping the reaction mixture at 0–5°C into ice-cold ethanol, 2-amino-imidazole-hemisulfate was obtained as a white crystalline precipitate in 86% yield.[9] This result was even more surprising as Storey, Sullivan and Moyer had used ethanol as a solvent in their work-up procedure. Therefore, it seems that the solubility of 2-amino-imidazole-hemisulfate strongly depends on the temperature.

In summary we have developed a new procedure for the preparation of 2-amino-imidazole which besides a very good yield and quality of the product has several other advantages related to technical, safety and environmental aspects. By using the new one-pot procedure not only a higher yield is obtained but also the work-up is drastically simplified.

Acknowledgements

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References

1. Jung, F.; Olivier, A.; Boucherot, D. *Tetrahedron Lett.* **1989**, *30*, 2379–2382.
2. Munk, S. A.; Harcourt, D. A.; Arasasingham, P. N.; Burke, J. A.; Kharlamb, A. B.; Manlapaz, C. A.; Padillo, E. U.; Roberts, D.; Runde, E.; Williams, L.; Wheeler, L. A.; Garst, M. E. *J. Med. Chem.* **1997**, *40*, 18–23.

3. Molina, P.; Fresneda, P. M.; Sanz, M. A. *J. Org. Chem.* **1999**, *64*, 2540–2544.
4. Pyman, Fargher, *J. Chem. Soc.* **1919**, *115*, 238.
5. Lawson, A. *J. Chem. Soc.* **1956**, 307.
6. Storey, B. T.; Sullivan, W. W.; Moyer, C. L. *J. Org. Chem.* **1964**, *29*, 3118.
7. Yamamoto, T. Production of 2-Aminoimidazole or Salt Thereof, JP63301869, 12.08.1988.
8. Fearing, R. B.; Fox, S. W. *J. Am. Chem. Soc.* **1954**, *76*, 4382.
9. **Preparation of 2-amino-imidazole-hemisulfate 3**:
88.74 g *O*-Methyl-isourea-hemisulfate was weighed into the reaction vessel. Under inert atmosphere (nitrogen) 150 ml deionised water and 109.2 2-amino-acetaldehyde-diethylacetale were added and the reaction mixture was stirred for 4 h at 50°C. TLC control showed complete transformation. The reaction mixture was then cooled to 20°C and 7 ml concentrated sulphuric acid were added (pH 2 and 5). The mixture was heated to 100°C and stirred for 2 h at this temperature. TLC control showed complete transformation. The reaction mixture was cooled to 20°C and slowly dropped over a 1 h period at 0–5°C into 3000 ml ice cold ethanol. The suspension was stirred for an additional hour at 0–5°C. The suspension was filtered off and washed twice with 50 ml ice-cold ethanol. The product was dried at 40°C in a vacuum drying oven. Yield: 84.87 g white crystals (86 %). All spectroscopic and physicochemical data were identical to the values reported in the literature: ^{1}H NMR (400 MHz, D_2O): 6.8 (s, 2H). Mass spectrum: ESMS m/z (fragment): 84 (M^++1), 83 (M^+). IR: (KBr) 3150, 3000, 2750, 1680, 1100.