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SYNTHESIS OF 2-AMINO-6-CHLOROPYRIDINE

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Abstract

Synthesis of 2-amino-6-chloropyridine by the reduction of 2-hydrazino-6-chloropyridine under various conditions is described. The way through 2-azido-6-chloropyridine and its reduction afforded the pure product, but it is laborious. The best results were achieved by the reduction with hydrazine and Ra/Ni catalysis. The method usually used – reduction with hydrogen – afforded the product containing large amount of dehalogenated by-product.

Key Words: Reduction, hydrazino derivative, amino derivative, pyridine.

Introduction

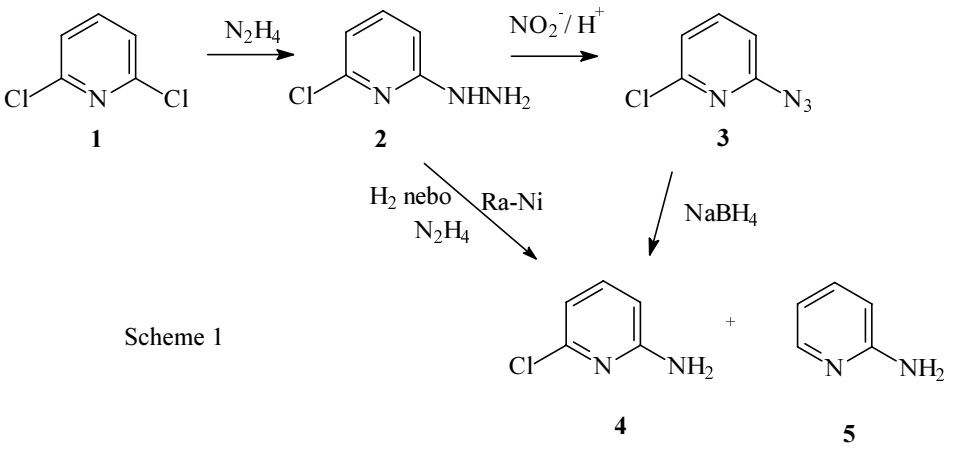
2-Amino-6-chloropyridine was studied as a key intermediate for the preparation of substituted "quinolones".[1] The synthesis of this compound has been described, but usage of the described methods is limited. An interesting method for the preparation of 2-aminopyridines was described twenty years ago. Starting 2-chloropyridine-1-oxide was converted to 2-amino-6-chloropyridine by the reaction with 4-chloro-2,2-dimethyl-2H-1,3-benzoxazine.[2] This method is useful only for the small laboratory scale because of unavailability of the starting material. Two other published methods start from simply available 2,6-dichloropyridine. The direct substitution of chlorine by the reaction with ammonium is problematic. The temperature 200 °C is necessary for this reaction.[3,4] The reaction must be done under pressure in an autoclave. As a potential synthetic method for the preparation of the amino derivative **4** the reduction of 2-hydrazino-6-chloropyridine (**2**) was selected.

The preparation of the amino derivatives by the reduction of 1,2-disubstituted hydrazino derivatives has been known for long time. Substituted anilines are prepared from substituted hydrazino derivatives by the reduction. Hydrogen under the

catalysis of Pd,[5] aluminium amalgam,[6] tin[7] or iron [8] are used as reduction agents. The reduction of mono substituted hydrazines has not been frequently used for the preparation of anilines. Usually opposite reaction is used and monosubstituted hydrazines are prepared from anilines through the reduction of diazonium compound. For these reasons the reaction is used only for the preparation of some special amino derivatives, provided that hydrazino derivatives are prepared in a different way than by reduction of diazonium salt. 2,3,5,6-tetrafluorophenylenediamine was prepared by the reduction of 1,4-dihydrazino tetrafluoro-benzene with 50% hydroiodic acid. The yield of the reaction is only 18 %.[9] These methods have been also applied in the heterocyclic area. Very high yield 94 % of 3,4-diaminopyridine was received by the reduction of 3-nitro-4-hydrazinopyridine with hydrogen in ethanol under the catalysis of Ra-Ni.[10] 3-Aminopyridazine derivatives were successfully prepared also by the reduction of 3-hydrazinopyridazine derivatives on the similar conditions.[11]

2-Hydrazino-6-chloropyridine (**2**) is simply available by the reaction of 2,6-dichloropyridine with hydrazine hydrate. The yield of this reaction is high and the reaction conditions are milde.[12] Hydrazino pyridine **2** was utilized in several ways. In the first case, the hydrazino derivative **2** was transformed to 2-azido-6-chloropyridine (**3**) by the reaction with sodium nitrite in diluted hydrochloric acid. The prepared azide **3** was surprisingly stable and did not indicate tendency to explode, but for the security reasons this compound was used only in the solution. The compound **3** was reduced with sodium borohydride. The yield of aminopyridine **4** was acceptable. Except of this main product, some unidentified compounds were formed. Pure product was isolated by crystallisation of crude compound from toluene. This method affords a very pure product, and no dehalogenated by-product **5** is present in the reaction mixture. This method is laborious and it is not suitable for industrial production. For this reason I tried direct reduction of hydrazino derivative **2** with hydrogen. The reaction speed was sufficient at 70 °C under the small pressure of hydrogen. The yield was acceptable, but a lot of 2-aminopyridine was formed by this reduction. Purification of this crude product is very problematic.

The reduction of the hydrazino derivative **2** with hydrazine hydrate under the catalysis of Ra-Ni at 90 °C was the best way for the preparation of the compound **4**. Under these conditions the reaction was fast and the yield was satisfactory. The crude product contains small amount of the dehalogenated impurity **5**. The final product was successfully crystallised from toluene. The courses of the reactions were checked by TLC. Quality of the prepared products was evaluated by GC. The impurity of 2-aminopyridine (**5**) was identified by comparing retention time with standard and MS spectres of the both compounds.



Scheme 1

Experimental

TLC was performed on Polygram Sil G/UV_{254} with UV light detection. Melting points were measured in the Kofler apparatus and are uncorrected. Gas chromatography (GC) and the mass spectra (MS) were measured on GCD plus – Hewlett Packard.

2-Hydrazino-6-chloropyridine (2)

The mixture of 2,6-dichloropyridine 10 g (67.6 mmol) and 80 % hydrazine hydrate (50 ml) was heated under the reflux for 45 minutes. Water (150 ml) was added and the reaction mixture was cooled at a laboratory temperature. The precipitated solid material was filtered off and dissolved again in the mixture of hydrochloric acid (10 ml) and water (40 ml). The solution was extracted with ethyl acetate (50 ml), charcoal (0.5 g) was added and the mixture was filtered. The solid compound **2** was precipitated by addition of sodium hydroxide. The final pH of the solution was 12. The solid material was filtered off, washed with water, and after drying it was recrystallized from toluene. The yield 8.2 g (84.6 %) of the product **2**, mp 118–119 °C, (lit.[12] mp 119 °C). GC assay 100%.

2-Amino-6-chloropyridine (4)

Method A

Hydrazino derivative **2** 10 g (69.7 mmol) was dissolved in the mixture of hydrochloric acid (10 ml) and water (40 ml). Diethyl ether (25 ml) was added and the

reaction mixture was cooled at 0 °C. Then the solution of sodium nitrite 8 g (116 mmol) in water (10 ml) was slowly added and temperature was kept at 0 to 5 °C. After the addition the reaction mixture was stirred for 30 minutes. Then the organic layer was separated and the water part extracted six times with diethyl ether (25 ml). The ether solution of azide **3** was slowly dropped into the solution of sodium borohydride 5 g (132 mmol) in ethanol (30 ml). Then the mixture was heated under the reflux for 4 hours. Then the reaction mixture was evaporated in vacuo to dryness. The rest was dissolved in water (50 ml) and extracted three times with ethyl acetate (50 ml). The organic layer was dried by sodium sulphate and after the filtration the solution was evaporated to dryness again. The solid part was recrystallized from toluene. The yield 5.8 g (65 %) of compound **4**, mp 70–72 °C (lit.[2,3] 70–72 °C). GC assay 100%.

Method B

Hydrazino derivative **2** 3.75 g (26.1 mmol) was dissolved in ethanol (150 ml), Ranney nickel (1 g) was added and the suspension was heated at 70 °C and stirred under the pressure (0.09 MPa) of hydrogen in an autoclave. The reaction was finished after 1 hour when hydrogen (26 mmol) was used for the reaction. The catalyst was filtered off and the solution was evaporated to dryness. The isolated evaporation residue 3.1 g was analyzed by GC and contained 85 % of the compound **4** and 15 % of the compound **5**. As this crude product contained a lot of the by-product **5,** the remainder was not utilized.

Method C

Hydrazino derivative **2** 3 g (21 mmol) was dissolved in butanol (25 ml) and Ranney nickel (0.5 g) was added. The reaction mixture was heated at 90 °C. Hydrazine hydrate 100% 2,5 ml (51.5 mmol) was slowly dropped into the reaction mixture at this temperature during 20 minutes. The catalyst was filtered off and the solution was evaporated to dryness. After the crystallization from toluene 2.1 g (81 %) of the compound **4** was received, purity 99.8 % (GC), mp 70 to 71 °C.

References

1. Hradil P.: Thesis, VÚFB Praha, 1991.
2. Kazuyuki W., Atsuke T.: Chem. Pharm. Bull. 28, 465 (1980).
3. Wibaut J. P., Nicolai J. R.: Rec. Trav. Chim. 58, 709 (1939).
4. Enomoto S.: (Sunimoto Chem. Co., Ltd.) JP 78 53662; Chem. Abstr. 89, P 197 341.
5. Skita A.: Ber. 45, 3312 (1912).
6. Fischer E., Groh R.: Ann. 383, 363 (1911).
7. Grandmougin E., Michel O.: Ber. 25, 981 (1892).
8. Lyons R. E., Smith L. T.: Ber. 60, 173 (1927).
9. Holland D. G., Moore G. J., Tamborski Ch.: J. Org. Chem. 29, 1562 (1964).
10. Campbell J. B. Greene J. H., Lavagnino E. R., Gardner D. N., Pike A. J.: J. Heterocycl. Chem. 23, 669 (1986).
11. Wermuth C. G., Bourguignon J. J., Schlewer G., Gils J. P., Schoenfelder A., Milikian A., Bouchet M. J., Chantreux D., Molimard J. C., Heaulme M., Chambon J. P., Biziere K.: J. Med. Chem. 30, 239 (1987).
12. Dusza J. P., Nannet N. Y.: (Am. Cyanamid Co.) US 4 260 767; Chem. Abstr. 95, 132 677.