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GABRIEL REACTION IN THE SYNTHESIS OF 2,6-DIFLUOROBENZYL AMINE.

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Abstract: 2,6-Difluorobenzyl amine was obtained by Gabriel reaction with a good yield. Intermediate N-(2,6-difluorobenzyl) phthalimide was obtained in the presence of phase transfer catalysts.

2,6-Difluorobenzyl amine (2,6-DFBA) is used as a reagent in the synthesis of various medicines¹⁻⁴. There are little literature data concerning this material and methods of its synthesis^{1-3,6}. Previously, 2,6-DFBA was obtained by formylating 2,6-difluorophenyl lithium followed by oxymation and oxime reduction to amine.¹ In other cases, it was obtained via reduction of 2,6-difluorobenzonitrile either by hydrogen on Pd/C catalyst² or by diborane³ or by sodium borhydride⁶. In one cases the amine was isolated as a chlorohydrate with unmentioned yield,¹⁻³ in others it was obtained with a yield of 86%, but its basic constants were not mentioned.⁶

In the present paper a method of synthesis of 2,6-DFBA from 2,6-difluorobenzyl chloride (2,6-DFBC) by Gabriel reaction is suggested:

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The use of phase-transfer catalyst⁶ allowed to obtain N-(2,6-difluorobenzyl) phthalimide not described before with a yield of 95%. The latter was hydrolyzed by boiling it with 30% KOH solution for 7-8 hours with simultaneous distillation of an azeotropic mixture of water and 2,6-difluorobenzyl amine into a Din-Stark attachment where a heavy organic layer containing 70-80% of 2,6-DFBA and 20-30% of water is separated. The amine was then dried with solid potassium hydroxide. This method of isolating 2,6-DFBA makes possible the exclusion of exhausting repeated extraction of the amine with ether and subsequent rectification of the mixture to remove the latter. The yield of 2,6-DFBA in the suggested method was 80% as calculated from N-(2,6-difluorobenzyl) phthalimide.

EXPERIMENTAL

IR-spectra were recorded on a Specord IR 75. ¹H and ¹⁹F NMR spectra were recorded on a Bruker WP SY spectrophotometer at 200 MHz (¹H) and 188.3 MHz (¹⁹F). CDCl₃ was used as a solvent. TMS and C_6F_6 were used as external

standards. 2,6-DFBC and ammonium trialkylmethyl methyl sulphate used in this work were of 96.6% and 66.8% purity, respectively.

N-(2,6-difluorobenzyl) phthalimide.

A mixture of 176.4 g (1.2 mol) of phthalimide, 165.6 g (1.2 mol) of potassium carbonate, 48.0 g (0.067 mol) of trialkylmethylammonium methyl sulphate⁸ and 1 liter of toluene was boiled with a Din-Stark attachment until water stops separating. Then 164.7 g (0.979 mol) of 2,6-DFBC were added and the mixture was boiled for 3 hours keeping separation of water. Then 800 ml of water were added to the reaction mixture, which was then stirred for 30 min at room temperature. The precipitated N-(2,6-difluorobenzyl) phthalimide was filtered off, washed with water and with toluene and then it was air-dried to yield 235.5 g of N-(2,6-difluorobenzyl) phthalimide.

Then 80-85% of the solvent were distilled off the filtrate to obtain additionally 35.0 g of N-(2,6-difluorobenzyl)phthalimide. The overall yield was 270.5 g. The product contained 1.2% of ash. According to GLC data the mass content of the main substance in the product's organic part was 95%. The yield was 94.9%.

Mp 155-157 °C (toluene). IR (KBr, cm $^{-1}$): 1715, 1780 (C=O). ¹H NMR, δ : 4.93 (s, 2H, CH₂-N), 6.85 (m, 2H, C-3), 7.21 (m, 1H, C-4), 7.70 (m, 2H, C-3'), 7.79 (m, 2H, C-4'). ¹⁹F NMR, δ : 47,86 (s). Anal. Calc. for C₁₅H₉F₂NO₂: C 65.94; H 3.32; N 5.12. Found: C 65.99; H 3.38; N 5.13.

2,6-difluorobenzyl amine.

A mixture of 340.0 g (1.168 mol) of N-(2,6-difluorobenzyl)phthalimide, 267.0 g (6.847 mol) of potassium carbonate, and 850 ml of water were boiled with a Din-Stark attachment until organic layer separation finished (normally for 8 hours). This resulted in 197.0 g of the product containing 70-80% of 2,6-DFBA and 20-30 % of water. Then 90.0 g of potassium hydroxide were added to the mixture and the it was held for 2-3 days. This resulted in separation of aqua- and organic layers. The former was then used in the subsequent experiments as hydrolyzing agent. The organic layer (149.0 g) was strewn again with 10.0 g of alkali, held for 1-2 days, resulting in separation of two layers. The organic one (142.0 g) was decanted and distilled with a dephlegmator (L = 5 cm). Two fractions were collected. The first one, containing 2,6-difluorobenzyl amine and water, was boiled over up to 175 °C. It was used when dehydrating amine with alkali in the subsequent experiment. The second (basic) fraction was boiled over at 175-177 °C yielding 138.0 g of 2,6-difluorobenzyl amine of 99.6% purity (according to GLC data). The yield was 60%.

An aqua-layer from the Din-Stark attachment and the residues from both distillations were joint and steam distilled. The distillate (300-400 ml) and concentrated alkali solutions after amine drying were reused for hydrolysis in subsequent experiments. This resulted in higher yields of 2,6-DFBA in subsequent experiments: up to 80% as calculated from N-(2,6-difluorobenzyl) phthalimide.

Bp 174-177 °C. IR (thin layer, cm ⁻¹): 3300, 3400 (NH₂). ¹H NMR, δ : 3.48 (s, 2H, CH₂-N), 5.77 (s, 2H, NH₂), 8.75 (m, 2H, C-H_{arom}). ¹⁹F NMR, δ : 14.9 (m).

Anal. Calc. for C₇H₇F₂: C 58.74; H 4.93; N 9.79; F 26.55. Found: C 58.40; H 4.84; N 9.44; F 26.58.

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