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SHORT COMMUNICATIONS

New Method for Preparation of (2-Aminopyridin-4-yl)methanol

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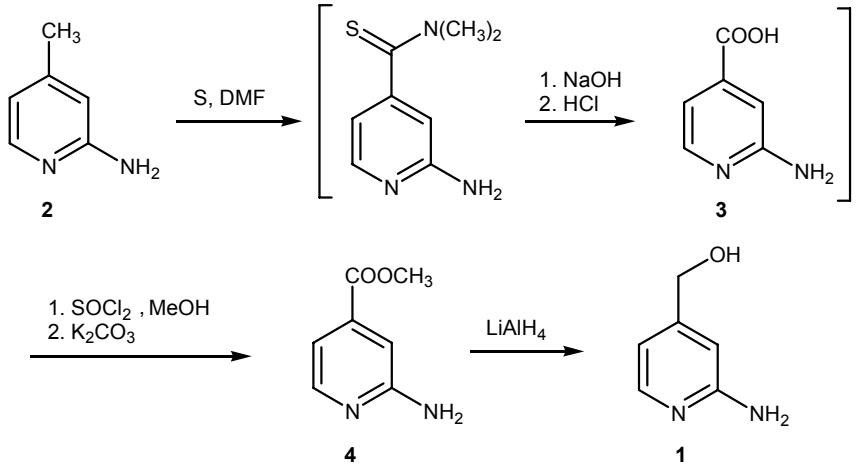
Imidazo[1,2-*a*]pyridine is one of the widely used pharmacophores. Published data contain numerous compounds with imidazo[1,2-*a*]pyridine fragment possessing different types of bioactivity [1]. The basic and the most investigated method of constructing the bicyclic imidazo[1,2-*a*]pyridine structure consists in the application of substituted 2-aminopyridines. Various methods of production of one of popular 2-aminopyridines, (2-aminopyridin-4-yl)methanol **1**, are described in [2–5]. However the basic drawback of the known methods is their multistage character and low efficiency. Unlike the methods applied previously, implying the preliminary acylation of 2-amino-4-methylpyridine **2**, we developed a method of direct oxidizing the methyl group in compound **1** without preliminary protection of amino group obtaining in one stage 2-aminoisonicotine acid **3**, the precursor of alcohol **1**. The use of elemental sulfur as an oxidizer [6] made it possible to realize a *one-pot* synthesis of the methyl ester of 2-aminoisonicotine acid **4**, suitable for reduction into the target compound **1** with lithium aluminum hydride (Scheme 1).

Overall yield of two stages is more than 49% that more than twice exceeds the yield of the best of described methods [2].

Methyl 2-aminoisonicotinate (4). A mixture of 108 g of 2-amino-4-methylpyridine, 110 g of sulfur, and 300 g of DMF was heated at 140–160°C during 20 h, then kept at 10 mmHg. To the residue 250 mL of 30% NaOH was added and the mixture was boiled while stirring for 50 h. The solution was filtered while hot and after cooling 20% HCl was added to pH 6. The precipitate was filtered off and dried at 120°C. To the obtained 2-aminoisonicotine acid was added while stirring 1 L of methanol, then at cooling 119 g of

Scheme 1.



$SOCl_2$. The reaction mixture was boiled for 10 h, methanol was distilled off in a vacuum, and 300 mL of 40% K_2CO_3 was added to the residue. The separated precipitate of methyl 2-aminoisonicotinate was crystallized from the mixture THF–methyl *tert*-butyl ether. Yield 103 g (68%), mp 146.5–147.5°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.90 s (3H), 4.65 s (2H), 7.06 s (1H), 7.06 s (1H), 7.15 d (1H), 8.17 d (1H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 52.4, 108.3, 112.8, 139.0, 148.9, 159.0, 165.9. Found, %: C 54.78; H 4.84; N 18.27. $C_7H_8N_2O_2$. Calculated, %: C 55.25; H 5.30; N 18.41.

(2-Aminopyridin-4-yl)methanol (1). 26 g of lithium aluminum hydride was dissolved in 800 mL of anhydrous THF. A solution of 103 g of methyl ether of 2-aminoisonicotinate in 600 mL of anhydrous THF was added at stirring and the formed slurry was boiled for 3 h. After cooling water was carefully added, the precipitate was filtered off and washed with 300 mL of THF. The combined filtrates were evaporated, the residue was crystallized from benzene. Yield 61 g (73%), mp 80–81.5°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.36 s (2H), 5.19 s (1H), 5.78 s (2H), 6.40 d (1H), 6.46 s (1H), 7.81 d (1H). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 62.3, 105.2, 110.3, 147.7, 152.7, 160.3. Found, %: C 57.63; H 6.32; N 22.68. $C_6H_8N_2O$. Calculated, %: C 58.05; H 6.4; N 22.56.

^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker AV-400 (400.13 and 100.61 MHz respectively).

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