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SHORT COMMUNICATIONS

Amination of Functionally Substituted Benzaldehydes in the Presence of Sodium Tetrahydroborate: New Preparation Method for Benzylamines

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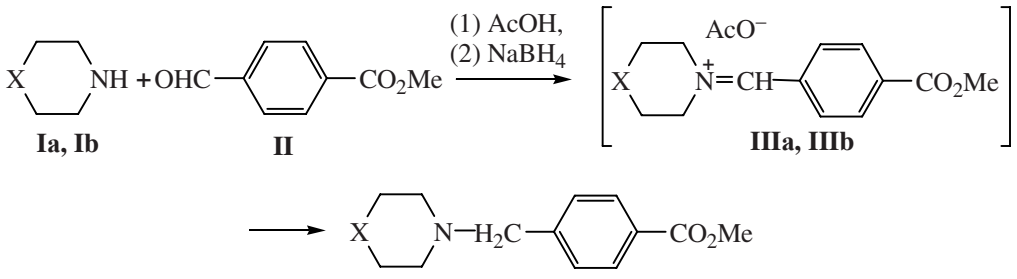
Reductive amination of benzaldehydes derivatives with heterocyclic amines results commonly in a low yield of tertiary amines save the methods using catalytic hydrogenation under pressure [1]. We found that in reaction of *N*-methylpiperazine (**Ia**) or morpholine (**Ib**) with 4-methoxycarbonylbenzaldehyde (**II**) in the presence of sodium tetrahydroborate and acetic acid benzylamines **IV** and **V** formed in up to 90% yield (see Scheme).

Iminium salt **III** formed in reaction of amine and aldehyde in the presence of acetic acid is reduced with sodium tetrahydroborate into the corresponding tertiary benzylamine **IV** and **V**. Therewith we did not detect any probable side reduction of initial methyl-4-formylbenzoate or of aromatic part of the benzylamine. Benzylamines thus obtained are separated from the reaction mixture by extraction and do not require additional purification.

The presence of a functional substituent in the aryl fragment of the benzylamine ensures access by known methods to a wide range of derivatives of heterocyclic amines endowed with versatile biological activity and also are precursors of many drugs [2, 3].

Reaction of secondary amines with 4-methoxycarbonylbenzaldehyde. To a solution of 1.6 g (0.01 mol) of 4-methoxycarbonylbenzaldehyde in 10 ml of methanol cooled to 0 ÷ –5°C was added at stirring 1 ml (0.01 mol) of amine **I**, after 40 min 0.6 ml (0.02 mol) of acetic acid was added, the mixture was thus maintained for 1 h, then it was heated at 60°C for 2 h. Then at cooling was added by portions 2.96 g (0.08 mol) of $NaBH_4$. The reaction mixture was stirred at 60–70°C for 10–12 h, evaporated in a vacuum, water was added, and the reaction mixture was acidified with diluted hydrochloric acid to pH 1, and the solution was extracted with ethyl acetate (3 × 50 ml). The extract was rejected, the water solution was alkalinized with 30% water solution of NaOH till pH 7–8, and the reaction product was extracted into ethyl acetate (3×50 ml), the extract was dried with Na_2SO_4, and on evaporating the solvent we obtained practically pure (by TLC data) product.

Scheme.



Ia, Ib **II** **IIIa, IIIb**

IV, V

X = NMe (**Ia, IIIa, IV**), O (**Ib, IIIb, V**).

1-Methyl-4-(4-methoxycarbonylbenzyl)piperazine (IV). Yield 90%, oily light-yellow fluid. IR spectrum (film) ν, cm^{-1}: 620, 765, 1275, 1725. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.30 s (3H, CH_3–N), 2.48 s (8H, CH_2 of piperazine), 3.57 s (2H, CH_2 Ar), 3.92 s (3H, OMe), 7.43 d and 7.99 d (4H_{arom}, *J* 8.0 Hz). Mass spectrum, *m/z* (I_{rel}, %): 248$[M]^+$ (90), 177 (60), 149 $[M - NC_4H_8NCH_3]^+$ (100), 99 $[NC_4H_8NCH_3]^+$ (80). Found, %: C 67.54; H 7.98; N 11.59. $C_{14}H_{20}N_2O_2$. Calculated, %: C 67.74; H 8.06; N 11.29.

1-(4-Methoxycarbonylbenzyl)morpholine (V). Yield 80%, colorless oily fluid. IR spectrum (thin film), ν, cm^{-1}: 1740. ^{1}H NMR spectrum, δ, ppm: 2.49 m and 3.77 m (8H, NC_4H_8O), 3.49 s (2H, CH_2 Ar), 3.95 s (3H, OMe), 7.42 d and 8.0 d (8H_{arom}, *J* 6.0 Hz). Mass spectrum, *m/z* (I_{rel}, %): 235 $[M]^+$ (55), 204 $[M - OCH_3]^+$ (45), 149 $[M - OC_4H_8NCH_2]^+$ (100), 121 $[C_6H_4COOH]^+$ (25), 86 $[OC_4H_8N]^+$ (35).

IR spectra were recorded on a Fourier spectrophotometer Nicolet Protégé-460. ^{1}H NMR spectra were registered on a spectrometer Bruker AC-500 (500 MHz) in $CDCl_3$, internal reference TMS. Mass spectra were measured on a GC-MS instrument Agilent Technologies 6850/5973 in an electon impact ionization mode, ionizing electrons energy 70 eV. TLC was performed on Kieselgel 60F_{254} plates (Merck) in a system chloroform–methanol, 85:15, development in iodine vapor or under UV irradiation.

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REFERENCES

1. Regnier, G.L., Cavenary, R.J., Laubie, M.J., and LeDouary, J.C. , *J. Med. Chem.,* 1968, vol. 11, p. 1151.
2. Horton, D.A., Bourne, G.T., and Smythe, M.L., *Chem. Rev*., 2003, vol. 103, p. 901.
3. Leopoldo, M., de, Giorgio, P., Berardi, F., Lacivita, E., Colabuto, N.A., Perrone, R., and Tortorella, V., *J. Med. Chem.,* 2002, vol. 45, p. 5727.