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INTERACTION OF SECONDARY AMINES WITH AROMATIC ALDEHYDES – EFFICIENT METHOD FOR SYNTHESIS OF THE FUNCTIONALIZED HETEROCYCLIC AMINES

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A method is proposed for the benzylation of secondary heterocyclic amines with functionalized derivatives of benzaldehyde in the presence of formic acid under conditions close to amination according to the Leuckart–Wallach reaction.

Keywords: N-methylpiperazine, benzaldehyde derivatives, formic acid, pyrrolidine, reductive amination.

The piperazine ring is a key structural fragment of a large group of compounds, the broad spectrum of activity of which explains the interest in the development of rational methods of obtaining them [1-3]. One of the variants of constructing compounds from piperazine is the synthesis of functionalized benzyl derivatives. Such derivatives may be obtained by the direct alkylation of an amine with benzyl halides or by the reductive amination of benzoic acid derivatives [4, 5]. We investigated the reaction of N-methylpiperazine, pyrrolidine, and morpholine with *p*-substituted benzaldehydes in the presence of formic acid. The reaction represents in essence the combination in one process of the preparation of a carbonyl derivative of an amine and its subsequent reduction. However the problem in this case includes not only the selection of a reducing agent for the imine formed *in situ*, but also the sensitivity of the of the functional groups in the aromatic compound towards the reducing agent used. The Leuckart–Wallach reaction (the reducing agent is formic acid) is applied in a more restricted manner than catalytic reduction with hydrogen [4]. Nonetheless this method enables compounds containing functional substituents labile in catalytic reduction reactions to be used and provides a satisfactory yield of tertiary amines.

Benzylamines **8-13** were obtained in preparative yield from secondary heterocyclic amines **1-3** and functionalized benzaldehyde derivatives **4-7** using formic acid as reducing agent and conditions close to the conditions of the Leuckart–Wallach reaction.

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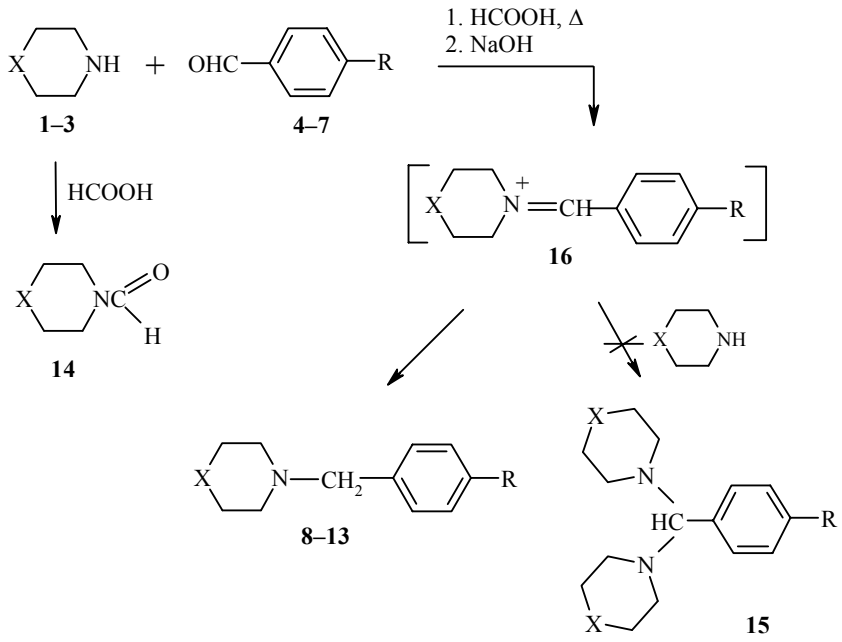

1–3, **8–11, 14** X = NMe; **4** R = COOH; **5** R = COOMe; **6** R = NO_2; **7** R = H; **8** R = COOH; **9** R = COOMe; **10** R = NO_2; **11** R = H; **12** R = COOMe, X = – ; **13** R = COOMe, X = O

The most important side process in the reaction being investigated was the formylation of the amine with the formation of formamide **14**, the yield of which reached 25% when using difficultly soluble benzaldehyde derivatives in the reaction. The product of the reduction of the aldehyde group of the initial benzaldehyde, the corresponding benzyl alcohol, was formed in less than 10% yield. The formation of aminals **15** by stabilization of the immonium ion **16**, possibly by addition of a second molecule of amine, and noticed previously in reactions for making amines according to Leuckart–Wallach, was not observed.

The presence of functional substituents in the aryl fragment of the benzylamine guarantees the conversion by known and available methods to a wide range of derivatives of heterocyclic amines, which are precursors of a large number of medicinal preparations, and also display high and varied biological activity [5-7].

EXPERIMENTAL

The IR spectra were taken on a Nicolet Protege 460 Fourier spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-500 (500 and 100 MHz respectively) and a Tesla BS-567 (100 MHz) spectrometer in $CDCl_3$ and D_2O, internal standards were TMS and 2,2-dimethyl-2-silapentane-5-sulfonate. The mass spectra were obtained on an Agilent Technologis 6850/5973 chromato-mass spectrometer in EI ionization mode at an energy of 70 eV. Column chromatography was carried out on silica gel 40/100 μ (Czech Republic), TLC on Kieselgel $60F_{254}$ plates (Merck) in the system chloroform–methanol, 85:15, visualization with iodine and UV.

Interaction of Secondary Amines with Benzaldehyde Derivatives. Amine (0.1 mol) was mixed with formic acid (0.5 mol) under ice cooling and the mixture left for 10-15 min to form the salt. The cooling was removed, aldehyde (0.12 mol) was added in one batch, and the reaction mixture was heated under reflux with stirring at 180-200°C for 6-8 h. At the end of the reaction, water (50 ml) was added to the reaction mixture,

which was acidified to pH 3 with 10% HCl, and then extracted with ether (3×100 ml). The extract, which contains mainly the formyl derivative of the amine and the initial aldehyde, was discarded. The aqueous remainder was treated with 20% NaOH to pH 9, the desired reaction product extracted with ether and chloroform, the combined extracts were dried over $MgSO_4$, and evaporated in vacuum. The solid products were recrystallized. To obtain analytically pure benzylamines **9-13** the solid reaction mixture after evaporation was chromatographed on a column of silica gel (chloroform–methanol, gradient elution).

4-(4-Carboxybenzyl)-1-methylpiperazine (8) was isolated in 40% yield by evaporating the neutral aqueous solution after exhaustive extraction of the reaction mixture with chloroform. Mp 228°C (dec.). IR spectrum (KBr), ν, cm^{-1}: 1296, 1350, 1461, 1643, 2820-3400. ^1H NMR spectrum (D_2O), δ, ppm (*J*, Hz): 2.81 (3H, s, CH_3N); 2.5-3.4 (8H, CH_2 piperazine); 3.72 (2H, s, CH_2Ar); 7.38 (2H, d, *J* = 8.0, arom.); 7.88 (2H, d, *J* = 8.0, arom.). ^{13}C NMR spectrum (D_2O), δ, ppm: 174.71 (COOH); 136.97; 135.80; 129.70; 128.79; 60.27 (CH_2Ar); 52.35; 48.98 (($CH_2)_4$); 42.50 (CH_3). Mass spectrum, *m/z* (I_{rel}), %: 234 $[M]^+$ (40), 190 $[M–COO]^+$ (30), 135 $[HO_2CC_6H_4CH_2]^+$ (100), 99 $[NC_4H_8NCH_3]^+$ (70), 44 $[CO_2]^+$ (90). Found, %: C 66.78; H 7.65; N 12.10. $C_{13}H_{18}N_2O_2$. Calculated, %: C 66.66; H 7.61; N 11.90.

4-(4-Methoxycarbonylbenzyl)-1-methylpiperazine (9). Yield 70%, oily liquid. IR spectrum (film), ν, cm^{-1}: 610, 755, 1280, 1735, 3200-3400. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.30 (3H, s, CH_3N); 2.48 (8H, m, CH_2 piperazine); 3.57 (2H, s, CH_2Ar); 3.92 (3H, s, OCH_3); 7.43 and 7.99 (4H, two d, *J* = 8.0, arom.). ^{13}C NMR spectrum (D_2O), δ, ppm: 45.99; 51.90; 53.06; 55.02; 62.52; 64.69; 128.81; 128.87; 129.46; 143.78; 167.05. 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-Methyl-4-(4-nitrobenzyl)piperazine (10). Yield 47%, oil. IR spectrum (film), ν, cm^{-1}: 1420, 1535, 1650. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.69 (3H, s, CH_3N); 2.67 (8H, m, CH_2 piperazine); 3.75 (2H, s, CH_2Ar); 7.89 and 7.99 (4H, two d, *J* = 8.0, arom.). Mass spectrum, *m/z* (I_{rel}, %): 235 $[M]^+$ (90), 136 $[M–N(CH_2)_4NMe]^+$ (100), 99 $[N(CH_2)_4NMe]^+$ (90). Found, %: C 61.39; H 7.23; N 18.07. $C_{12}H_{17}N_3O_2$. Calculated, %: C 61.29; H 7.19; N 17.87.

4-Benzyl-1-methylpiperazine (11) was isolated as an oily liquid, R_f 0.6 (chloroform–methanol, 9:1). Yield 77%. IR spectrum (thin layer), ν, cm^{-1}: 980, 1060, 1100, 1440. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.26 (3H, s, CH_3N); 2.44 (8H, m, CH_2 piperazine); 3.49 (2H, s, CH_2Ar); 7.27 (5H, m, arom.). Mass spectrum, *m/z* (I_{rel}, %): 190 $[M]^+$ (70), 146 (20), 119 (45), 99 $[NC_4H_8NCH_3]^+$ (40), 91 $[H_2CC_6H_5]^+$ (100). Found, %: C 76.04; H 9.49; N 15.03. $C_{13}H_{18}N_2$. Calculated, %: C 75.80; H 9.42; N 14.83. (Synthesized for the first time and characterized as the hydrochloride in [8].)

1-(4-Methoxycarbonylbenzyl)pyrrolidine (12). Oil, R_f 0.54 (chloroform–methanol, 9:1). Yield 50%. IR spectrum (thin layer), ν, cm^{-1}: 1730. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.97, m and 2.97, m (8H, CH_2 pyrrolidine); 3.87 (3H, s, OCH_3); 4.11 (2H, s, CH_2Ar); 7.41 and 7.95 (4H, two d, *J* = 8.0, arom.). Mass spectrum, *m/z* (I_{rel}, %): 219 $[M]^+$ (100), 149 $[M–C_4H_8N]^+$ (70), 121 $[C_6H_4COOH]^+$ (45), 135 $[M–C_4H_8NCH_2]^+$ (90). Found, %: C 71.48; H 7.70; N 6.51. $C_{13}H_{17}NO_2$. Calculated, %: C 71.23; H 7.76; N 6.39.

1-(4-Methoxycarbonylbenzyl)morpholine (13) was isolated as an oil, R_f 0.55. Yield 50%. IR spectrum (thin layer), ν, cm^{-1}: 1740. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.2, m and 3.48, m (8H, NC_4H_8O); 3.63 (2H, s, CH_2Ar); 3.81 (3H, s, OCH_3); 7.32 and 7.80 (8H, two d, *J* = 8.5, arom.). Mass spectrum, *m/z* (I_{rel}, %): 235 $[M]^+$ (80), 149 $[M\text{-}OC_4H_8N]^+$ (100), 121 $[C_6H_4COOH]^+$ (45), 86 $[OC_4H_8N]^+$ (65). Found, C 66.66; H 7.12; N 6.0. $C_{13}H_{17}NO_3$. Calculated, %: C 66.42; H 7.22; N 5.9.

4-Formyl-1-methylpiperazine (14) was isolated as an oily liquid, R_f 0.4 (chloroform–methanol, 9 : 1). IR spectrum (film), ν, cm^{-1}: 1040, 1460, 1690. ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.28 (3H, s, CH_3N); 2.34 and 2.39 (4H, two t, *J* = 5.1, $(CH_2)_2NCH_3$); 3.36 and 3.53 (4H, two t, *J* = 5.0, $(CH_2)_2NC(O)H$); 7.99 (1H, s, HC=O). Mass spectrum, *m/z* (I_{rel}, %): 128 $[M]^+$ (100), 99 [M–C(O) (80) H]$^+$, 70 (80), 56 (75), 42 (75). Found, %: C 56.60; H 9.22; N 21.50. $C_6H_{12}N_2O$. Calculated, %: C 56.25; H 9.37; N 21.88. (According to [9, 10]: bp 94-95°C (3 mm Hg). IR spectrum, ν, cm^{-1}: 1660 (C=O); mass spectrum, *m/z* (I_{rel}, %): 128 $[M]^+$)

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