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Polyfunctional Imidazoles: IV.* Synthesis of 2-Aryl-4-chloro-1-methyl(aryl)-1*H*-imidazole-5-carbaldehydes

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Abstract—2-Aroyl-2-[methyl(aryl)amino]acetamides reacted with the Vilsmeier–Haak reagent to give 2-aryl-4-chloro-1-methyl(aryl)-1*H*-imidazole-5-carbaldehydes.

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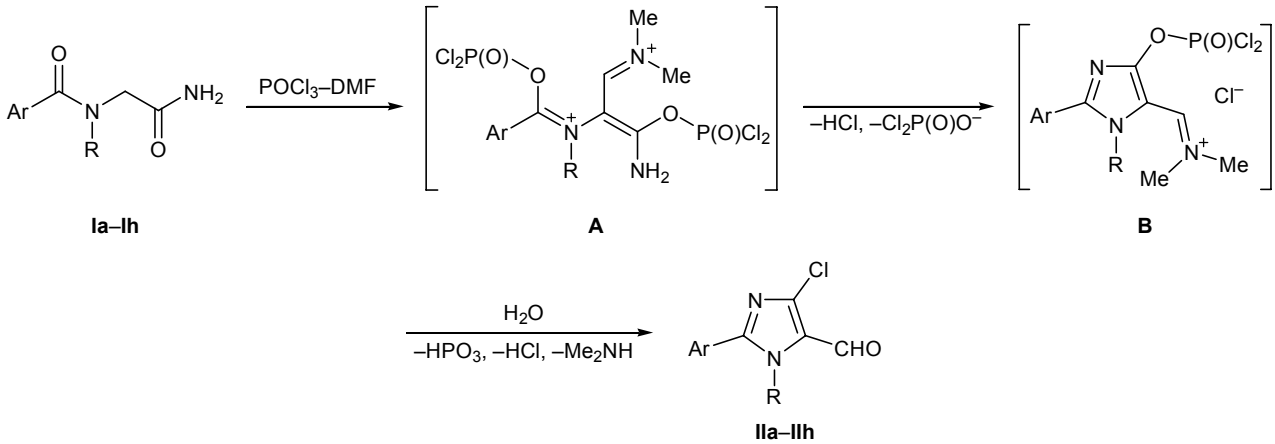
Functional derivatives of 1-alkyl-2-arylimidazole can be used as synthons in the design of new biologically active compounds [2–5]. Among these, of particular interest are 2-aryl-1-benzyl-4-chloro-1*H*-imidazole-5-carbaldehydes as base compounds for the preparation of AVE0991 [nonpeptide angiotensine-(1–7) receptor agonist] and its analogs [6–9]. The key step in their synthesis is benzylation [8–10] of fairly accessible 2-aryl-4-chloro-1*H*-imidazole-5-carbaldehydes having no substituent on N^1 [11]. However, this procedure has not been used so far for direct arylation of such imidazole derivatives at position *1*, which considerably restricts the series of compounds available for further study.

We propose a different approach to 2-aryl-4-chloro-1-methyl(aryl)-1*H*-imidazole-5-carbaldehydes, which implies direct formation of 1-methyl(aryl)-2-aryl-substituted imidazole ring functionalized with additional chlorine atom and aldehyde group. It is based on the Vilsmeier–Haak reaction of *N*-aroyl-*N*-methyl(aryl)-glycinamides. Analogous procedure was successfully used previously [12] to obtain 1-alkyl(aryl)-4-chloro-1*H*-imidazole-5-carbaldehydes from N-substituted glycinamides.

Scheme 1.



Ia–Ih **A** **B** **IIa–IIh**

R = Me, Ar = 3-$O_2NC_6H_4$ (**a**), 4-IC_6H_4 (**b**); R = Ph, Ar = Ph (**c**), 2-ClC_6H_4 (**d**), 4-$O_2NC_6H_4$ (**e**); R = 4-MeC_6H_4, Ar = Ph (**f**); R = 4-$MeOC_6H_4$, Ar = 3-BrC_6H_4 (**g**); R = 2,5-$Me_2C_6H_3$, Ar = 4-FC_6H_4 (**h**).

* For communication III, see [1].

Initial glycinamides **Ia**–**Ih** were prepared by acylation of the corresponding *N*-methyl(aryl) glycinamides with substituted benzoyl chlorides. Treatment of compounds **Ia**–**Ih** with 3 equiv of dimethylformamide and 6 equiv of phosphoryl chloride, followed by heating of the reaction mixture for 6 h under reflux, led to the formation of 2-aryl-4-chloro-1-methyl(aryl)-1*H*-imidazole-5-carbaldehydes **IIa**–**IIh** in 32–44% yield (Scheme 1). Taking into account the data reported in [12, 13], the most probable reaction scheme involves initial formation of acyclic intermediate **A** which undergoes cyclization to intermediate **B** at elevated temperature; the subsequent hydrolysis yields final products **II**.

The structure of compounds **Ia**–**Ih** and **IIa**–**IIh** was confirmed by elemental analysis and IR and NMR spectroscopy. The ^{1}H NMR spectra of glycinamides contained a singlet at δ 3.81–3.91 (**Ia**, **Ib**) or 4.31–4.44 ppm (**Ic**–**Ig**) due to methylene protons. The corresponding protons in the spectrum of **Ih** gave rise to two doublets at δ 3.82 and 4.64 ppm (*AB* system); nonequivalence of the methylene protons in **Ih** was attributed to steric effect of the 2,5-dimethylphenyl substituent on the nitrogen atom.

The aldehyde group in imidazoles **IIa**–**IIh** was characterized by an IR absorption band in the region 1685–1695 cm^{-1} and by a singlet at δ 9.57–9.84 ppm in the ^{1}H NMR spectra; the aldehyde carbonyl carbon atom resonated in the ^{13}C NMR spectra at δ_C 177–178 ppm. Carbon atoms in the imidazole ring appeared in the ^{13}C NMR spectra at δ_C 138–140 (C^2), 147–150 (C^4), and 121–126 ppm (C^5).

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from thin films (compounds **Ib** and **Ig**) or KBr pellets (all other compounds). The ^{1}H and ^{13}C NMR spectra were measured from solutions in DMSO-d_6 on a Bruker Avance DRX-500 spectrometer at 500.13 and 125.75 MHz, respectively, using tetramethylsilane as internal reference. The mass spectra were obtained on an Agilent 1100\DAD\HSD\VLG 119562 instrument.

***N*-Aroyl-*N*-methyl(aryl) glycinamides Ia–Ih (*general procedure*).** Triethylamine, 1.11 g (0.011 mol), was added to a solution of 0.01 mol of the corresponding *N*-aryl(methyl)-substituted glycinamide in 20 ml of anhydrous acetonitrile, the mixture was cooled with ice water, and 0.01 mol of substituted benzoyl chloride in 10 ml of acetonitrile was added under stirring. The mixture was heated for 2 h under reflux and poured into 200 ml of water. Solid compounds **Ia**, **Ic**–**If**, and **Ih** were filtered off, washed with water, and recrystallized from ethanol. Oily products **Ib** and **Ig** were extracted into methylene chloride, and the extract was washed with a 5% solution of sodium carbonate and a 1% solution of hydrochloric acid, dried over sodium sulfate, and evaporated.

***N*-(2-Amino-2-oxoethyl)-*N*-methyl-3-nitrobenzamide (Ia).** Yield 80%, mp 148–150°C. IR spectrum, ν, cm^{-1}: 3310, 3200 (NH_2); 1710, 1640 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.93 s (3H, CH_3), 3.81 s (2H, CH_2), 7.46–7.92 m (6H, H_{arom}, NH_2). Found, %: C 50.58; H 4.60; N 17.78. $C_{10}H_{11}N_3O_4$. Calculated, %: C 50.63; H 4.67; N 17.71.

***N*-(2-Amino-2-oxoethyl)-4-iodo-*N*-methylbenzamide (Ib).** Yield 84%, viscous oily substance. IR spectrum, ν, cm^{-1}: 3330, 3240 (NH_2); 1700, 1655 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.01 s (3H, CH_3), 3.91 s (2H, CH_2), 7.46 d (2H, H_{arom}, J = 7.5 Hz), 7.64 br.s (2H, NH_2), 7.93 d (2H, H_{arom}, J = 7.5 Hz). Found, %: C 37.42; H 3.65; N 8.45. $C_{10}H_{11}IN_2O_2$. Calculated, %: C 37.76; H 3.49; N 8.81.

***N*-(2-Amino-2-oxoethyl)-*N*-phenylbenzamide (Ic).** Yield 87%, mp 172–173°C; published data [14]: mp 175°C. IR spectrum, ν, cm^{-1}: 3320, 3205 (NH_2); 1715, 1645 (C=O). ^{1}H NMR spectrum, δ, ppm: 4.31 s (2H, CH_2), 7.24–7.70 m (12H, H_{arom}, NH_2).

***N*-(2-Amino-2-oxoethyl)-2-chloro-*N*-phenylbenzamide (Id).** Yield 81%, mp 119–120°C. IR spectrum, ν, cm^{-1}: 3315, 3220 (NH_2); 1710, 1650 (C=O). ^{1}H NMR spectrum, δ, ppm: 4.39 s (2H, CH_2), 7.08–7.48 m (9H, H_{arom}), 7.72 br.s (2H, NH_2). Found, %: C 62.14; H 4.69; N 9.55. $C_{15}H_{13}ClN_2O_2$. Calculated, %: C 62.40; H 4.54; N 9.70.

***N*-(2-Amino-2-oxoethyl)-*N*-phenyl-4-nitrobenzamide (Ie).** Yield 76%, mp 165–167°C. IR spectrum, ν, cm^{-1}: 3310, 3200 (NH_2); 1720, 1645 (C=O). ^{1}H NMR spectrum, δ, ppm: 4.43 s (2H, CH_2), 7.19–7.64 m (9H, H_{arom}, NH_2), 8.09 d (2H, H_{arom}, J = 8.6 Hz). Found, %: C 60.28; H 4.30; N 14.12. $C_{15}H_{13}N_3O_4$. Calculated, %: C 60.20; H 4.38; N 14.04.

***N*-(2-Amino-2-oxoethyl)-*N*-(4-methylphenyl)-benzamide (If).** Yield 84%, mp 108–110°C. IR spectrum, ν, cm^{-1}: 3320, 3205 (NH_2); 1715, 1645 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.39 s (3H, CH_3), 4.42 s (2H, CH_2), 7.17–7.52 m (9H, H_{arom}), 7.68 br.s (2H, NH_2). Found, %: C 71.68; H 6.05; N 10.40. $C_{16}H_{16}N_2O_2$. Calculated, %: C 71.62; H 6.01; N 10.44.

***N*-(2-Amino-2-oxoethyl)-3-bromo-*N*-(4-methoxyphenyl)benzamide (Ig).** Yield 78%, viscous oily substance. IR spectrum, ν cm^{-1}: 3315, 3210 (NH_2); 1710, 1650 (C=O). ^1H NMR spectrum, δ, ppm: 3.84 s (3H, CH_3O), 4.44 s (2H, CH_2), 6.99 d (2H, H_{arom}, J = 8.8 Hz), 7.49 d (2H, H_{arom}, J = 8.8 Hz), 7.83 br.s (2H, NH_2). Found, %: C 53.25; H 4.02; N 7.36. $C_{16}H_{15}BrN_2O_3$. Calculated, %: C 52.91; H 4.16; N 7.71.

***N*-(2-Amino-2-oxoethyl)-*N*-(2,5-dimethylphenyl)-4-fluorobenzamide (Ih).** Yield 83%, mp 162–164°C. IR spectrum, ν, cm^{-1}: 3320, 3225 (NH_2); 1715, 1650 (C=O). ^1H NMR spectrum, δ, ppm: 2.05 s (3H, CH_3), 2.23 s (3H, CH_3), 3.82 d and 4.64 d (1H each, CH_2, J = 16.0 Hz), 6.96–7.68 m (9H, H_{arom}, NH_2). Found, %: C 68.23; H 5.59; N 9.50. $C_{17}H_{17}FN_2O_2$. Calculated, %: C 67.99; H 5.71; N 9.33.

2-Aryl-4-chloro-1-methyl(aryl)-1*H*-imidazole-5-carbaldehydes IIa–IIh (*general procedure*). A mixture of 0.03 mol of amide **Ia–Ih** in 6.75 g (0.09 mol) of dimethylformamide was cooled to 0–5°C, 26.7 g (0.18 mol) of phosphoryl chloride was added under stirring, and the mixture was heated for 6 h under reflux. Excess phosphoryl chloride was removed under reduced pressure, the residue was treated with 50 ml of water, and crystalline sodium hydrogen carbonate was added until pH 8.0. The precipitate was filtered off, washed with water, dried, and purified by chromatography on silica gel using hexane–ethyl acetate (1:1) as eluent. The product was additionally recrystallized from 70% aqueous ethanol.

4-Chloro-1-methyl-2-(3-nitrophenyl)-1*H*-imidazole-5-carbaldehyde (IIa). Yield 44%, mp 129–130°C. IR spectrum: ν 1695 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 3.97 s (3H, CH_3), 7.84 t (1H, H_{arom}, J = 8.0 Hz), 8.20 d (1H, H_{arom}, J = 7.5 Hz), 8.41 d (1H, H_{arom}, J = 7.5 Hz), 8.53 s (1H, H_{arom}), 9.84 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 34.33 (CH_3); 123.99, 124.93, 129.11, 130.50, 135.43, 147.86 (C_{arom}); 128.85 (C^5), 140.32 (C^2), 148.63 (C^4), 178.73 (CHO). Found, %: C 49.50; H 3.08; N 15.97. *m*/*z* 266 $[M + 1]^+$. $C_{11}H_8ClN_3O_3$. Calculated, %: C 49.73; H 3.04; N 15.82. *M* 265.6.

4-Chloro-2-(4-iodophenyl)-1-methyl-1*H*-imidazole-5-carbaldehyde (IIb). Yield 32%, mp 157–159°C. IR spectrum: ν 1690 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 3.89 s (3H, CH_3), 7.50 d (2H, H_{arom}, J = 7.5 Hz), 7.91 d (2H, H_{arom}, J = 7.5 Hz), 9.78 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 34.32 (CH_3); 97.84, 126.97, 130.98, 137.56, 147.86 (C_{arom}); 125.59 (C^5), 140.54 (C^2), 150.05 (C^4), 178.35 (CHO). Found, %: C 38.36; H 2.22; N 8.22. *m*/*z* 347 $[M + 1]^+$. $C_{11}H_8ClIN_2O$. Calculated, %: C 38.12; H 2.33; N 8.08. *M* 346.6.

4-Chloro-1,2-diphenyl-1*H*-imidazole-5-carbaldehyde (IIc). Yield 38%, mp 111–112°C. IR spectrum: ν 1685 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 7.36–7.58 m (10H, H_{arom}), 9.60 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 126.54 (C^5); 127.71, 127.97, 128.34, 128.81, 129.39, 129.74, 130.04, 135.22 (C_{arom}); 139.46 (C^2), 149.31 (C^4), 178.22 (CHO). Found, %: C 67.73; H 3.96; N 9.70. *m*/*z* 283 $[M + 1]^+$. $C_{16}H_{11}ClN_2O$. Calculated, %: C 67.97; H 3.92; N 9.91. *M* 282.7

4-Chloro-2-(2-chlorophenyl)-1-phenyl-1*H*-imidazole-5-carbaldehyde (IId). Yield 39%, mp 131–132°C. IR spectrum: ν 1685 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 7.34–7.71 m (9H, H_{arom}), 9.71 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 125.83 (C^5); 126.84, 127.33, 127.58, 127.78, 129.22, 129.36, 132.01, 132.65, 132.99, 134.24 (C_{arom}); 138.90 (C^2), 147.88 (C^4), 177.41 (CHO). Found, %: C 60.86; H 3.02; N 8.61. *m*/*z* 318 $[M + 1]^+$. $C_{16}H_{10}Cl_2N_2O$. Calculated, %: C 60.59; H 3.18; N 8.83. *M* 317.2.

4-Chloro-2-(4-nitrophenyl)-1-phenyl-1*H*-imidazole-5-carbaldehyde (IIe). Yield 39%, mp 134–135°C. IR spectrum: ν 1690 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 7.50–7.62 m (7H, H_{arom}), 8.15 d (2H, H_{arom}, J = 8.6 Hz), 9.62 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 123.42 (C^5); 127.10, 127.89, 129.67, 130.09, 133.70, 134.70, 135.30, 147.03 (C_{arom}); 139.24 (C^2), 147.82 (C^4), 177.66 (CHO). Found, %: C 58.89; H 3.22; N 12.56. *m*/*z* 328 $[M + 1]^+$. $C_{16}H_{10}ClN_3O_3$. Calculated, %: C 58.64; H 3.08; N 12.82. *M* 327.7.

4-Chloro-1-(4-methylphenyl)-2-phenyl-1*H*-imidazole-5-carbaldehyde (IIf). Yield 35%, mp 111–112°C. IR spectrum: ν 1685 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 2.39 s (3H, CH_3), 7.32–7.44 m (9H, H_{arom}), 9.58 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 20.72 (CH_3), 126.57 (C^5); 127.67, 127.78, 128.34, 128.79, 129.88, 129.99, 132.61, 139.26 (C_{arom}); 139.37 (C^2), 149.27 (C^4), 177.22 (CHO). Found, %: C 69.04; H 4.36; N 9.20. *m*/*z* 297 $[M + 1]^+$. $C_{17}H_{13}ClN_2O$. Calculated, %: C 68.81; H 4.42; N 9.44. *M* 296.8.

2-(3-Bromophenyl)-4-chloro-1-(4-methoxyphenyl)-1*H*-imidazole-5-carbaldehyde (IIg). Yield 33%, mp 97–98°C. IR spectrum: ν 1685 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 3.81 s (3H, CH_3O), 7.04 d

(2H, H_{arom}, J = 9.0 Hz), 7.28–7.31 m (2H, H_{arom}), 7.42 d (2H, H_{arom}, J = 9.0 Hz), 7.52–7.60 m (2H, H_{arom}), 9.57 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 55.48 (CH_3O), 121.41 (C^5); 114.59, 126.91, 127.36, 127.57, 129.13, 129.96, 130.43, 131.38, 132.67, 159.96 (C_{arom}); 138.96 (C^2), 147.64 (C^4), 177.44 (CHO). Found, %: C 52.38; H 3.01; N 6.93. m/z 392 $[M + 1]^+$. $C_{17}H_{12}BrClN_2O_2$. Calculated, %: C 52.14; H 3.09; N 7.15. M 391.6.

4-Chloro-2-(4-fluorophenyl)-1-(2,5-dimethylphenyl)-1*H*-imidazole-5-carbaldehyde (IIh). Yield 30%, mp 104–105°C. IR spectrum: ν 1690 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 1.88 s (3H, CH_3), 2.26 s (3H, CH_3), 7.12–7.43 m (7H, H_{arom}), 9.57 s (1H, CHO). ^{13}C NMR spectrum, δ_C, ppm: 16.27 (CH_3), 20.21 (CH_3), 115.66 d ($^2J_{CF}$ = 27.5 Hz), 124.24 (C^5); 126.02, 128.30, 130.58, 130.65, 131.03, 131.74, 134.26, 136.88 (C_{arom}); 139.88 (C^2), 148.01 (C^4), 162.95 d ($^1J_{CF}$ = 251.4 Hz), 177.07 (CHO). Found, %: C 65.93; H 4.44; N 8.36. m/z 329 $[M + 1]^+$. $C_{18}H_{14}ClFN_2O$. Calculated, %: C 65.76; H 4.29; N 8.52. M 328.8.

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