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Polyfunctional Imidazoles: I. Synthesis of 1-Substituted 4-Chloro-1*H*-imidazole-5-carbaldehydes by Vilsmeier-Haack Reaction

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Abstract—2-[Alkyl(aryl)amino]acetamides in reaction with Vilsmeier–Haack reagent afforded 1-alkyl(aryl)-4-chloro-1*H*-imidazole-5-carbaldehydes.

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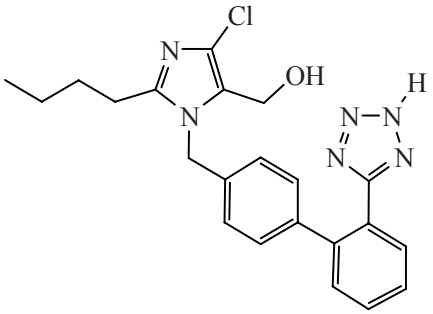
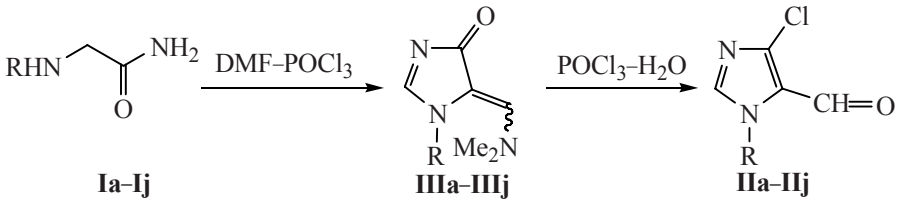
Functional imidazole derivatives possess a considerable biological potential. They inhibit the HIV-1 reverse transcriptase [1], cell fission [2], aldosterone biosynthesis [3]. Especially important is their ability to act as nonpeptide antagonists of the angiotensin **II** receptors II [4] that has been used in designing the drug losartan against the arterial hypertension [5, 6]. The key synthon in preparation of the latter was 2-butyl-4(5)-chloro-1*H*-imidazole-5(4)carbaldehyde. In the synthesis of losartan analogs [7–12] alongside this compounds also the other 2-alkyl(aryl)-4(5)-chloro-1*H*-imidazole-5(4)-carbaldehydes were employed.



To prepare 2-alkyl-4(5)-chloro-1*H*-imidazole-5(4)-carbaldehydes unsubstituted at the position *1* (*3*) several approaches were used, commonly multistage, requiring special conditions and providing side products. In particular, a synthesis was described of 2-butyl-5-chloro-3*H*-imidazole-4-carbaldehyde by oxidation with manganese(II) oxide of the corresponding 4-hydroxymethyl-5-chloro-3*H*-imidazole that in its turn was obtained by condensation of ethylpentane imidate hydrochloride with dihydroxyacetone and ammonia at elevated temperature and pressure followed by the chlorination into the position *4* of the imidazole ring with N-chlorosuccinimide [13]. The chloroformylation of 2-substituted imidazolin-5-ones [6] with a Vilsmeier–Haack reagent although was preparatively simple but required the application of difficultly available alkyl imidates for the preparation of the initial imidazolin-5-ones. One other procedure of the synthesis of the 2-butyl-5-chloro-3*H*-imidazole-4-carbaldehyde [14] involved the use of 2-butylimidazole that in five reaction stages was transformed into the target product in 24% yield.

The methods of N^1-alkylation were well developed by the example of 2-substituted 5-chloro-3*H*-imidazole-4-carbaldehydes [8–10]. At the same time the N^1-aryl-substituted 4-chloroimidazole-5-carbaldehydes with the free position *2* of the heterocycle remain unknown. However they also due to the polyfunctional character are important synthetic objects for a purposeful designing of potentially bioactive substances. Therefore the present report concerns the development of a synthetic procedure for new 1-substituted 4-chloro-1*H*-imidazole-5-carbaldehydes.

The Vilsmeier–Haack reaction was formerly successively applied to the synthesis of some α,β-chloroformyl-functionalized nitrogen heterocycles. It was established



Ia–Ij **IIIa–IIIj** **IIa–IIj**

R = Bu (**a**), $PhCH_2$ (**b**), Ph (**c**), 2-MeC_6H_4 (**d**), 4-ClC_6H_4 (**e**), 4-BrC_6H_4 (**f**), 4-MeC_6H_4 (**g**), 4-$MeOC_6H_4$ (**h**), 2,5-$Me_2C_6H_3$ (**i**), 1-naphthyl (**j**).

in particular that N-aryl-2-azidoacetamides in reaction with a system DMF–$POCl_3$ formed 1-aryl-2-(dimethylamino)-5-chloro-1*H*-imidazole-4-carbaldehydes[15], and N-acetylglycine gave 3,5-diformyl-2,4-dichloropyrrole [16]. We investigated in this study the behavior in the Vilsmeier–Haack reaction of available [17, 18] 2-aminosubstituted acetamides **Ia–Ij** that reacted with the mixture of DMF and $POCl_3$ in the molar ratio 1:2 at 90°C affording 1-substituted 4-chloro-1H-imidazole-5-carbaldehydes **IIa–IIj** in 45–54% yields. Taking into consideration the rules of the reaction of 1,4-bifunctional nitrogen nucleophiles with Vilsmeier–Haack reagent [19] it is presumable that the interaction proceeds through a stage of intermediate 1-substituted 5-dimethylaminomethyleneimidazolin-4-ones **IIIa–IIIj** that undergo further chlorination and hydrolysis to yield the target compounds. This assumption was confirmed by a special experiment that provided a possibility to isolate from the reaction mixture 5-dimethylaminomethylene-1-(4-tolyl)imidazolin-4-one (**IIIg**) at the ratio DMF–$POCl_3$ 1:1.

The composition and structure of all compounds obtained were confirmed by elemental analyses , IR, ^{1}H and ^{13}C NMR spectra. In particular, in the ^{1}H NMR spectra of compounds **IIa–IIj** singlet signals were observed from the protons H^2 of the imidazole ring (7.62–8.23 ppm) and from the formyl group (9.64–9.82 ppm). The signals from the corresponding carbon atoms in the ^{13}C NMR spectra appeared in the range 140–144 and 177 ppm, respectively.

EXPERIMENTAL

IR spectra of compound **IIa** in CH_2Cl_2 and of compounds **IIb–IIj** in pellets with KBr were recorded on a spectrophotometer UR-20. ^{1}H NMR spectra in DMSO-d_6 were registered on a spectrometer Varian-Gemini (299.94 MHz), internal reference TMS. ^{13}C NMR spectra in DMSO-d_6 were registered on a spectrometer Bruket Arano DRX-500 (125.75 MHz), internal reference TMS.

1-Aryl-4-chloro-1H-imidazole-5-carbaldehydes IIa–IIj. To a suspension of 0.03 mol of acetamide **Ia–Ih** in 6.75 g (0.09 mol) of DMF was added at stirring and cooling to 0–5°C 26.7 g (0.18 mol) of phosphorus oxychloride. The mixture obtained was heated for 4 h on a water bath at 90°C. The excess phosphorus oxychloride was removed in a vacuum, to the residue 50 ml of water was added, and the solution was neutralized with crystalline $NaHCO_3$ till pH 8.0. The formed precipitate was filtered off, the filtrate was extracted with ethyl acetate (3×20 ml), the extract was evaporated, the residue was combined with the precipitate, and the mixture was dissolved in hexane–ethyl acetate, 3:1, the solution was slowly filtered through a bed of alumina, and then it was subjected to chromatography on alumina (eluent hexane–ethyl acetate, 1:1) (in the case of compound **IIa**) or crystallized from 60% aqueous ethanol (for compounds **IIb–IIj**).

1-Butyl-4-chloro-1*H*-imidazole-5-carbaldehyde (IIa). Yield 48%, viscous fluid. IR spectrum, cm^{-1}: 1685 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.92 t (CH_3), 1.24–1.30 m (2H, CH_2), 1.95–2.02 m (2H, CH_2), 4.28 t (2H, NCH_2), 8.02 s (1H, H^2), 9.74 s (1H, CH=O). ^{13}C NMR spectrum, δ, ppm: 13.43 (CH_3), 19.50 (CH_2), 32.75 (CH_2), 47.80 (CH_2), 124.46 (C^5), 140.82 (C^2), 142.93 (C^4), 178.33 (CH=O). Found, %: C 51.16; H 12.03; N 14.82. $C_8H_{11}ClN_2O$. Calculated, %: C 51.48; H 11.88; N 15.01.

1-Benzyl-4-chloro-1*H*-imidazole-5-carbaldehyde (IIb). Yield 52%, mp 70–71°C. IR spectrum, cm^{-1}: 1670 (C=O). ^{1}H NMR spectrum, δ, ppm: 5.50 s (2H, CH_2), 7.24–7.32 m ($5H_{arom}$), 8.20 s (1H, H^2), 9.71 s (1H, CH=O). ^{13}C NMR spectrum, δ, ppm: 51.06 (CH_2), 124.56 (C^5), 127.89, 128.70, 129.10, 134.75 (C_{Ar}), 140.96 (C^2), 143.14 (C^4), 178.52 (CH=O). Found, %: C 60.11; H 4.27; N 12.85. $C_{11}H_9ClN_2O$. Calculated, %: C 59.88; H 4.11; N 12.70.

1-Phenyl-4-chloro-1*H*-imidazole-5-carbaldehyde (IIc). Yield 47%, mp 116–117°C. IR spectrum, cm^{-1}: 1675 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.32 m ($2H_{arom}$), 7.49 m ($3H_{arom}$), 7.62 s (1H, H^2), 9.82 s (1H, CH=O).

^{13}C NMR spectrum, δ, ppm: 125.21 (C^5), 125.72, 129.43, 129.69, 135.12 (C_{Ar}), 140.87 (C^2), 142.80 (C^4), 177.27 (CH=O). Found, %: C 58.39; H 3.47; N 13.75. $C_{10}H_7ClN_2O$. Calculated, %: C 58.13; H 3.41; N 13.56.

1-(2-Methylphenyl)-4-chloro-1*H*-imidazole-5-carbaldehyde (IId). Yield 45%, mp 105–106°C. IR spectrum, cm^{-1}: 1670 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.05 s (3H, CH_3), 7.16–7.42 m ($4H_{arom}$), 7.51 s (1H, H^2), 9.76 s (1H, CH=O). ^{13}C NMR spectrum, δ, ppm: 17.25 (CH_3), 125.88 (C^5), 126.92, 130.16, 131.11, 134.64, 135.09 (C_{Ar}), 140.87 (C^2), 141.96 (C^4), 177.22 (CH=O). Found, %: C 60.07; H 4.29; N 12.61. $C_{11}H_9ClN_2O$. Calculated, %: C 59.88; H 4.11; N 12.70.

4-Chloro-1-(4-chlorophenyl)-1*H*-imidazole-5-carbaldehyde (IIe). Yield 49%, mp 159–160°C. IR spectrum, cm^{-1}: 1675 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.27 d ($2H_{arom}$), 7.45 d ($2H_{arom}$), 7.61 s (1H, H^2), 9.82 s (1H, CH=O). ^{13}C NMR spectrum, δ, ppm: 125.12 (C^5), 127.03, 129.58, 133.63, 135.69 (C_{Ar}), 140.90 (C^2), 142.25 (C^4), 177.21 (CH=O). Found, %: C 50.04; H 2.37; N 11.70. $C_{10}H_6Cl_2N_2O$. Calculated, %: C 49.82; H 2.51; N 11.62.

1-(4-Bromophenyl)-4-chloro-1*H*-imidazole-5-carbaldehyde (IIf). Yield 54%, mp 176–177°C. IR spectrum, cm^{-1}: 1670 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.44 d ($2H_{arom}$), 7.69 d ($2H_{arom}$), 8.18 s (1H, H^2), 9.71 s (1H, CH=O). ^{13}C NMR spectrum, δ, ppm: 125.11 (C^5), 123.78, 127.28, 132.62, 134.15 (C_{Ar}), 143.38 (C^2), 147.05 (C^4), 177.26 (CH=O). Found, %: C 42.31; H 2.05; N 9.71. $C_{10}H_6BrClN_2O$. Calculated, %: C 42.07; H 2.12; N 9.81.

1-(4-Methylphenyl)-4-chloro-1*H*-imidazole-5-carbaldehyde (IIg). Yield 49%, mp 117–118°C. IR spectrum, cm^{-1}: 1665 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.36 s (3H, CH_3), 7.33 m ($4H_{arom}$), 8.11 s (1H, H^2), 9.67 s (1H, CH=O). ^{13}C NMR spectrum, δ, ppm: 21.25 (CH_3), 121.39 (C^5), 125.30, 130.01, 132.60, 139.96 (C_{Ar}), 140.85 (C^2), 142.69 (C^4), 177.35 (CH=O). Found, %: C 59.59; H 4.33; N 12.53. $C_{11}H_9ClN_2O$. Calculated, %: C 59.88; H 4.11; N 12.70.

1-(4-Methoxyphenyl)-4-chloro-1H-imidazole-5-carbaldehyde (IIh). Yield 46%, mp 102–103°C. IR spectrum, cm^{-1}: 1675 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.85 s (3H, CH_3), 6.96 d ($2H_{arom}$), 7.23 d ($2H_{arom}$), 7.58 s (1H, H^2), 9.80 s (1H, CH=O). ^{13}C NMR spectrum, δ, ppm: 55.64 (CH_3O), 125.38 (C^5), 114.52, 126.99, 127.85, 140.99 (C_{Ar}), 142.50 (C^2), 160.38 (C^4), 177.37 (CH=O). Found, %: C 55.59; H 3.97; N 11.75. $C_{11}H_9ClN_2O_2$. Calculated, %: C 55.83; H 3.83; N 11.84.

1-(2,5-Dimethylphenyl)-4-chloro-1H-imidazole-5-carbaldehyde (IIi). Yield 51%, mp 110–111°C. IR spectrum, cm^{-1}: 1675. ^{1}H NMR spectrum, δ, ppm: 1.98 s (3H, CH_3), 2.34 s (3H, CH_3), 7.12 s ($1H_{arom}$), 7.26 s ($2H_{arom}$), 8.03 s (1H, H^2), 9.64 s (1H, CH=O). ^{13}C NMR spectrum, δ, ppm: 16.78 (CH_3), 20.75 (CH_3), 125.87 (C^5), 127.39, 130.86, 131.79, 134.38, 136.90 (C_{Ar}), 140.83 (C^2), 141.78 (C^4), 177.22 (CH=O). Found, %: C 61.19; H 4.85; N 12.12. $C_{12}H_{11}ClN_2O$. Calculated, %: C 61.41; H 4.72; N 11.94.

1-(1-Naphthyl)-4-chloro-1*H*-imidazole-5-carbaldehyde (IIj). Yield 52%, mp 140–141°C. IR spectrum, cm^{-1}: 1680 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.28 d ($2H_{arom}$), 7.53–7.65 m ($4H_{arom}$), 8.06–8.14 m ($2H_{arom}$), 8.23 s (H^2), 9.64 s (CH=O). Found, %: C 65.28; H 5.59; N 11.06. $C_{14}H_9ClN_2O$. Calculated, %: C 65.51; H 3.53; N 10.91.

5-Dimethylaminomethylene-1-(4-tolyl)-1,5-dihydro-4H-imidazol-4-one (IIIg) was obtained in the same way as compounds **IIa–IIh**, but at the use of equimolar mixture of DMF and $POCl_3$. The reaction mixture was heated on a water bath for 1 h instead of 4 h and at 60°C. Yield 57%, mp 156–157°C. IR spectrum, cm^{-1}: 1650 (C=C), 1695 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.34 s (3H, CH_3), 3.25 s (3H, CH_3), 3.51 s (3H, CH_3), 7.19 s (1H, CH=), 7.22 d ($2H_{arom}$), 7.46 d ($2H_{arom}$), 7.73 s (1H, H^2). Found, %: C 67.86; H 6.42; N 18.57 $C_{13}H_{15}N_3O$. Calculated, %: C 68.10; H 6.59; N 18.32.

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