Alkylation of NH-, OH-, and SH-acids in the presence of potassium carbonate
1. Functionalization of chloromethyl group of alkoxy-substituted aromatic aldehydes

D. S. Khachatryan,[a] A. L. Razinov,[a] A. V. Kolotaev,[a] S. K. Belus´,[a] and K. R. Matevosyan[b]*

[a]Labor Red Banner order Federal State Unitary Enterprise "Research Institute of Chemical Reactants and Ultrapure Compounds (IREA)", 3 Bogorodskii val, 107076 Moscow, Russian Federation. E-mail: derenik-s@yandex.ru

[b]D. I. Mendeleev University of Chemical Technology of Russia, 9 Miusskaya pl., 125047 Moscow, Russian Federation

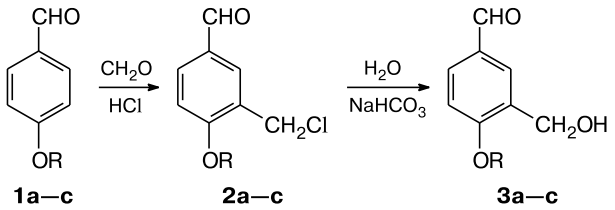
An easily scalable, economocal, and more safe method for the preparation of 3-chloromethyl-4-methoxybenzaldehyde was developed. The latter was subjected to reactions with NH-, OH-, and SH-acids in the presence of potassium carbonate to obtain new aromatic aldehydes in high yields.

Key words: 3-chloromethyl-4-methoxybenzaldehyde, NH-, OH-, and SH-acids, alkylation, potassium carbonate, aromatic aldehydes.

The importance of aromatic aldehydes in the construction of biologically active molecules is of common knowledge. Their heterocyclization reaction was used to obtain symmetrically substituted porphyrins,[1—4] carbolines,[5—10] dihydroquinazolones,[11—17] tetrahydropyrimidinones,[18—21] and xanthines.[22—25]

From a plethora of methods for the preparation of polyfunctional aromatic aldehydes,[26,27] we have chosen the chloromethylation reaction[28—30] of 4-methoxybenzaldehyde (anisic aldehyde (**1a**)) with subsequent replacement of the chlorine atom with different O-, N-, and S-nucleophiles (Scheme 1). This gave us a possibility to obtain a wide range of substituted aromatic aldehydes from simple and inexpensive reactants. This choice is also explained by the suggestion that the introduction of an alkoxyphenyl group in an organic molecule can impart a certain biological activity to this molecule.[31]

Scheme 1



1a—c **2a—c** **3a—c**

R = Me (**a**), Et (**b**), Pr (**c**)

It is necessary to avoid a direct contact with 3-chloromethyl-4-methoxybenzaldehyde (**2a**) because of its irritating properties. We developed a convenient procedure for its synthesis which uses paraform aldehyde in concentrated hydrochloric acid without additional reagents and solvents. A multiple use of the mother liquor of the hydrochloric acid solution gave a possibility to increase the yield of the target product to 99% (according to the ^{1}H NMR data, the purity of the product was >95%) and make the process of low-waste. A decrease in the amount of operations of the technological process allowed us to improve safety conditions.

Other 4-alkoxybenzaldehydes (for example, **1b**,**c**) can be also involved in such transformations. The thus obtained 3-chloromethyl derivatives **2a—c** readily undergo hydrolyzation upon reflux with 2% aqueous solution of sodium hydrogen carbonate, leading to 3-hydroxymethylbenzaldehydes **3a—c** in high yields (see Scheme 1, Table 1).

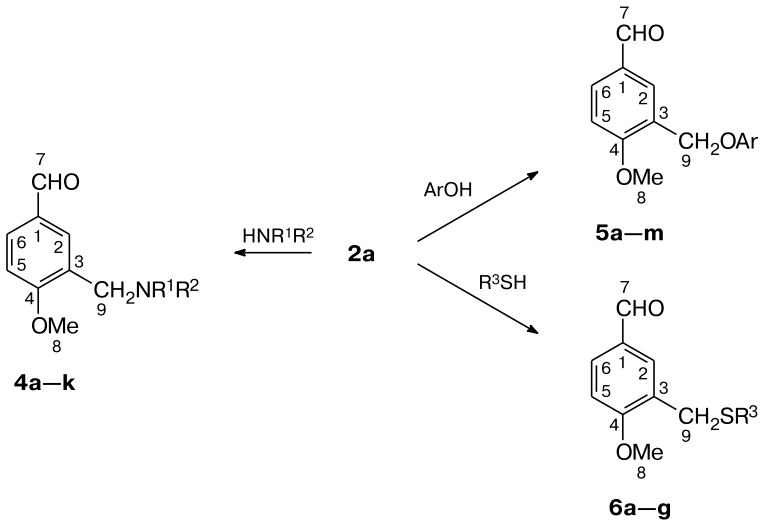
Based on our experience on alkylation of CH-acids,[32—35] we have chosen potassium carbonate as a base for the substitution of chlorine with different nucleophiles (phenols, secondary amines, thiols). The solvents were ethanol, acetonitrile, and DMF, in which the starting nucleophiles are soluble, whereas the final products are isolated in the solid state.

The reaction of morpholine with 3-chloromethyl-4-methoxybenzaldehyde (**2a**) upon reflux in ethanol gave rise to 4-methoxy-3-morpholinomethylbenzaldehyde (**4a**) in 91% yield and more than 97% purity. Other amino derivatives were also synthesized in high yields (82—95%) (Scheme 2, Table 2).

When phenols in an alcohol were used as nucleophiles, up to 10% of 3-ethoxymethyl derivatives were formed

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 2, pp. 0395—0404, February, 2015.

Scheme 2



4: NR^1R^2 = (**a**), (**b**), (**c**), (**d**), (**e**), (**f**)*, (**g**), (**h**), (**i**), (**j**), (**k**)

5: Ar = (**a**), (**b**), (**c**), (**d**), (**e**), (**f**), (**g**), (**h**), (**i**), (**j**), (**k**), (**l**), (**m**)

6: R^3 = (**a**), (**b**), (**c**), (**d**), (**e**), (**f**), (**g**)

* As a hydrochloride.

Table 1. Yields, melting points, elemental analysis data, and ^{1}H NMR spectra (in DMSO-d_6) of aldehydes **2a—c** and **3a—c**

Compound	Yield (%)	M.p./°C	Found / Calculated (%)		Molecular formula	^{1}H NMR, δ (*J*/Hz)
			C	H		
2a	99	56—58	58.61 58.23	5.16 5.43	$C_9H_9ClO_2$	3.96 (s, 3 H, C(9)H_3); 4.78 (s, 2 H, C(8)H_2); 7.27 (d, 1 H, C(5)H_{Ar}, *J* = 8.3); 7.93 (d, 1 H, C(2)H_{Ar}, *J* = 2.1); 7.95—7.97 (m, 1 H, C(6)H_{Ar}); 9.88 (s, 1 H, C(7)HO)
2b	98	75—76	60.31 60.45	5.63 5.54	$C_{10}H_{11}ClO_2$	1.38 (t, 3 H, C(9)H_3, *J* = 6.9); 4.23 (q, 2 H, C(8)H_2, *J* = 6.9); 4.77 (s, 2 H, C(10)H_2); 7.24 (d, 1 H, C(5)H_{Ar}, *J* = 8.5); 7.92 (dd, 1 H, C(6)H_{Ar}, *J* = 8.5, *J* = 2.1); 7.96 (d, 1 H, C(2)H_{Ar}, *J* = 2.1); 9.88 (s, 1 H, C(7)HO)
2c	95	47—48	62.01 62.11	6.26 6.12	$C_{11}H_{13}ClO_2$	0.99 (t, 3 H, C(11)H_3, *J* = 6.9); 1.70—1.85 (m, 2 H, C(10)H); 4.10 (t, 2 H, C(9)H_3, *J* = 6.9); 5.11 (s, 2 H, C(8)H_2); 7.21 (d, 1 H, C(5)H_{Ar}, *J* = 8.4); 7.80 (s, 1 H, C(2)H_{Ar}); 7.87 (d, 1 H, C(6)H_{Ar}, *J* = 8.4); 9.87 (s, 1 H, C(7)HO)
3a	83	55—56.5	65.32 65.05	6.44 6.06	$C_9H_{10}O_3$	3.89 (s, 3 H, C(9)H_3); 4.52 (s, 2 H, C(8)H_2); 5.23 (br.s, 1 H, OH); 7.16 (d, 1 H, C(5)H_{Ar}, *J* = 8.4); 7.83 (dd, 1 H, C(6)H_{Ar}, *J* = 8.4, *J* = 2.2); 7.92—7.95 (m, 1 H, C(2)H_{Ar}); 9.89 (s, 3 H, C(7)HO)
3b	90	58-59	66.85 66.65	6.58 6.71	$C_{10}H_{12}O_3$	1.36 (t, 3 H, C(10)H_3); 4.16 (q, 2 H, C(9)H_2); 4.52 (s, 2 H, C(8)H_2); 5.22 (s, 1 H, OH); 7.14 (d, 1 H, C(5)H_{Ar}, *J* = 8.4); 7.80 (dd, 1 H, C(6)H_{Ar}, *J* = 8.4, *J* = 2.0); 7.92—7.95 (m, 1 H, C(2)H_{Ar}); 9.88 (s, 1 H, C(7)HO)
3c	81	45-46	68.25 68.04	7.54 7.22	$C_{11}H_{14}O_3$	1.00 (t, 3 H, C(11)H_3, *J* = 6.9); 1.69—1.83 (m, 2 H, C(10)H); 4.09 (t, 2 H, C(9)H_2, *J* = 6.9); 4.53 (s, 2 H, C(8)H_2); 5.21 (t, 1 H, OH); 7.12 (d, 1 H, C(5)H_{Ar}, *J* = 8.4); 7.80 (d, 1 H, C(6)H_{Ar}, *J* = 8.4); 7.93 (s, 1 H, C(2)H_{Ar}); 9.88 (s, 1 H, C(7)HO)

Table 2. Yields, melting points, elemental analysis data, and ^{1}H NMR spectra (in DMSO-d_6) of aldehydes **4a—k**, **5a—m**, and **6a—g**

Compound	Yield (%)	M.p./°C	Found / Calculated (%)				Molecular formula	^{1}H NMR, δ (*J*/Hz)
			C	H	N	S		
4a	91	77.5—78	66.21 66.36	7.11 7.28	5.87 5.95	—	$C_{13}H_{17}NO_3$	2.39 (t, 4 H, C(10)H_2, *J* = 4.6); 3.50 (s, 2 H, C(9)H_2); 3.59 (t, 4 H, C(11)H_2, *J* = 4.6); 3.92 (s, 3 H, C(8)H_3); 7.19 (d, 1 H, C(5)H_{Ar}, *J* = 8.3); 7.82 (d, 1 H, C(2)H_{Ar}, *J* = 2.2); 7.84—7.88 (m, 1 H, C(6)H_{Ar}); 9.88 (s, 1 H, C(7)HO)
4b	89	88—88.5	76.69 76.84	6.64 6.81	4.78 4.98	—	$C_{18}H_{19}NO_2$	1.96 (m, 2 H, C(11)H_2, *J* = 6.0); 2.76 (t, 2 H, C(12)H_2, *J* = 6.0); 3.37 (t, 2 H, C(10)H_2, *J* = 6.0); 3.96 (s, 3 H, C(8)H_3); 4.41 (s, 2 H, C(9)H_2); 6.23 (d, 1 H, CH_{Ar}, *J* = 7.8); 6.46 (t, 1 H, CH_{Ar}, *J* = 8.3); 6.84 (t, 1 H, CH_{Ar}, *J* = 8.3); 6.91 (d, 1 H, CH_{Ar}, *J* = 7.8); 7.25 (d, 1 H, C(5)H_{Ar}, *J* = 8.5); 7.55 (d, 1 H, C(2)H_{Ar}, *J* = 2.0); 7.85 (dd, 1 H, C(6)H_{Ar}, *J* = 8.5, *J* = 2.0); 9.80 (s, 1 H, C(7)HO)
4c	92	80—80.5	70.41 70.56	7.02 7.10	8.11 8.23	—	$C_{20}H_{24}N_2O_3$	2.56 (br.s, 4 H, C(10)H_2); 2.98 (br.s, 4 H, C(11)H_2); 3.57 (s, 2 H, C(9)H_2); 3.76 (s, 3 H, C(18)H_3); 3.91 (s, 3 H, C(8)H_3); 6.82—6.98 (m, 4 H, CH_{Ar}); 7.21 (d, 1 H, C(5)H_{Ar}, *J* = 8.4); 7.85 (dd, 1 H, C(6)H_{Ar}, *J* = 8.4, *J* = 2.0); 7.89 (d, 1 H, C(2)H_{Ar}, *J* = 2.0); 9.89 (s, 1 H, C(7)HO)
4d	82	71.5—72	64.57 64.72	7.74 7.97	9.89 10.06	—	$C_{15}H_{22}N_2O_3$	2.39 (t, 2 H, C(12)H_2, *J* = 6.3); 2.33—2.49 (m, 8 H, C(10)H_2, C(11)H_2); 3.48 (t, 2 H, C(13)H_2, *J* = 6.3); 3.49 (s, 2 H, C(9)H_2); 3.89 (s, 3 H, C(8)H_3); 4.40 (br.s, 1 H, OH); 7.18 (d, 1 H, C(5)H_{Ar}, *J* = 8.2); 7.79—7.87 (m, 2 H, CH_{Ar}); 9.87 (s, 1 H, C(7)HO)

(*to be continued*)

Table 2 (*continued*)

Compound	Yield (%)	M.p./°C	Found / Calculated (%)				Molecular formula	^{1}H NMR, δ (*J*/Hz)
			C	H	N	S		
4e	90	87—87.5	69.31 69.49	6.34 6.44	8.40 8.53	—	$C_{19}H_{21}FN_2O_2$	2.55 (t, 4 H, C(11)H_2, *J* = 4.8); 3.09 (t, 4 H, C(10)H_2, *J* = 4.8); 3.57 (s, 2 H, C(9)H_2); 3.91 (s, 3 H, C(8)H_3); 6.89—6.97 (m, 2 H, C(14)H_{Ar}); 6.98—7.08 (m, 2 H, C(13)H_{Ar}); 7.21 (d, 1 H, C(5)H_{Ar}, *J* = 8.5); 7.85 (dd, 1 H, C(6)H_{Ar}, *J* = 8.5, *J* = 2.1); 7.89 (d, 1 H, C(2)H_{Ar}, *J* = 2.1); 9.89 (s, 1 H, C(7)HO)
4f	87	202—203	54.97 54.89	5.23 5.09	6.82 6.74	—	$C_{19}H_{21}Cl_3N_2O_2$	3.07—3.50 (m, 6 H, CH_2); 3.78—3.92 (m, 2 H, CH_2); 3.97 (s, 3 H, C(8)H_2); 4.40 (br.s, 2 H, C(9)H_2); 6.97 (dd, 1 H, C(17)H_{Ar}, *J* = 8.9, *J* = 2.7); 7.21 (d, 1 H, C(13)H_{Ar}, *J* = 2.1); 7.35 (d, 1 H, C(5)H_{Ar}, *J* = 8.6); 7.44 (d, 1 H, C(16)H_{Ar}, *J* = 8.9); 8.08 (dd, 1 H, C(6)H_{Ar}, *J* = 8.6, *J* = 1.8); 8.17 (d, 1 H, C(2)H_{Ar}, *J* = 1.8); 9.90 (s, 1 H, C(7)HO); 11.06 (N^+H)
4g	93	178.5—179	70.87 70.98	6.43 6.55	8.46 8.55	—	$C_{20}H_{22}N_2O_3$	1.67—1.91 (m, 2 H, CH_2); 2.27—2.47 (m, 2 H, CH_2); 2.40 (br.s, 1 H, CH); 2.73—2.98 (m, 2 H, CH_2); 3.01 (br.s, 1 H, CH); 3.45 (s, 2 H, C(9)H_2); 3.65—3.95 (m, 2 H, CH_2); 3.81 (s, 3 H, C(8)H_3); 6.05 (dd, 1 H, C(13)H_{Ar}, *J* = 6.9, *J* = 1.3); 6.27 (dd, 1 H, C(15)H_{Ar}, *J* = 9.0, *J* = 1.3); 7.12 (d, 1 H, C(5)H_{Ar}, *J* = 8.5); 7.29 (d, 1 H, C(2)H_{Ar}, *J* = 2.1); 7.34 (dd, 1 H, C(14)H_{Ar}, *J* = 9.0, *J* = 6.9); 7.73 (dd, 1 H, C(6)H_{Ar}, *J* = 8.5, *J* = 2.1); 9.60 (s, 1 H, C(7)HO)
4h	88	88—88.5	69.32 69.49	6.21 6.44	8.38 8.53	—	$C_{19}H_{21}FN_2O_2$	2.58 (t, 4 H, C(10)H_2, *J* = 4.6); 3.03 (t, 4 H, C(11)H_2, *J* = 4.6); 3.58 (s, 2 H, C(9)H_2); 3.91 (s, 3 H, C(8)H_3); 6.90—7.16 (m, 4 H, CH_{Ar}); 7.21 (d, 1 H, C(5)H_{Ar}, *J* = 8.5); 7.85 (dd, 1 H, C(6)H_{Ar}, *J* = 8.5, *J* = 2.0); 7.90 (d, 1 H, C(2)H_{Ar}, *J* = 2.0); 9.89 (s, 1 H, C(7)HO)
4i	95	129—130	54.98 55.17	4.12 4.24	16.01 16.08	—	$C_{12}H_{11}N_3O_4$	3.93 (s, 3 H, C(8)H_3); 5.43 (s, 2 H, C(9)H_2); 7.26 (d, 1 H, C(5)H_{Ar}, *J* = 8.5); 7.65 (d, 1 H, C(2)H_{Ar}, *J* = 2.1); 7.94 (dd, 1 H, C(6)H_{Ar}, *J* = 8.5, *J* = 2.1); 8.27 (s, 1 H, C(10)H); 8.95 (s, 1 H, C(12)H); 9.85 (s, 1 H, C(7)HO)
4j	85	123.5—124	51.92 52.03	4.49 4.68	8.51 8.67	—	$C_{14}H_{15}BrN_2O_2$	2.09 (s, 3 H, C(13)H_3); 2.21 (s, 3 H, C(14)H_3); 3.94 (s, 3 H, C(8)H_3); 5.22 (s, 2 H, C(9)H_2); 7.25 (d, 1 H, C(5)H_{Ar}, *J* = 8.5); 7.29 (d, 1 H, C(2)H_{Ar}, *J* = 2.1); 7.89 (dd, 1 H, C(6)H_{Ar}, *J* = 8.5, *J* = 2.1); 9.82 (s, 1 H, C(7)HO)
4k	94	140.5—141	58.03 58.13	5.12 5.23	14.29 14.52	—	$C_{14}H_{15}N_3O_4$	2.37 (s, 3 H, C(14)H_3); 2.63 (s, 3 H, C(13)H_3); 3.93 (s, 3 H, C(8)H_3); 5.31 (s, 2 H, C(9)H_2); 7.26 (d, 1 H, C(5)H_{Ar}, *J* = 8.5); 7.52 (d, 1 H, C(2)H_{Ar}, *J* = 1.9); 7.92 (dd, 1 H, C(6)H_{Ar}, *J* = 8.5, *J* = 1.9); 9.85 (s, 1 H, C(7)HO)
5a	96	49—49.5	69.08 69.22	4.89 5.03	—	—	$C_{15}H_{13}FO_3$	3.94 (s, 3 H, C(8)H_3); 5.09 (s, 2 H, C(9)H_2); 6.99—7.07, 7.08—7.18 (both m, 2 H each, CH_{Ar}); 7.25—7.31 (m, 1 H, CH_{Ar}); 7.90—7.97 (m, 2 H, CH_{Ar}); 9.89 (s, 1 H, C(7)HO)
5b	93	85.5—86	64.99 65.11	4.58 4.74	—	—	$C_{15}H_{13}ClO_3$	3.94 (s, 3 H, C(8)H_3); 5.11 (s, 2 H, C(9)H_2); 7.01—7.08, 7.25—7.30 (both m, 2 H each, CH_{Ar}); 7.31—7.37 (m, 1 H, CH_{Ar}); 7.91—7.96 (m, 2 H, CH_{Ar}); 9.88 (s, 1 H, C(7)HO)
5c	89	76.5—78	68.47 68.57	6.29 6.36	—	—	$C_{19}H_{21}ClO_3$	1.15 (d, 6 H, C(18)H_3, *J* = 6.9); 2.28 (s, 3 H, C(16)H_3); 3.22 (m, 1 H, C(17)H); 3.94 (s, 3 H, C(8)H_3); 5.11 (s, 2 H, C(9)H_2); 7.06 (br.s, 1 H, C(15)H_{Ar}); 7.16 (br.s, 1 H, C(12)H_{Ar}); 7.28 (d, 1 H, C(5)H_{Ar}, *J* = 8.4); 7.90—8.00 (m, 2 H, CH_{Ar}); 9.89 (s, 1 H, C(7)HO)

(*to be continued*)

Table 2 (*continued*)

Compound	Yield (%)	M.p./°C	Found / Calculated (%)				Molecular formula	^{1}H NMR, δ (*J*/Hz)
			C	H	N	S		
5d	85	88—90	70.02 70.16	6.34 6.48	—	—	$C_{20}H_{22}O_5$	0.96 (d, 6 H, C(17)H_3, *J* = 6.6); 2.00 (m, 1 H, C(16)H, *J* = 6.6); 3.95 (s, 3 H, C(8)H_3); 4.02 (d, 2 H, C(15)H_2, *J* = 6.6); 5.20 (s, 2 H, C(9)H_2); 7.11—7.18 (m, 2 H, CH_{Ar}); 7.26—7.32 (m, 1 H, CH_{Ar}); 7.90—7.98 (m, 4 H, CH_{Ar}); 9.89 (s, 1 H, C(7)HO)
5e	97	114—114.5	61.02 61.13	3.98 4.10	—	—	$C_{15}H_{12}ClFO_3$	3.94 (s, 3 H, C(8)H_3); 5.12 (s, 2 H, C(9)H_2); 6.99—7.07 (m, 1 H, CH_{Ar}); 7.25—7.40 (m, 3 H, CH_{Ar}); 7.91—7.98 (m, 2 H, CH_{Ar}); 9.89 (s, 1 H, C(7)HO)
5f	87	39—40	70.45 70.57	5.79 5.92	—	—	$C_{16}H_{16}O_4$	3.69 (s, 3 H, C(16)H_3); 3.94 (s, 3 H, C(8)H_3); 5.04 (s, 2 H, C(9)H_2); 6.82—6.99 (m, 4 H, CH_{Ar}); 7.26 (d, 1 H, CH_{Ar}, *J* = 8.7); 7.88—7.96 (m, 2 H, CH_{Ar}); 9.88 (s, 1 H, C(7)HO)
5g	96	92—92.5	55.91 56.09	3.96 4.08	—	—	$C_{15}H_{13}BrO_3$	3.94 (s, 3 H, C(8)H_3); 5.11 (s, 2 H, C(9)H_2); 6.96—7.04 (m, 2 H, CH_{Ar}); 7.25—7.31 (m, 1 H, CH_{Ar}); 7.42—7.50, 7.90—7.97 (both m, 2 H each, CH_{Ar}); 9.88 (s, 1 H, C(7)HO)
5h	87	73—73.5	76.31 76.48	7.33 7.43	—	—	$C_{19}H_{22}O_3$	1.25 (s, 9 H, C(15)H_3); 3.95 (s, 3 H, C(8)H_3); 5.08 (s, 2 H, C(9)H_2); 6.89—6.96 (m, 2 H, CH_{Ar}); 7.24—7.34 (m, 3 H, CH_{Ar}); 7.89—7.96 (m, 2 H, CH_{Ar}); 9.89 (s, 1 H, C(7)HO)
5i	97	119—121	62.60 62.72	4.42 4.56	4.71 4.88	—	$C_{15}H_{13}NO_5$	3.94 (s, 3 H, C(8)H_3); 5.30 (s, 2 H, C(9)H_2); 7.11—7.19 (m, 1 H, CH_{Ar}); 7.29 (d, 1 H, CH_{Ar}, *J* = 8.7); 7.46 (d, 1 H, CH_{Ar}, *J* = 8.0); 7.62—7.71 (m, 1 H, CH_{Ar}); 7.87—8.01 (m, 3 H, CH_{Ar}); 9.88 (s, 1 H, C(7)HO)
5j	91	99.5—100	65.92 66.09	5.08 5.20	—	—	$C_{16}H_{15}ClO_3$	2.30 (s, 3 H, C(16)H_3); 3.94 (s, 3 H, C(8)H_3); 5.09 (s, 2 H, C(9)H_2); 6.87 (dd, 1 H, CH_{Ar}, *J* = 8.7, *J* = 3.0); 7.06 (d, 1 H, CH_{Ar}, *J* = 3.0); 7.25—7.33, 7.91—7.97 (both m, 2 H each, CH_{Ar}); 9.89 (s, 1 H, C(7)HO)
5k	90	88—90	64.58 64.75	4.19 4.35	—	—	$C_{15}H_{12}F_2O_3$	3.94 (s, 3 H, C(8)H_3); 5.16 (s, 2 H, C(9)H_2); 6.96—7.06 (m, 1 H, CH_{Ar}); 7.22—7.36 (m, 3 H, CH_{Ar}); 7.92—7.98 (m, 2 H, CH_{Ar}); 9.89 (s, 1 H, C(7)HO)
5l	94	69—69.5	77.56 77.75	7.33 7.46	—	—	$C_{21}H_{24}O_3$	1.20—1.50, 1.65—1.85 (both m, 5 H each, CH_2); 2.97 (m, 1 H, CH); 3.95 (s, 3 H, C(8)H_3); 5.11 (s, 2 H, C(9)H_2); 6.88—6.95, 6.99—7.04 (both m, 1 H each, CH_{Ar}); 7.11—7.21 (m, 2 H, CH_{Ar}); 7.25—7.32, 7.90—7.97, 7.99—8.03 (all m, 1 H each, CH_{Ar}); 9.89 (s, 1 H, C(7)HO)
5m	87	104—104.5	74.82 74.98	6.18 6.29	—	—	$C_{16}H_{16}O_3$	2.22 (s, 3 H, C(16)H_3); 3.95 (s, 3 H, C(8)H_3); 5.11 (s, 2 H, C(9)H_2); 6.86 (t, 1 H, CH_{Ar}, *J* = 7.0); 6.98 (d, 1 H, CH_{Ar}, *J* = 7.8); 7.11—7.19 (m, 2 H, CH_{Ar}); 7.28 (d, 1 H, C(5)H_{Ar}, *J* = 8.5); 7.93 (dd, 1 H, C(6)H_{Ar}, *J* = 8.5, *J* = 2.0); 7.97 (d, 1 H, C(2)H_{Ar}, *J* = 2.0); 9.89 (s, 1 H, C(7)HO)
6a	79	65—67	59.29 59.52	5.14 5.38	10.42 10.68	12.08 12.20	$C_{13}H_{14}N_2O_2S$	3.38 (s, 3 H, C(13)H_3); 3.89 (s, 3 H, C(8)H_3); 4.16 (s, 2 H, C(9)H_2); 6.95 (d, 1 H, CH_{Im}, *J* = 1.1); 7.19 (d, 1 H, C(5)H_{Ar}, *J* = 8.5); 7.20 (d, 1 H, CH_{Im}, *J* = 1.1); 7.55 (d, 1 H, C(2)H_{Ar}, *J* = 2.1); 7.84 (dd, 1 H, CH_{Ar}, *J* = 8.5, *J* = 2.1); 9.78 (s, 1 H, C(7)HO)
6b	89	73.5—75	60.85 60.93	4.06 4.15	4.33 4.44	20.28 20.33	$C_{16}H_{13}NO_2S_2$	3.95 (s, 3 H, C(8)H_3); 4.65 (s, 2 H, C(9)H_2); 7.25 (d, 1 H, CH_{Ar}, *J* = 8.5); 7.32—7.40, 7.43—7.51 (both m, 1 H each, CH_{Ar}); 7.86—7.93, 7.96—8.06 (both m, 2 H each, CH_{Ar}); 9.84 (s, 1 H, C(7)HO)

(*to be continued*)

Table 2 (*continued*)

Compound	Yield (%)	M.p./°C	Found / Calculated (%)				Molecular formula	^{1}H NMR, δ (*J*/Hz)
			C	H	N	S		
6c	87	114—114.5	64.00 64.19	4.16 4.38	4.44 4.68	10.63 10.71	$C_{16}H_{13}NO_3S$	3.95 (s, 3 H, C(8)H_3); 4.62 (s, 2 H, C(9)H_2); 7.26 (d, 1 H, C(5)H_{Ar}, *J* = 8.5); 7.28—7.38 (m, 2 H, C(13)H_{Ar}, C(14)H_{Ar}); 7.60—7.70 (m, 2 H, C(12)H_{Ar}, C(15)H_{Ar}); 7.90 (dd, 1 H, C(6)H_{Ar}, *J* = 8.5, *J* = 2.1); 8.03 (d, 1 H, C(2)H_{Ar}, *J* = 2.1); 9.85 (s, 1 H, C(7)HO)
6d	85	41—43	72.99 73.13	7.31 7.36	—	9.62 9.76	$C_{20}H_{24}O_2S$	1.16 (s, 9 H, C(18)H_3); 2.24 (s, 3 H, C(16)H_3); 3.87 (s, 3 H, C(8)H_3); 4.13 (s, 2 H, C(9)H_2); 7.08—7.12 (m, 3 H, CH_{Ar}); 7.18 (d, 1 H, C(5)H_{Ar}, *J* = 8.5); 7.65 (d, 1 H, C(2)H_{Ar}, *J* = 2.1); 7.82 (dd, 1 H, C(6)H_{Ar}, *J* = 8.5, *J* = 2.1); 9.78 (s, 1 H, C(7)HO)
6e	96	171—171.5	64.17 64.41	4.65 4.73	9.14 9.39	10.57 10.74	$C_{16}H_{14}N_2O_2S$	3.93 (s, 3 H, C(8)H_3); 4.57 (s, 2 H, C(9)H_2); 7.07—7.14 (m, 2 H, C(12)H_{Ar}, C(13)H_{Ar}); 7.23 (d, 1 H, C(5)H_{Ar}, *J* = 8.5); 7.40—7.47 (m, 2 H, C(11)H_{Ar}, C(14)H_{Ar}); 7.86 (dd, 1 H, C(5)H_{Ar}, *J* = 8.5, *J* = 2.1); 7.96 (d, 1 H, C(3)H_{Ar}, *J* = 2.1); 9.81 (s, 1 H, C(7)HO)
6f	86	81—82	64.72 64.84	5.03 5.05	5.37 5.40	12.22 12.37	$C_{14}H_{13}NO_2S$	4.43 (s, 2 H, C(9)H_2); 7.10—7.14 (m, 1 H, C(13)H_{Py}); 7.22 (d, 1 H, C(5)H_{Ar}, *J* = 8.5); 7.29 (dt, 1 H, C(11)H_{Py}, *J* = 8.0, *J* = 1.0); 7.59—7.67 (m, 1 H, C(12)H_{Py}); 7.84 (dd, 1 H, C(6)H_{Ar}, *J* = 8.5, *J* = 2.1); 7.91 (d, 1 H, C(2)H_{Ar}, *J* = 2.1); 8.45—8.49 (m, 1 H, C(14)H_{Py}); 9.82 (s, 1 H, C(7)HO)
6g	89	92—94	54.41 54.53	4.42 4.58	10.39 10.60	12.01 12.13	$C_{12}H_{12}N_2O_3S$	2.67 (s, 3 H, C(12)H_3); 3.93 (s, 3 H, C(8)H_3); 4.52 (s, 2 H, C(9)H_2); 7.25 (d, 1 H, C(5)H_{Ar}, *J* = 8.3); 7.86—7.94 (m, 2 H, CH_{Ar}); 9.84 (s, 1 H, C(7)HO)

together with the major 3-aryloxymethyl-4-methoxybenzaldehydes. To avoid this side reaction, we studied alkylation of 4-fluorophenol with chloride **2a** (see Scheme 2) upon reflux in different solvents (Table 3).

The solvent system DMF—acetonitrile = (1 : 9)—(2 : 8) was found to be optimal not only for the case of phenols (85—95% yields), but also for that of thiols (see Scheme 2). This procedure was also used for the preparation of other aldehydes **8a**,**b**, **9**—**12** (Scheme 3, Table 4).

The structures of all the synthesized aldehydes were characterized by ^{1}H NMR spectra, their composition was confirmed by elemental analysis. ^{13}C NMR, IR, and mass spectra were also recorded for some samples.

The ^{1}H NMR spectra of compounds **2**—**6** exhibit signals characteristic of the aromatic protons of 3,4-disubstituted benzaldehydes (see Tables 1 and 2).

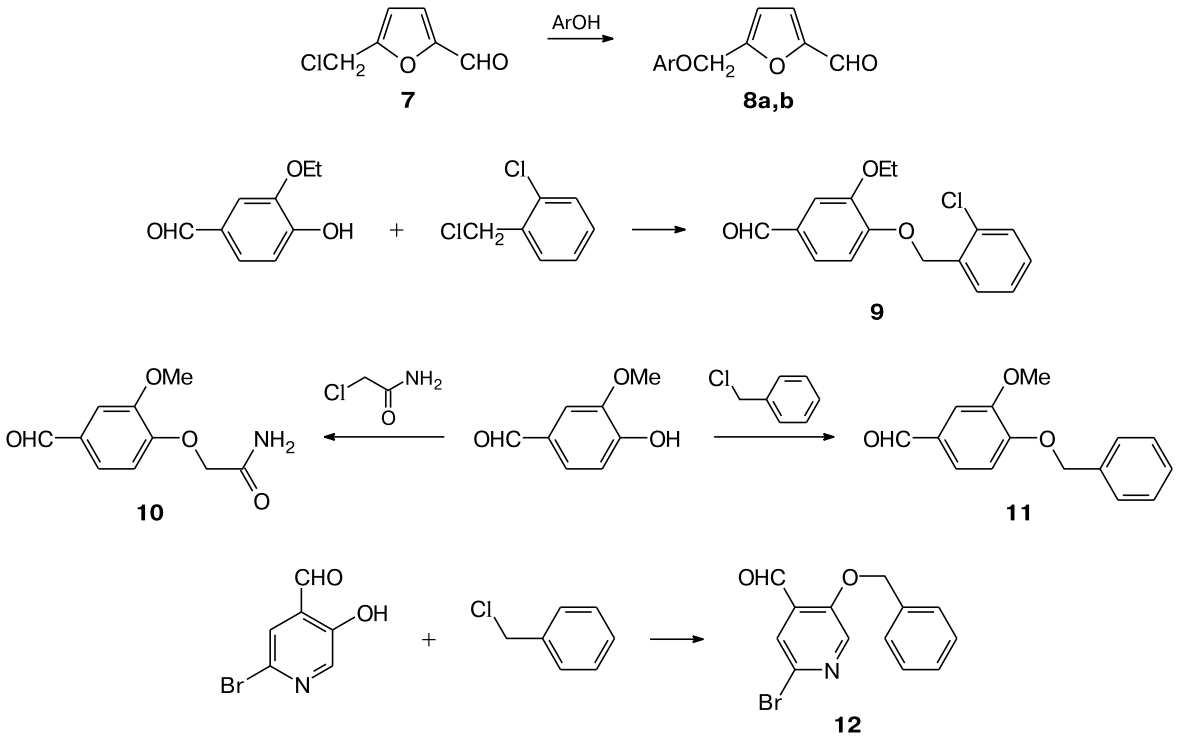
Interestingly, if chemical shifts for protons H(5) in benzaldehyde do not virtually change (δ 7.2—7.3) (see Table 2), the chemical shifts for protons H(2) and H(6) vary within a wide range (δ 7.2—8.2) depending on the electron-withdrawing properties of substituent CH_2X after substitution of chlorine in the CH_2Cl group. The nature of this substituent also greatly affects chemical shift of the methylene group directly bonded to the aromatic ring of the aldehyde from one side and to the incoming nucleophile from the other side (δ from 3.45 in the case of cytisine to 5.45 in the case of nitropyrazole, see Table 2). Similar phenomenon is observed

Table 3. Alkylation of 4-fluorophenol with chloride **2a** in various solvents

Solvent	ε	*T*/°C	*t*[a]/h	Yield[b] (%)	
				method *1*	method *2*
DMF	36.7	90—100	5	92	78
Benzene	2.28	80	20[c]	71	—
Toluene	2.38	110	20[c]	77	—
MeCN	36.2	80	20	94	81
DMF—MeCN[d]	—	80—85	7	96	82

[a] Reaction duration, TLC monitoring of the reaction progress.
[b] In method *1*, the product was isolated by evaporation of the solvent on a rotary evaporator with subsequent treatment of the reaction mixture with water; in method *2*, the product was isolated by the dilution of the reaction mixture with water with subsequent extraction of the product with dichloromethane.
[c] The reaction did not reach completion (TLC showed the presence of **2a**). To isolate the pure product the residue was additionally treated with 50% aqueous ethanol.
[d] The best results were obtained for the ratios (1 : 9)—(2 : 8).

Scheme 3



Ar = 2-$O_2NC_6H_4$ (**8a**), 4-O_2N-3-MeC_6H_3 (**8b**)

Table 4. Yields, melting points, elemental analysis data, and ^{1}H NMR spectra (in DMSO-d_6) of compounds **8a**,**b** and **9**—**12**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)			Molecular formula	^{1}H NMR, δ (*J*/Hz)
			C	H	N		
8a	77	130	58.28 58.30	3.59 3.67	5.62 5.67	$C_{12}H_9NO_5$	5.42 (s, 2 H, C(7)H_2); 6.89 (d, 1 H, C(9)H, *J* = 3.5); 7.13—7.21 (m, 1 H, CH_{Ar}); 7.49—7.56 (m, 2 H, CH_{Ar}, C(10)H); 7.64—7.72 (m, 1 H, CH_{Ar}); 7.89 (dd, 1 H, CH_{Ar}, *J* = 8.0, *J* = 1.6); 9.60 (s, 1 H, C(12)H)
8b	83	110	59.72 59.77	4.13 4.24	5.29 5.36	$C_{13}H_{15}NO_5$	2.55 (s, 3 H, C(7)H); 5.35 (s, 2 H, C(8)H); 6.92 (d, 1 H, C(10)H, *J* = 3.5); 7.10 (dd, 1 H, C(5)H_{Ar}, *J* = 9.1, *J* = 2.7); 7.17 (d, 1 H, C(3)H_{Ar}, *J* = 2.7); 7.54 (d, 1 H, C(11)H, *J* = 3.5); 8.06 (d, 1 H, C(6)H_{Ar}, *J* = 9.1); 9.61 (s, 1 H, C(13)H)
9	91	81—81.5	66.02 66.10	5.13 5.20	—	$C_{16}H_{15}ClO_3$	1.34 (t, 3 H, C(9)H_3, *J* = 6.9); 4.12 (q, 2 H, C(8)H_2, *J* = 6.9); 7.27 (d, 1 H, CH_{Ar}, *J* = 8.3); 7.37—7.45, 7.49—7.63 (both m, 3 H each, CH_{Ar}); 9.84 (s, 1 H, C(7)H)
10	86	158	57.29 57.41	5.19 5.30	6.52 6.70	$C_{10}H_{11}NO_4$	3.86 (s, 3 H, C(10)H_3); 4.59 (s, 2 H, C(8)H_2); 7.05 (d, 1 H, CH_{Ar}, *J* = 8.3); 7.39 (br.s, 2 H, NH_2); 7.42 (d, 1 H, CH_{Ar}, *J* = 1.9); 7.53 (dd, 1 H, C(6)H_{Ar}, *J* = 8.3, *J* = 1.9); 9.85 (s, 1 H, C(7)H)
11	93	62	74.22 74.36	5.73 5.82	—	$C_{15}H_{14}O_3$	3.84 (s, 3 H, C(8)H_3); 5.22 (s, 2 H, C(9)H_2); 7.27 (d, 1 H, CH_{Ar}, *J* = 8.2); 7.31—7.49 (m, 6 H, CH_{Ar}); 7.54 (m, 1 H, CH_{Ar}); 9.84 (s, 1 H, C(7)H)
12	94	136—137	53.34 53.45	3.33 3.45	4.65 4.79	$C_{13}H_{10}BrNO_2$	5.37 (s, 2 H, C(8)H); 7.30 (d, 1 H, C(3)H_{Ar}, *J* = 8.6); 7.33—7.39 (m, 1 H, C(11)H_{Py}); 7.63 (d, 1 H, C(13)H_{Py}, *J* = 7.8); 7.76—7.80 (m, 1 H, C(4)H_{Ar}); 7.82 (d, 1 H, C(6)H_{Ar}, *J* = 2.8); 7.86 (td, 1 H, C(12)H_{Py}, *J* = 7.8, *J* = 1.8); 8.56—8.61 (m, 1 H, C(10)H_{Py}); 10.38 (s, 1 H, C(7)HO)

for analogous methylene protons in compounds **8**—**12** (see Table 4).

In conclusion, we developed convenient preparative procedures for the preparation of a wide range of benzaldehydes. The use of potassium carbonate as a base allowed us to regioselectively and in high yield conduct nucleophilic substitution of chlorine in the intermediate 4-alkoxy-3-chloromethylbenzaldehydes with the preservation of the aldehyde function.

Experimental

Reaction progress and purity of aldehydes **2**—**12** were monitored by TLC on Silufol UV-254 plates, eluent chloroform—methanol (8 : 2), visualization under UV light and in iodine vapors. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE III NanoBay spectrometer (300 MHz) in the deuterium stabilization mode, thermostabilization 25 °C, internal standard Me_4Si. Elemental composition was determined on a Eurovector EuroEA 3000 CHNS-analyzer. IR spectra were obtained on a Bruker Vertex 70 IR Fourier-transform spectrometer in KBr pellets (16 scans, resolution 4 cm^{-1}). Mass spectra (EI) were recorded on a GLC-MS spectrometric system based on a Khromatek Crystal 5000.2 gas chromatograph with a Thermo ISQ mass spectrometric detector, a TR-5MS quartz capillary column, carrier gas helium, energy of ionizing electrons 70 eV, temperature of the source of ions 200 °C. Melting points were measured on a standard PTP instrument with certified thermometers.

4-Alkoxy-3-chloromethylbenzaldehydes 2a—c (general procedure). A mixture of 4-alkoxybenzaldehyde (0.10 mol), paraformaldehyde (4.00 g, 0.133 mol), and concentrated hydrochloric acid (100 g, d = 1.19 g cm^{-3}) was stirred for 3 h at 70—80 °C with a simultaneous bubbling of hydrogen chloride (30—40 mL min^{-1}). After cooling, the crystals formed were separated and dried in air. The mother liquors were reused in the next syntheses (the cycles were repeated thrice without considerable changes in the quality of the product). Total yields and physicochemical characteristics of aldehydes **2a**—**c** are given in Table 1.

3-Chloromethyl-4-ethoxybenzaldehyde (2b). MS (EI, 70 eV), m/z (I_{rel} (%)): 200 (30), 198 $[M]^+$ (90), 163 $[M - Cl]^+$ (98), 135 $[M - Cl - C_2H_4]^+$ (100). ^{13}C NMR (DMSO-d_6), δ: 14.39 ($OCH_2\underline{C}H_3$), 41.05 (CH_2Cl), 64.38 ($O\underline{C}H_2CH_3$), 112.31 ($C(5)_{Ar}$), 126.36 ($C(3)_{Ar}$), 129.13 ($C(1)_{Ar}$), 131.40 ($C(6)_{Ar}$), 133.12 ($C(2)_{Ar}$), 161.29 ($C(4)_{Ar}$), 191.12 (CHO). IR (KBr), ν/cm^{-1}: 3041 (C_{Ar}—H), 2979—2740 (C—H), 1683 (C=O), 1597 (C_{Ar}—H), 1473—1392 (CH_2, CH_3), 1268 (C—O—C), 1039 (C—O—C), 809 (C—Cl).

4-Alkoxy-3-hydroxymethylbenzaldehydes 3a—c (general procedure). A mixture of the corresponding chloromethyl derivative **2a**—**c** (0.01 mol) and a 2% aqueous solution of sodium hydrogen carbonate (100 mL) was refluxed for 3—4 h with stirring (TLC monitoring). After cooling of the reaction mixture, the white crystals formed were filtered off and dried in air. Yields and physicochemical characteristics of products **3a**—**c** are given in Table 1.

4-Ethoxy-3-hydroxymethylbenzaldehyde (3b). MS (EI, 70 eV), m/z (I_{rel} (%)): 180 $[M]^+$ (70), 151 $[M - CHO]^+$ (60), 134 $[M - H_2O - C_2H_4]^+$ (84), 106 [PhCHO] (100). ^{13}C NMR (DMSO-d_6), δ: 14.46 ($OCH_2\underline{C}H_3$), 57.47 (CH_2OH), 63.83 ($O\underline{C}H_2CH_3$), 110.98 ($C(5)_{Ar}$), 127.16 ($C(2)_{Ar}$), 129.04 ($C(3)_{Ar}$), 131.21 ($C(6)_{Ar}$), 131.44 ($C(1)_{Ar}$), 160.17 ($C(4)_{Ar}$), 191.57 (CHO). IR (KBr), ν/cm^{-1}: 3399—3205 (OH assoc.), 2985—2724 (C—H), 1681 (C=O), 1602 (C_{Ar}—C), 1492—1436 (CH_3, CH_2), 1260 (C—O—C), 1041 (C—O—C).

3-Aminomethyl-4-methoxybenzaldehydes 4a—k (general procedure). A mixture of 3-chloromethyl-4-methoxybenzaldehyde (1.85 g, 0.010 mol), the corresponding secondary amine (0.011 mol), and potassium carbonate (2.00 g, 0.0145 mol) in ethanol (20 mL) was refluxed for 3—5 h with stirring (TLC monitoring). After evaporation of ethanol, the residue was treated with water, a precipitate formed was filtered off, washed with 40% aqueous ethanol, and dried in air. In the case of aldehyde **4f**, an oil obtained after treatment of the residue with water was dissolved in 4 *M* solution of a mixture of dioxane—HCl and a precipitate of hydrochloride **4f** was filtered off and dried *in vacuo*.

Yields and physicochemical characteristics of aldehydes **4a**—**k** are given in Table 2.

4-Methoxy-3-[(6-oxo-7,11-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4-dien-11-yl)methyl]benzaldehyde (4g). MS (EI, 70 eV), m/z (I_{rel} (%)): 338 $[M]^+$ (20), 149 [3-CHO-6-MeO-Bn]$^+$ (100). ^{13}C NMR (DMSO-d_6), δ: 25.09 (C(20)), 27.54 (C(18)), 34.58 (C(11)), 49.65 (C(17)), 54.35 (C(10)), 55.86 (C(8)), 59.71 (C(9)), 59.78 (C(19)), 103.77 (C(13)), 111.13 ($C(5)_{Ar}$), 115.28 (C(15)), 126.72 ($C(3)_{Ar}$), 128.96 ($C(1)_{Ar}$), 129.07 ($C(2)_{Ar}$), 130.93 ($C(6)_{Ar}$), 138.77 (C(14)), 152.00 (C(12)), 162.05 (C(16)), 162.19 ($C(4)_{Ar}$), 190.92 (CHO). IR (KBr), ν/cm^{-1}: 3057 (C_{Ar}—H), 2944—2710 (C—H), 1685 (C=O of aldehyde), 1644 (C=O of ketone), 1604 (C_{Ar}—C), 1562—1543 (C—N), 1434 (CH_3, CH_2), 1256 (C—O—C), 1023 (C—O—C).

4-Methoxy-3-[(4-nitro-1*H*-pyrazol-1-yl)methyl]benzaldehyde (4i). MS (EI, 70 eV), m/z (I_{rel} (%)): 261 $[M]^+$ (20), 230 $[M - MeO]^+$ (90). ^{13}C NMR (DMSO-d_6), δ: 50.99 (C(9)), 56.31 (OCH_3), 111.53 ($C(5)_{Ar}$), 124.36 ($C(3)_{Ar}$), 129.30 ($C(1)_{Ar}$), 130.15 ($C(2)_{Ar}$), 131.08 (C(12)), 133.09 (C(10)), 134.88 (C(11)), 135.92 ($C(6)_{Ar}$), 161.74 ($C(4)_{Ar}$), 191.25 (CHO). IR (KBr), ν/cm^{-1}: 3136 (C—H pyrazole), 2951—2752 (C—H), 1678 (C=O), 1605 (C=N, C_{Ar}—C), 1501 (C—N=O), 1315 (NO_2), 1268 (C—O—C), 1122 (C—N), 1019 (C—O—C).

3-Aryloxymethyl- (5a—m) and 3-hetarylthiomethyl-4-methoxybenzaldehydes (6a—g) (general procedure). A mixture of 3-chloromethyl-4-methoxybenzaldehyde (**2a**) (1.85 g, 0.01 mol), the corresponding phenol or thiol (0.011 mol), and potassium carbonate (2.00 g, 0.0145 mol) in a mixture of acetonitrile—DMF (20 mL, from 9 : 1 to 8 : 2, v/v) was refluxed for 5—7 h with stirring (TLC monitoring). After evaporation of the solvents, the residue was treated with water, a precipitate formed was filtered off, washed with 40% aqueous ethanol, and dried in air. Yields and physicochemical characteristics of aldehydes **5a**—**m** and **6a**—**g** are given in Table 2.

Isobutyl 4-(5-formyl-2-methoxybenzyloxy)benzoate (5d). MS (EI, 70 eV), m/z (I_{rel} (%)): 342 $[M]^+$ (2), 149 [3-CHO-6-MeO-Bn]$^+$ (100). ^{13}C NMR (DMSO-d_6), δ: 18.92 (C(17), C(17′)), 27.41 (C(16)), 56.22 (C(8)), 64.48 (C(9)), 70.06 (C(15)), 111.37 ($C(5)_{Ar}$), 114.72 (C(11), C(11′)), 122.38 (C(13)), 125.14 ($C(3)_{Ar}$), 129.30 ($C(1)_{Ar}$), 129.50 ($C(2)_{Ar}$), 131.21 (C(12), C(12′)), 132.65 ($C(6)_{Ar}$), 161.73 ($C(4)_{Ar}$), 162.10 (C(10)), 165.30 (C(14)), 191.33 (CHO). IR (KBr), ν/cm^{-1}: 2955—2710 (C—H), 1709 (C=O ether), 1689 (C=O), 1606 (C_{Ar}—H), 1471—1441 (CH_2, CH_3), 1275 (C—O), 1176 ($CH(CH_3)_2$), 1038 (C—O—C).

3-(2-Cyclohexylphenoxymethyl)-4-methoxybenzaldehyde (5l). MS (EI, 70 eV), m/z (I_{rel} (%)): 324 $[M]^+$ (2), 149 [3-CHO-6-

MeO-Bn]$^+$ (100). IR (KBr), ν/cm^{-1}: 3067 (C_{Ar}—H), 2926—2730 (C—H), 1690 (C=O), 1603 (C_{Ar}—C), 1498—1453 (CH_3, CH_2), 1255 (C—O—C), 1024 (C—O—C).

3-[(1,3-Benzoxazol-2-yl)thiomethyl]-4-methoxybenzaldehyde (6c). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 299 [M]$^+$ (10), 149 [3-CHO-6-MeO-Bn]$^+$ (100). ^{13}C NMR (DMSO-d_6), δ: 30.74 (C(9)), 56.38 (C(8)), 110.18 (C(12)), 111.48 (C(5)$_{Ar}$), 118.31 (C(15)), 124.35 (C(14)), 124.64 (C(13)), 125.15 (C(3)$_{Ar}$), 129.20 (C(1)$_{Ar}$), 130.82 (C(2)$_{Ar}$), 132.71 (C(6)$_{Ar}$), 141.19 (C(14)), 151.28 (C(11)), 162.05 (C(4)$_{Ar}$), 163.85 (C(10)), 191.22 (CHO). IR (KBr), ν/cm^{-1}: 3030 (C_{Ar}—H), 2972—2759 (C—H), 1686 (C=O), 1600 (C=N), 1502 (oxazole), 1452 (CH_3, CH_2), 1399 (oxazole), 1262 (C—O—C), 1020 (C—O—C), 739 (oxazole).

3-[(5-Methyl-1,3,4-oxadiazol-2-yl)thiomethyl]-4-methoxybenzaldehyde (6g). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 280 [M]$^+$ (20), 206 (30), 149 [3-CHO-6-MeO-Bn]$^+$ (100). ^{13}C NMR (DMSO-d_6), δ: 15.20 (C(12)), 32.45 (C(9)), 56.31 (C(8)), 111.47 (C(5)$_{Ar}$), 125.28 (C(3)$_{Ar}$), 129.17 (C(1)$_{Ar}$), 130.76 (C(2)$_{Ar}$), 132.67 (C(6)$_{Ar}$), 162.05 (C(11)), 164.35 (C(4)), 165.79 (C(10)), 191.22 (CHO). IR (KBr), ν/cm^{-1}: 3035 (C_{Ar}—H), 2942—2710 (C—H), 1690 (C=O), 1598 (C_{Ar}—C), 1496—1469 (CH_2, CH_3), 1380 (S—CH_2), 1261 (C—O—C), 1019 (C—O—C), 822 (thiadiazole).

5-Aryloxymethylfurfurals 8a,b (general procedure). A mixture of 5-chloromethylfurfural[36] (0.010 mol), the corresponding phenol (0.011 mol), and potassium carbonate (2.00 g, 0.0145 mol) in a mixture of acetonitrile—DMF (20 mL, 9 : 1, v/v) was refluxed for 5—6 h with stirring (TLC monitoring). After evaporation of the solvents, the residue was treated with water, a precipitate formed was filtered off, washed with 30% aqueous methanol, and dried in air. Yields and physicochemical characteristics of aldehydes **8a,b** are given in Table 4.

5-[(3-Methyl-4-nitrophenoxy)methyl]-2-furancarbaldehyde (8b). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 261 [M]$^+$ (2), 109 [5-CHO-furyl-2-CH_2]$^+$ (100). ^{13}C NMR (DMSO-d_6), δ: 20.61 (C(7)), 62.11 (C(8)), 113.06 (C(3)$_{Ar}$), 113.24 (C(10)), 118.22 (C(5)$_{Ar}$), 123.67 (C(11)), 127.26 (C(6)$_{Ar}$), 136.39 (C(2)$_{Ar}$), 142.23 (C(1)$_{Ar}$), 152.58 (C(12)), 155.18 (C(9)), 161.05 (C(4)$_{Ar}$), 178.54 (CHO). IR (KBr), ν/cm^{-1}: 3112 (C—H of furan), 2869 (C—H), 1678 (C=O), 1606—1588 (C=C), 1504 (C—N=O), 1490—1459 (CH_3, CH_2), 1333 (NO_2), 1249 (C—O—C), 1192—1074 (furan), 1025 (C—O—C).

Aldehydes 9—12 (general procedure). A mixture of the corresponding halide (0.010 mol), hydroxybenzaldehyde (0.011 mol), and potassium carbonate (2.00 g, 0.0145 mol) in a mixture of acetonitrile—DMF (20 mL, 8 : 2, v/v) was refluxed for 5—7 h with stirring (TLC monitoring). After evaporation of the solvents, the residue was treated with water, a precipitate formed was filtered off, washed with 30% aqueous methanol, and dried in air. Yields and physicochemical characteristics of aldehydes **9—12** are given in Table 4.

4-(2-Chlorobenzyloxy)-3-ethoxybenzaldehyde (9). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 290 [M]$^+$ (6), 127 (30), 125 [2-Cl-Bn]$^+$ (100). ^{13}C NMR (DMSO-d_6), δ: 14.54 (C(9)), 64.00 (C(10)), 67.56 (C(8)), 111.33 (C(2)$_{Ar}$), 113.11 (C(5)$_{Ar}$), 125.58 (C(6)$_{Ar}$), 127.41 (C(15)$_{Ar}$), 129.41 (C(13)$_{Ar}$), 129.89 (C(16)$_{Ar}$), 129.97 (C(14)$_{Ar}$), 130.13 (C(1)$_{Ar}$), 132.51 (C(12)$_{Ar}$), 133.81 (C(11)), 148.62 (C(3)$_{Ar}$), 153.04 (C(4)$_{Ar}$), 191.41 (CHO). IR (KBr), ν/cm^{-1}: 3073 (C_{Ar}—H), 2981—2707 (C—H), 1692 (C=O), 1588 (C_{Ar}—C), 1476—1430 (CH_3, CH_2), 1266 (C—O—C), 1124 (C—Cl), 1039 (C—O—C).

2-(4-Formyl-2-methoxyphenoxy)acetamide (10). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 209 [M]$^+$ (100), 165 [M – Ph]$^+$ (76), 151 [M – Bn]$^+$ (82). ^{13}C NMR (DMSO-d_6), δ: 55.61 (C(10)), 67.22 (C(8)), 109.99 (C(2)$_{Ar}$), 112.76 (C(5)$_{Ar}$), 125.59 (C(6)$_{Ar}$), 130.21 (C(1)$_{Ar}$), 149.32 (C(3)$_{Ar}$), 152.69 (C(4)$_{Ar}$), 169.15 (C(9)), 191.40 (CHO). IR (KBr), ν/cm^{-1}: 3458 (NH free), 3167 (NH bonded), 3078—3010 (C_{Ar}—H), 2917—2723 (C—H), 1717 (C=O of amide), 1682 (C=O), 1587—1508 (NH), 1470—1426 (CH_3, CH_2), 1264 (C—O—C), 1023 (C—O—C).

4-Benzyloxy-3-methoxybenzaldehyde (11). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 242 [M]$^+$ (30), 91 [Bn]$^+$ (100). ^{13}C NMR (DMSO-d_6), δ: 55.54 (C(8)), 70.00 (C(9)), 109.72 (C(13)$_{Ar}$), 112.59 (C(5)$_{Ar}$), 125.86 (C(2)$_{Ar}$), 127.95 (C(11)$_{Ar}$, C(11′)$_{Ar}$), 128.08 (C(6)$_{Ar}$), 128.48 (C(12)$_{Ar}$, C(12′)$_{Ar}$), 129.80 (C(1)$_{Ar}$), 136.29 (C(10)$_{Ar}$), 149.39 (C(3)$_{Ar}$), 153.15 (C(4)$_{Ar}$), 191.33 (CHO). IR (KBr), ν/cm^{-1}: 3060—3012 (C_{Ar}—H), 2948—2761 (C—H), 1676 (C=O), 1596 (C_{Ar}—C), 1465—1425 (CH_3, CH_2), 1261 (C—O—C), 1031 (C—O—C).

5-Benzyloxy-2-bromopyridine-4-carbaldehyde (12). MS (EI, 70 eV), *m/z* (I_{rel} (%)): 293, 291 [M]$^+$ (2), 264 (20), 262 [M – CHO]$^+$ (20), 92 [2-Py-CH_2]$^+$ (100). ^{13}C NMR (DMSO-d_6), δ: 71.08 (C(8)), 112.87 (C(5)$_{Ar}$), 116.84 (C(3)$_{Ar}$), 121.68 (C(13)$_{Ar}$), 123.15 (C(11)$_{Ar}$), 126.04 (C(1)$_{Ar}$), 130.15 (C(6)$_{Ar}$), 137.14 (C(12)$_{Ar}$), 138.36 (C(4)$_{Ar}$), 149.14 (C(10)$_{Ar}$), 155.73 (C(9)$_{Ar}$), 159.36 (C(2)$_{Ar}$), 188.12 (CHO). IR (KBr), ν/cm^{-1}: 3075—3048 (C_{Ar}—H), 2879 (C—H), 1681 (C=O), 1590 (C_{Ar}—H), 1482—1431 (CH_2, CH_3), 1287 (C—O—C), 1030 (C—O—C, C—Br).

The authors are grateful to Prof. M. A. Yurovskaya for the help in the discussion of the work results and compilation of this paper.

This work was financially supported by the Ministry of Education and Science of the Russian Federation (Agreement on Grant No. 14.576.21.0044 from 05.08.14, the Federal Target Program "Research and Development on Priority Directions of Scientific and Technological Complex of Russia for the years 2014—2020", a unique identification RFMEFI57614X0044).

References

1. P. Rothemund, *J. Am. Chem. Soc.*, 1935, **57**, 2010.
2. R. G. Little, *J. Heterocycl. Chem.*, 1981, **18**, 833.
3. R. De Paula, M. A. F. Faustino, D. C. Pinto, M. G. Neves, J. A. S. Cavaleiro, *J. Heterocycl. Chem.*, 2008, **45**, 453.
4. L. Maqueira, A. Iribarren, A. C. Valdés, C. P. de Melo, C. G. dos Santos, *J. Porphyrins Phthalocyanines*, 2012, **16**, 267.
5. W. M. Whaley, T. R. Govindachari, *Org. React.*, 1951, **6**, 151.
6. A. Couture, E. Deniau, P. Grandclaudon, S. Lebrun, *Tetrahedron: Asymmetry*, 2003, **14**, 1309.
7. J. M. Tinsley, *Pictet—Spengler Isoquinoline Synthesis*, in *Name Reactions in Heterocyclic Chemistry*, Eds J. J. Li, E. J. Corey, Wiley and Sons, Hoboken, 2005, 469.
8. D. J. Mergott, S. J. Zuend, E. N. Jacobsen, *Org. Lett.*, 2008, **10**, 745.
9. C. N. Eid, J. Shim, J. Bikker, M. Lin, *J. Org. Chem.*, 2009, **74**, 423.
10. E. Awuah, A. Capretta, *J. Org. Chem.*, 2010, **75**, 5627.
11. L.-Y. Zeng, C. Cai, *J. Heterocycl. Chem.*, 2010, **47**, 1035.
12. A. Strakovsk, F. Avotins, M. Petrova, *Rigas Tehniskas Universitates Zinatniskie Raksti, Serija 1: Materialzinatne un Lietiska Kimija*, 2003, **6**, 122.

13. X.-S. Wang, K. Yang, J. Zhou, S.-J. Tu, *J. Comb. Chem.*, 2010, **12**, 417.
14. D. Shi, C. Shi, J. Wang, L. Rong, Q. Zhuang, X. Wang, *J. Heterocycl. Chem.*, 2005, **42**, 173.
15. A. Gharib, B. R. H. Khorasani, M. Jahangir, M. Roshani, R. Safaee, *Hindawi Publishing Corporation Organic Chemistry International*, 2013, Article ID 848237.
16. K. Ramesh, K. Karnakar, G. Satish, B. S. P. Anil Kumar, Y. V. D. Nageswar, *Tetrahedron Lett.*, 2012, **53**, 69.
17. S. B. Bharate, N. Mupparapu, S. Manda, J. B. Bharate, R. Mudududdla, R. R. Yadav, R. A. Vishwakarma, *ARKIVOC*, 2012, **8**, 308.
18. P. Biginelli, *Ber.*, 1891, **24**, 1317; 2962.
19. H. E. Zaugg, W. B. Martin, *Org. React.*, 1965, **14**, 88.
20. J. Lu, H. Ma, *Synlett*, 2000, 63.
21. B. R. P. Kumar, G. Sankar, R. B. Nasir Baig, S. Chandrashekaran, *Eur. J. Med. Chem.*, 2009, **44**, 4192.
22. A. Hantzsch, *Ann.*, 1882, **215**, 72.
23. P. Galatsis, *Hantzsch Dihydro-Pyridine Synthesis*, in *Name Reactions in Heterocyclic Chemistry*, Eds J. J. Li, E. J. Corey, Wiley and Sons, Hoboken, 2005, 304.
24. R. Gupta, R. Gupta, S. Paul, A. Loupy, *Synthesis*, 2007, **18**, 2835.
25. J. J. Vanden Eynde, A. Mayence, *Molecules*, 2003, **8**, 381.
26. L. N. Ferguson, *Chem. Rev.*, 1946, **38**, 227.
27. W. Kantlehner, *Eur. J. Org. Chem.*, 2003, 2530.
28. D. Grobelny, S. Witek, *J. Prakt. Chem.*, 1980, **322**, 536.
29. Z.-L. Chen, W.-Q. Wan, J.-R. Chen, F. Zhao, D.-Y. Xu, *Heterocycles*, 1998, **48**, 1739.
30. A. McKillop, F. A. Madjdabadi, D. A. Long, *Tetrahedron Lett.*, 1983, **24**, 1933.
31. R. S. Vardanyan, *Sintez osnovnykh lekarstvennykh sredstv* [*Synthesis of Principal Medicines*], MIA Publ., Moscow, 2004, 845 (in Russian).
32. N. M. Morlyan, D. S. Khachatryan, Sh. O. Badanyan, *Arm. Khim. Zh.* [*Arm. Chem. J.*], 1978, **31**(2), 866 (in Russian).
33. D. S. Khachatryan, N. M. Morlyan, R. G. Mirzoyan, Sh. O. Badanyan, *Arm. Khim. Zh.* [*Arm. Chem. J.*], 1981, **34**(8), 672 (in Russian).
34. D. S. Khachatryan, A. A. Vardapetyan, G. A. Panosyan, R. G. Mirzoyan, N. M. Morlyan, *Zh. Org. Khim.*, 1990, **26**, 2092 [*J. Org. Chem. USSR (Engl. Transl.)*, 1990, **26**].
35. D. S. Khachatryan, A. A. Vardapetyan, N. M. Morlyan, A. L. Razinov, K. R. Matevosyan, *Russ. Chem. Bull.* (*Int. Ed.*), 2015,**64**, 385 [*Izv. Akad. Nauk*, *Ser. Khim.*, 2015, 385].
36. K. Sanda, L. Rigal, M. Delmas, A. Gaset, *Synthesis*, 1992, 541.

Received September 8, 2014;
in revised form October 30, 2014