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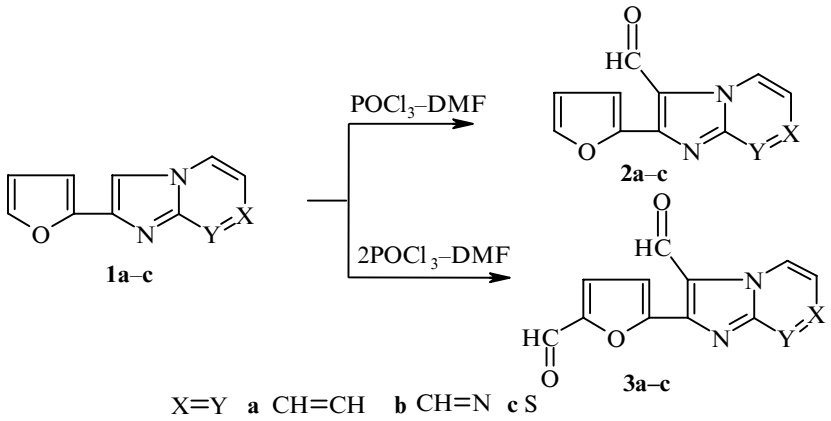
FORMYLATION OF FURYL-SUBSTITUTED IMIDAZO[1,2-*a*]PYRIDINE, IMIDAZO[1,2-*a*]PYRIMIDINE AND IMIDAZO[2,1-*b*]THIAZOLE

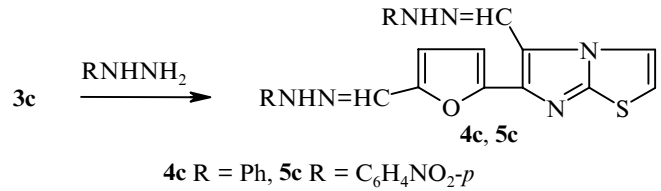
N. O. Saldabol, J. Popelis, and V. A. Slavinskaya

Vilsmeier formylation of 2-(2-furyl)-substituted imidazo[1,2-a]pyridine and imidazo[1,2-a]pyrimidine, and also 6-(2-furyl)imidazo[2,1-b]thiazole with 1 mole of reagent occurs at the free position of the imidazole ring, while with an excess of the reagent it also occurs at the position 5 of the furyl group.

Keywords: furyl-substituted imidazo[1,2]pyridine, imidazo[1,2-*a*]pyrimidine and imidazo[2,1-*b*]-thiazole, formylation.

2-Alkyl- and 2-arylfurans undergo Vilsmeier formylation at the position 5 [1]. The reaction is directed towards the same position of the furan ring in the case of 2-(2-furyl)-1-methylimidazole [2]. 6-Bromoimidazo[2,1-*b*]thiazole is formylated at the position 5 [3]. We have studied formylation of 2-(2'-furyl)-substituted imidazo[1,2-*a*]pyridine (**1a**) and imidazo[1,2-*a*]pyrimidine (**1b**), and also 6-(2'-furyl)imidazo[2,1-*b*]-thiazole (**1c**) using this method.





4c R = Ph, **5c** R = $C_6H_4NO_2$-*p*

Latvian Institute of Organic Synthesis, Riga LV-1006; e-mail: elmira@osi.lv. Translated from Khimiya Geterotsiklichesikh Soedinenii, No. 8, pp. 1112-1115, August, 2001. Original article submitted March 24, 2000.

The reaction occurred to be highly selective. On treatment with 1 mole of phosphorus oxychloride in dimethylformamide, only the derivatives monosubstituted at the imidazole ring (3-formyl-substituted compounds **2a,b** and 5-formyl-substituted **2c** respectively) are obtained, while on treatment with 2 moles of the reagent, the formyl group is also introduced at the position 5' of the furan ring. We did not observe differences in formylation of furylimidazopyridine and furylimidazopyrimidine as seen in the case of nitration, when the first compound upon treatment with 1 mole of nitric acid in concentrated H_2SO_4 was converted to the 3,5'-dinitro-substituted derivative [4], and the second compound was converted to the 5'-nitro-substituted derivative, while further nitration of it at the position 3 proved to be quite hindered [5].

The structure of the formylation products was confirmed by ^{1}H NMR and IR spectra. The absorption bands of the aldehyde groups bonded to the imidazole ring are found in the 1645-1620 cm^{-1} region, while the absorption bands of the 5'-formyl group on the furan ring are found in the region of 1675-1668 cm^{-1}. We have prepared bisphenylhydrazone and bis-4-nitrophenylhydrazone of 5-formyl-6-(5'-formyl-2'-furyl)imidazo[2,1-*b*]-thiazole (**4c, 5c**).

EXPERIMENTAL

The composition and purity of the products were monitored using TLC on Silufol UV-254 plates in the systems benzene–dioxane–acetic acid, 20:4:1, benzene–ethylacetate, 1:1. The ^{1}H NMR spectra were recorded on a Perkin-Elmer R-12A (60 MHz) apparatus in trifluoroacetic acid (internal standard sodium salt of 3-(trimethylsilyl)propanesulfonic acid) or in hexadeuteroacetone (internal standard HDMS). The IR spectra in vaseline oil were obtained on an UR-20 spectrometer. The melting points were determined on a Boetius hot stage with microscope attachment and were uncorrected.

The characteristics of the synthesized compounds are presented in Tables 1 and 2.

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	IR spectrum, cm^{-1} (ν CHO)	Yield, %
		C	H	N(S)			
2a	$C_{12}H_8N_2O_2$	68.22 / 67.92	4.01 / 3.80	13.42 / 13.20	153-154*	1645	80
2b	$C_{11}H_7N_3O_2$	61.73 / 61.97	3.10 / 3.31	19.80 / 19.71	218-219	1631	72
2c	$C_{10}H_6N_2O_2S$	54.73 / 55.04	2.70 / 2.77	12.91 / 13.11	177-178*	1645	94
3a	$C_{13}H_8N_2O_3$	64.55 / 64.30	3.44 / 3.34	11.60 / 11.68	248-249*[2]	1671, 1628	77
3b	$C_{12}H_7N_3O_3$	59.60 / 59.75	2.89 / 2.93	17.13 / 17.42	265-268*[2]	1668, 1621	72
3c	$C_{11}H_6N_2O_3S$	53.57 / 53.65	2.61 / 2.62	11.19 / 11.38	220-221*	1675, 1638	85
4c	$C_{23}H_{18}N_6OS$	65.05 / 64.77	4.49 / 4.35	(7.29) / (7.52)	110-111*	—	91
5c	$C_{23}H_{16}N_8O_5S$	53.13 / 53.46	3.46 / 3.12	(5.97) / (6.21)	270-272*	—	95

* From ethanol.

*[2] From an ethanol–DMF mixture.

TABLE 2. ^{1}H NMR Spectral Characteristics of Formyl-substituted Compounds **2a-c** and **3a-c**

Com-pound	Solvent*	Chemical shifts, δ, ppm							
		5-H (3-H)*^{2}	6-H (2-H)*^{2}	7-H	8-H	3'-H	4'-H	5'-H	CHO
2a	A	9.95 dt	7.79 td	8.32 td	8.10 td	7.86 dd	6.86 q	7.95 dd	10.65 s
2b	A	10.27 dd	7.89 dd	9.26 dd	—	7.76 dd	6.88 q	7.98 dd	10.68 s
2c	B	(8.12 d)	(7.62 d)	—	—	6.90 dd	6.75 q	7.78 dd	10.27 s
3a	A	10.08 dt		8.1-8.7 m		7.93 s	7.93 s	—	9.90 s; 10.83 s
3b	A	10.25 dd	7.91 dd	9.30 dd	—	7.88 d	7.80 d	—	9.82 s; 10.74 s
3c	B	(8.21 d)	(7.70 d)	—	—	7.27 d	7.53 d	—	9.78 s; 10.37 s

Com-pound	Solvent*	Spin-spin coupling constants, *J*, Hz								
		5,6 (2,3)*^{2}	5,7	5,8	6,7	6,8	7,8	3',4'	3',5'	4',5'
2a	A	7.0	1.0	1.0	6.8	1.7	9.0	3.8	0.6	1.8
2b	A	7.1	1.5	—	4.0	—	—	3.7	0.6	1.7
2c	B	(4.5)	—	—	—	—	—	3.5	0.7	1.8
3a	A	6.7	1.0	1.0	—	—	—	0	—	—
3b	A	6.5	1.6	—	4.5	—	—	3.9	—	—
3c	B	(4.5)	—	—	—	—	—	3.5	—	—

* A – CF_3COOH; B – acetone-d_6.

*^{2} Values for the protons of imidazo[2,1-*b*]thiazole.

Monoformyl-substituted Derivatives (2a-c). Freshly distilled $POCl_3$ (0.92 ml, 10 mmol) was added to DMF (10 ml) cooled down to 0-5°C. Solution of compound **1a** (or **1b,c** respectively) (10 mmol) in DMF (15 ml), cooled down to 0-3°C, was added to the complex obtained. The mixture was held for 2 h on a steam bath, poured on ice (50 g), neutralized with an aqueous solution of sodium acetate to pH 6-7; the compound **2a** (or **2b,c**) was filtered off and washed with water. The product was purified by crystallization from ethanol or from its mixture with DMF.

Diformyl-substituted Derivatives (3a-c). Obtained similarly, from **1a-c** with doubled amount of $POCl_3$.

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