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DIPYRROLO[1,2-*a*;2',1'-*c*]PYRAZINES. 7*. ELECTROPHILIC SUBSTITUTION OF DIPYRROLO[1,2-*a*;2',1'-*c*]PYRAZINES AND 5,6-DIHYDRODIPYRROLO[1,2-*a*;2',1'-*c*]PYRAZINES *via* FORMYLATION OF DIPYRROLO[1,2-*a*;2',1'-*c*]PYRAZINES

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A series of previously unreported aldehydes has been prepared by the formylation reaction of dipyrrolo[1,2-a;2',1'-c]pyrazines and their 5,6-dihydro analogs by DMF and phosphorus oxychloride.

Keywords: 5,6-dihydrodipyrrolo[1,2-*a*;2',1'-*c*]pyrazines, dipyrrolo[1,2-*a*;2',1'-*c*]pyrazines, formylation.

Dipyrrolo[1,2-*a*;2',1'-*c*]pyrazines readily take part in electrophilic substitution reactions such as, for example, nitration, acylation, and phosphorylation [2].

We have studied the reactivity of the dipyrrolopyrazines **1a,b** and their 5,6-dihydro analogs **1c,d** under Vilsmeier formylation reaction conditions using phosphorus oxychloride and DMF. It is known that N-methylpyrrole and an excess of the reagent under these conditions form monoformyl derivatives at the α-position of the pyrrole ring [3]. In the case of the dipyrrolopyrazines the formylation can take place at one or at two of the pyrrole rings in the molecule, moreover the result of the reaction depends on the ratio of substrate to reagent.

With the formylation of the dipyrrolopyrazines **1a,c** which have both pyrrole ring α-positions free an excess of the reagent gave, as expected, the products of 3,8-diformylation – 3,8-diformyl-2-methyldipyrrolo-[1,2-*a*;2',1'-*c*]pyrazine (**4a**) and 3,8-diformyl-2-methyl-5,6-dihydrodipyrrolo[1,2-*a*;2',1'-*c*]pyrazine (**4c**). The structure of the reaction products was confirmed using IR, NMR, and mass spectroscopic data.

According to data in [2], when carrying out the electrophilic substitution reaction on the **1a,c** models, the attack of the electrophile occurs principally at the $C_{(3)}$ atom of the pyrrole ring which contains the methyl substituent. Analogously, in the case of the formylation of the dipyrrolopyrazines **1a,c** with an equimolar ratio of substrate to reagent a mixture of products is found containing the 3,8-diformyl derivatives **4a,c** and the 3-monoformyl derivatives **2a,c** together with trace amounts of the 8-monoformylated derivatives **3a,c**. These products were identified from the ^{1}H NMR spectra of the corresponding mixtures.

* For Communication 6 see [1].

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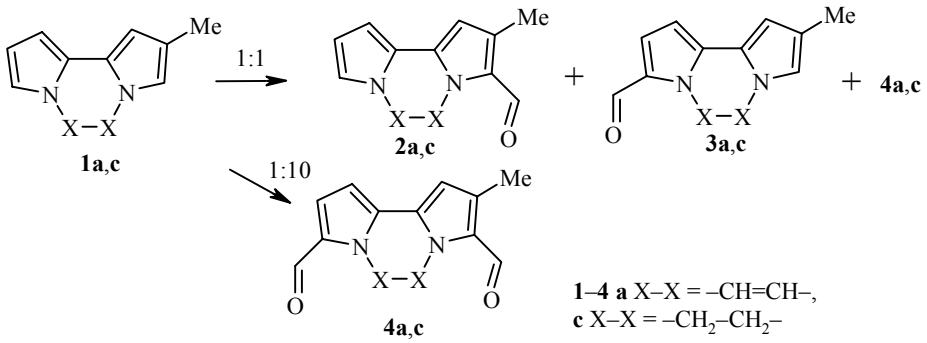
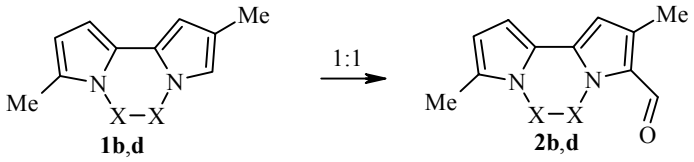
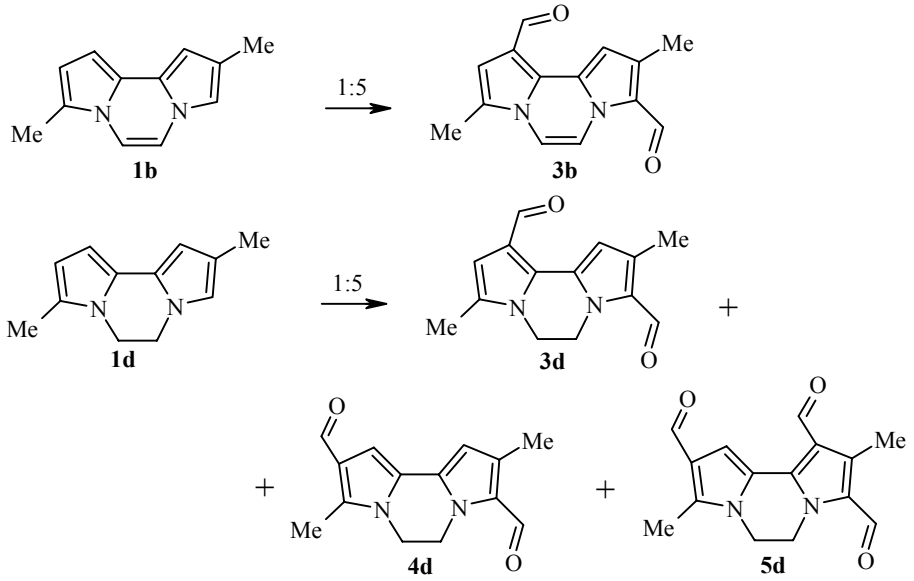


With the systems **1b,d** in which only one pyrrole ring α-position is free the most likely attack by the electrophile is, in fact, at this position. It was actually found that a equimolar amount of substrate to reagent for compound **1b,d** gives rise to the monoformylation products at position 3 of the given heterocyclic system 3-formyl-2,8-dimethyldipyrrolo[1,2-*a*;2',1'-*c*]pyrazine (**2b**) and 3-formyl-2,8-dimethyl-5,6-dihydrodipyrrolo-[1,2-*a*;2',1'-*c*]pyrazine (**2d**) respectively, moreover when the formylation of the dipyrrolopyrazine **1b** is carried out at lower temperature (-5°C) the yield of compound **2b** increases from 32 to 50%.



An excess of the reagent leads to formation of the diformyl derivatives and, in the case of the 2,8-dimethyldipyrrolo[1,2-*a*;2',1'-*c*]pyrazine, the reaction with a five fold excess of the reagent gives solely the 3,10-diformyl-2,8-dimethyldipyrrolo[1,2-*a*;2',1'-*c*]pyrazine.



Under the same conditions for 2,8-dimethyl-5,6-dihydrodipyrrolo[1,2-*a*;2',1'-*c*]pyrazine a mixture is formed of two diformyl and of one triformyl derivatives 3,9-diformyl-2,8-dimethyl-5,6-dihydrodipyrrolo-[1,2-*a*;2',1'-*c*]pyrazine (47%), 3,10-diformyl-2,8-dimethyl-5,6-dihydrodipyrrolo[1,2-*a*;2',1'-*c*]pyrazine (44%),

TABLE 1. Properties of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	*m/z* (I_{rel}, %)	Yield*, %
		C	N	H			
2b	$C_{13}H_{12}N_2O$	72.65 / 73.57	13.34 / 13.20	5.92 / 5.70	240 (dec.)	M^+ 212 (100), 211 (68), 184 (8), 183 (29), 181 (7), 169 (6), 168 (8), 91 (12), 77 (6), 63 (6)	68
2d	$C_{13}H_{14}N_2O$	72.33 / 72.87	13.64 / 13.07	6.59 / 6.59	280 (dec.)	M^+ 214 (100), 213 (76), 199 (7), 185 (19), 183 (6), 170 (8), 169 (6), 92 (7), 77 (7), 63 (5)	50
3b	$C_{14}H_{12}N_2O_2$	69.87 / 69.99	10.92 / 11.66	4.93 / 5.03	260 (dec.)	M^+ 240 (100), 239 (35), 211 (14), 184 (27), 183 (48), 182 (14), 142 (17), 91 (12), 63 (14)	60
3d	$C_{14}H_{14}N_2O_2$					M^+ 242 (100), 241 (45), 214 (13), 213 (23), 186 (27), 185 (32), 170 (13), 77 (13), 63 (13)	44
4a	$C_{13}H_{10}N_2O_2$	68.73 / 69.02	12.18 / 12.38	4.49 / 4.46	195-197	M^+ 226 (100), 225 (33), 198 (11), 197 (26), 170 (6), 169 (15), 168 (9), 115 (8), 63 (6)	69
4c	$C_{13}H_{12}N_2O_2$	68.54 / 68.41	12.17 / 12.27	5.43 / 5.30	162-164	M^+ 228 (100), 227 (71), 200 (7), 199 (14), 171 (7), 169 (8), 156 (6), 114 (6), 69 (6)	58
4d	$C_{14}H_{14}N_2O_2$					M^+ 242 (100), 241 (51), 213 (16), 186 (10), 185 (13), 170 (6), 121 (5), 120 (6), 77 (5)	47
5d	$C_{15}H_{14}N_2O_3$					M^+ 270 (100), 242 (49), 241 (32), 214 (24), 213 (37), 186 (15), 185 (24), 170 (13), 77 (14)	25

* Optimal yields are given for the monoformyl dipyrrolopyrazines at a substrate to reagent ratio of 1:1 and a ratio of 1:5 for the di- and triformyldipyrrolopyrazines.

TABLE 2. ^{1}H NMR Spectra of Compounds **2-5**

Com-pound	Chemical shift, δ, ppm, spin-spin coupling (*J*, Hz)							
	Pyrrole ring protons and substituents						Pyrazine ring protons	
	H (1) (1H)	CH_3 (2) (3H, br. s)	CHO (3) (1H)	CH_3(CHO) (8)	H(CHO) (9) (1H)	H(CHO) (10) (1H)	H(5)	H (6)
2b	6.39 (br. s)	2.50	9.72 (s)	2.46 (1H, br. s)	6.69 (d, $J_{9,10}$ = 3.7)	6.43 (dd, $J_{10,9}$ = 3.7, $J_{10,8}$ = 0.7)	8.72 (1H, d, $J_{5,6}$ = 6.3)	7.15 (1H, d, $J_{6,5}$ = 6.3)
2d	6.15 (d, J_{1,CH_3} = 0.7)	2.38	9.59 (s)	2.32 (3H, d, $J_{CH_3,H}$ = 0.8)	6.00 (d, $J_{9,10}$ = 3.5)	6.39 (dd, $J_{10,9}$ = 3.5, $J_{10,8}$ = 0.7)	4.81 (2H, m)	4.08 (2H, m)
3b	6.08 (br. s)	2.50	9.82 (s)	2.41 (3H, d, $J_{CH_3,H}$ = 0.5)	8.93 (d, *J* = 4.2)	10.00 (s)	7.40 (1H, br. s)	7.12 (1H, d, *J* = 6.1)
3d	6.43 (d, *J* = 1.0)	2.39	9.70 (s)	2.28 (3H, d, *J* = 1.0)	6.89 (s)	9.96 (s)	4.81 (2H, m)	4.07 (2H, m)
4a	6.60 (br. s)	2.54	9.72 (d, *J* = 1.3)	9.86 (1H, d, *J* = 1.3)	7.30 (dd, *J* = 4.2, $J_{CH_3,H}$ = 0.9)	6.76 (d, *J* = 4.4)	8.79 (1H, d, $J_{5,6}$ = 6.4)	8.69 (1H, d, $J_{6,5}$ = 6.3)
4c	6.30 (d, *J* = 0.9)	2.32	9.49 (d, *J* = 0.9)	9.67 (1H, d, *J* = 0.9)	6.91 (dd, *J* = 4.2, $J_{CH_3,H}$ = 0.9)	6.46 (dd, *J* = 4.2, $J_{CH_3,H}$ = 0.9)	4.72 (4H, m)	
4d	6.21 (s)	2.57	9.64 (s)	2.36 (3H, br. s)	9.87 (s)	6.81 (s)	4.81 (2H, t, *J* = 5.8)	4.12 (2H, t, *J* = 6.1)
5d	9.89 (s)	2.63	9.81 (s)	2.62 (3H, br. s)	10.15 (s)	7.72 (s)	4.87 (2H, m)	4.17 (2H, m)

and 1,3,9-triformyl-2,8-dimethyl-5,6-dihydrodipyrrolo[1,2-*a*;2',1'-*c*]pyrazine (6%). An increase in the excess of the reagent causes a change in the ratio of reaction products to 6, 19, and 25% respectively. Evidently, under these reaction conditions, there occurs a further formylation of the 3,9-diformyl derivative at position 1 while the 3,10-diformyl derivative does not take part in a subsequent reaction and this may be due to electronic factors.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian VXR-400 (400 MHz) spectrometer using $CDCl_3$ at 28°C with TMS internal standard. Mass spectra were recorded on a Kratos MS-90 instrument with an ionization energy of 70 eV. Monitoring of the course of the reaction was carried out using TLC on Silufol UV-254 plates.

The physicochemical and spectroscopic properties of the compounds studied are given in Tables 1 and 2.

3-Formyl-2-methyl-, 3-formyl-2-methyl-5,6-dihydro-, 8-formyl-2-methyl-, 8-formyl-2-methyl-5,6-dihydro-, 3,8-diformyl-2-methyl-, 3,8-diformyl-2-methyl-5,6-dihydro-, 3-formyl-2,8-dimethyl-, 3-formyl-2,8-dimethyl-5,6-dihydro-, 3,10-diformyl-2,8-dimethyl-, 3,9-diformyl-2,8-dimethyl-5,6-dihydro-, 3,10-diformyl-2,8-dimethyl-5,6-dihydro-, and 1,3,9-triformyl-2,8-dimethyl-5,6-dihydrodipyrrolo[1,2-*a*;2',1'-*c*]pyrazines were synthesized by the general method.

General Formylation Method. Freshly distilled phosphorus oxychloride was added dropwise to absolute DMF with stirring and cooling (0-5°C) and the mixture was stirred at this temperature for 0.5 h. A solution of the dipyrrolopyrazine in the minimum amount of DMF was then added dropwise. The reaction mixture was heated at 35°C for 0.5-1 h and then poured into crushed ice. The product was treated with sodium hydroxide solution to pH 10. The precipitated product was filtered off and recrystallized from heptane.

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