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FORMYLATION OF PYRROLO-[1,2-*a*]PYRAZINES

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The formylation of pyrrolo[1,2-a]pyrazines containing alkyl, aryl, or hetaryl substituents in positions 1 and 6 of the heterocycle has been studied. It has been shown that formylation of 1-phenyl- and 1-(2 thienyl)pyrrolo[1,2-a]pyrazine occurs selectively at the α-position of the pyrrole ring. In all of the remaining examples the reaction course depends on substituent, reagent ratio, and reaction time.

Keywords: pyrrolo[1,2-*a*]pyrazine, formylation, electrophilic substitution, Vilsmeier-Haack reaction.

The broad spectrum of biological activity of heteroaromatic polycyclic systems with a common bridging nitrogen atom and containing a pyrrole ring is the basis for the continuing interest in the synthesis of this class of compounds. One such structure is the aromatic pyrrolo[1,2-*a*]pyrazine bicyclic system which contains both a π-electron-rich pyrrole ring and a π-electron-deficient pyrazine ring.

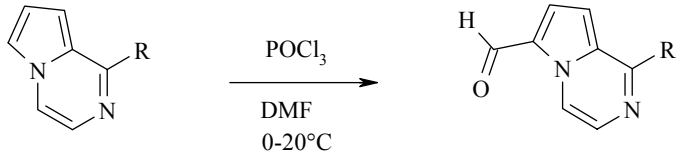
Within the scope of a systematic investigation of electrophilic reactions in such a series of compounds we have studied the formylation of 1- and 6-alkyl-, aryl-, and hetaryl-substituted pyrrolo[1,2-*a*]pyrazines **1a-g**.

It is known that unsubstituted pyrrolo[1,2-*a*]pyrazine is formylated at the β'-position of the pyrrole ring in 60% yield [1]. However, the ^{1}H NMR spectrum of this compound reported by the authors casts doubt upon the correctness of this structural identification. The low field shift of the H-4 proton signal (9.38 ppm) points to α- rather than β'-formylation.

In our laboratory we have also previously studied the formylation of the 3,4-dihydro analogs of pyrrolo[1,2-*a*]pyrazines. It was found that the reaction occurs nonspecifically and the result is governed by the structure of the starting substrates [2].

We have found that in the case of 1-substituted aromatic pyrrolo[1,2-a]pyrazines only 1-phenyl-pyrrolo[1,2-*a*]pyrazine (**1a**) and 1-(2-thienyl)pyrrolo[1,2-*a*]pyrazine (**1b**) are selectively formylated to give the 6-formyl derivatives **2a and 2b** respectively.

The low field shift of the pyrazine proton signal at position 4 in the formylated products when compared with the starting 1-phenyl- and 1-(2-thienyl)pyrrolo[1,2-*a*]pyrazines (9.44 and 9.39 ppm compared with 7.75 and 7.64 ppm respectively) indicates that the formyl group occurs at position 6 of the heterocycles.



1a,b **2a,b**

1, 2 a R = Ph, **b** R = 2-thienyl

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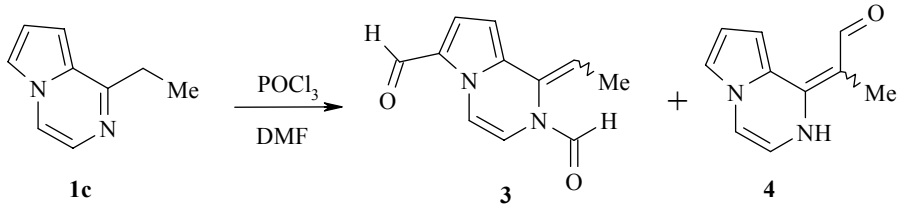
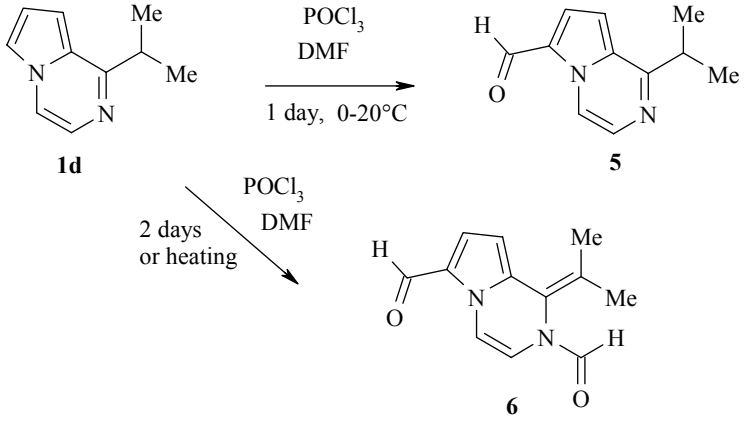
When the phenyl or thienyl group in position 1 in the heterocyclic system is exchanged for ethyl a 3:1 mixture of compounds **3** and **4** is formed, even when using an equimolar ratio of reagents. In addition to the α-position of the pyrrole ring of the heterocycle, electrophilic attack occurs at the pyrazine nitrogen atom and the methylene group of the ethyl substituent.



1c **3** **4**

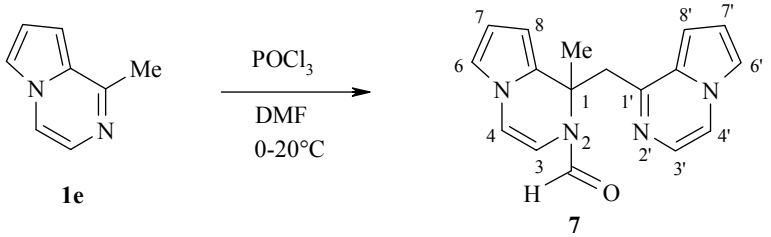
It was not possible to separate the 1-ethylidene-2,6-diformyl-1,2-dihydropyrrolo[1,2-*a*]pyrazine (**3**) and 1-(1-methyl-2-oxoethylidene)-1,2-dihydropyrrolo[1,2-*a*]pyrazine (**4**) and their structure was based on their ^{1}H NMR spectra.

Similarly to 1-phenyl- and 1-(2-thienyl)pyrrolo[1,2-*a*]pyrazine, the 1-isopropylpyrrolo[1,2-*a*]pyrazine (**1d**) is selectively formylated at the α-position of the pyrrole ring when the reaction was carried out at room temperature for 1 day to give 6-formyl-1-isopropylpyrrolo[1,2-*a*]pyrazine (**5**). However, when the reaction time was increased to 2 days or when heated the diformyl derivative **6** was formed exclusively:



1d **5** **6**

With the formylation of 1-methylpyrrolo[1,2-*a*]pyrazine (**1e**) under conditions similar to the pyrrolo[1,2-*a*]pyrazines **1a** and **1b** in the presence of a five-fold excess of phosphorus oxychloride we did not observe formylation products. With use of equimolar amounts of reagents and also with a two-fold excess of phosphorus oxychloride an 8:1 mixture of two materials is obtained. The ^{1}H NMR spectrum of this mixture shows doubling of the signals of all of the proton signals in each of the components. From the spectroscopic data the major compound can be assigned the structure **7**:

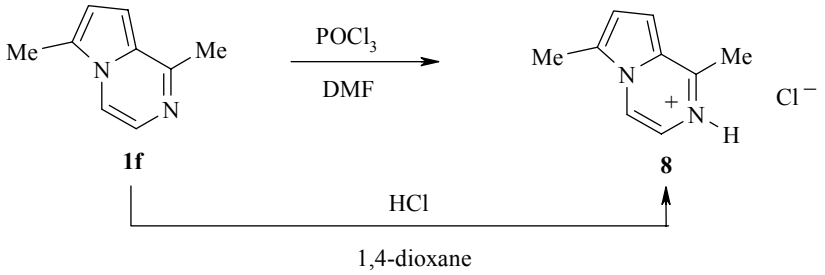


1e **7**

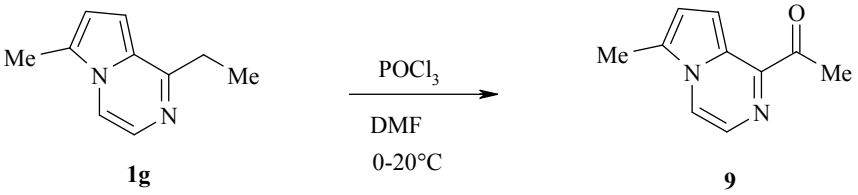
Similar condensation products of two molecules of the pyrrolo[1,2-a]pyrazine were previously obtained by us when acylating the pyrazine **1e** with acetyl chloride [3]. The minor component is evidently also itself a dimer but we were unable to separate it and identify its exact structure due to its virtually identical chromatic mobility.

If a methyl substituent occurs in the α-position of the pyrrole ring formylation of pyrrolo[1,2-*a*]pyrazine under Vilsmeier-Haack conditions is not observed.

When the reaction of 1,6-dimethylpyrrolo[1,2-*a*]pyrazine (**1f**) is carried out with a five-fold excess of phosphorus oxychloride an inseparable mixture of a large number of compounds is produced. With the use of the same reagents in the ratio 1:1 or 1:2 there is almost instantly formed a hygroscopic precipitate which dissolves readily in water and instantly darkens in air. The ^{1}H NMR spectrum of this compound shows just low field shifts for the signals of all of the protons when compared with the starting material. In addition, this spectrum is identical to that of 1,6-dimethylpyrrolo[1,2-*a*]pyrazine hydrochloride (**8**) prepared independently by the action of hydrogen chloride solution on 1,6-dimethylpyrrolo[1,2-*a*]pyrazine (**1f**) in dioxane:



Under Vilsmeier-Haack conditions the 1-ethyl-6-methylpyrrolo[1,2-*a*]pyrazine (**1g**) gave only the starting material in the reaction mixture. Use of methylene chloride as solvent or variation of the temperature conditions did not give a positive outcome. Only when the reaction was carried out by a method of reverse addition of reagent (in which the electrophilic substitution occurs with an excess of substrate and deficiency of reagent) was a low yield (4%) obtained of the product of oxidation of the ethyl group in position 1 of the heterocycle **9**:



We propose that an initial chlorination of the methylene group of the ethyl substituent occurs with subsequent hydrolysis during the tratment of the reaction mixture with sodium carbonate to give the 1-acetyl-6-methylpyrrolo-[1,2-*a*]pyrazine (**9**).

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-400 instrument (400 and 100 MHz respectively) using $CDCl_3$ and with TMS as internal standard. Mass spectra were taken on a Kratos MS-30 instrument at 70 eV (T = 210ºC). Monitoring of the reaction course was carried out by TLC on Silufol UV-254 plates in the system benzene–ethyl acetate (1:1).

6-Formyl-1-phenylpyrrolo[1,2-*a*]pyrazine (2a). Phosphorus oxychloride (10 mmol) was added dropwise with stirring and cooling to dry DMF (25 ml). The product was stirred for 30 min at 0ºC and then a solution of 1-phenylpyrrolo[1,2-*a*]pyrazine (**1a**, 2 mmol) in DMF (3 ml) was added dropwise. Cooling was removed and the product was stirred for 24 h at 20ºC and poured onto crushed ice. The aqueous solution was neutralized with sodium carbonate and the precipitate formed was filtered off, washed with warm water, dried, and recrystallized from hexane. Yield 72%; mp 166ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.07 (1H, dd, $J_{8,7}$ = 4.70, $J_{8,4}$ = 0.83, H-8); 7.55-7.59 (4H, m, *m*-C_6H_5, *p*-C_6H_5); 7.94-7.97 (2H, m, H-*o*-C_6H_5); 8.10 (1H, d, $J_{3,4}$ = 4.74, H-3); 9.44 (1H, dd, $J_{4,3}$ = 4.74, $J_{4,8}$ = 0.83, H-4); 9.96 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 106.59, 118.75, 125.29, 125.74, 128.64, 128.81, 130.17, 137.34, 153.96, 179.64 (CHO). Mass spectrum, *m/z* (I_{rel}, %); 222 $[M]^+$ (100), 193 (53.36), 168 (64.91), 149 (10.14), 138 (28.60), 124 (28.6), 101 (12.95), 76 (12.15). Found, %: C 75.53; H 4.92; N 12.63. $C_{14}H_{10}N_2O$. Calculated, %: C 75.67; H 4.50; N 12.61.

6-Formyl-1-(2-thienyl)pyrrolo[1,2-*a*]pyrazine (2b) was prepared similarly to compound **2a** at 0-20ºC with a reaction time of 1 day. Yield 66%; mp 99-100ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.23 (1H, d, $J_{8,7}$ = 5.09, H-8); 7.25 (1H, d, $J_{\beta',\beta}$ = 3.81, H-β'-Th); 7.57 (1H, $J_{7,8}$ = 5.09, H-7); 7.59 (1H, dd, $J_{\alpha',\beta'}$ = 5.67, $J_{\alpha',\beta}$ = 0.78, H-α'-Th); 7.91 (1H, dd, $J_{\beta,\beta'}$ = 3.81, $J_{\beta,\alpha'}$ = 0.78, H-β-Th); 8.00 (1H, d, $J_{3,4}$ = 4.69, H-3); 9.39 (1H, d, $J_{4,3}$ = 4.69, H-4); 9.94 (1H, s, CHO). Mass spectrum, *m/z* (I_{rel}, %): 228 $[M]^+$ (100), 199 (52.49), 172 (20.90), 155 (20.16), 146 (9.07), 120 (6.76), 101 (9.61), 78 (5.43). Found, %: C 63.67; H 3.81; N 12.17. $C_{12}H_8N_2OS$. Calculated, %: C 63.16; H 3.51; N 12.28.

1-Ethylidene-2,6-diformyl-1,2-dihyropyrrolo[1,2-*a*]pyrazine (3) and 1-(1-Methyl-2-oxoethylidene)-1,2-dihydropyrrolo[1,2-*a*]pyrazine (4). Phosphorus oxychloride (210 mmol) was added dropwise with stirring and cooling to dry DMF (540 mmol). The product was stirred for 30 min at 0ºC and then a solution of 1-ethylpyrrolo[1,2-*a*]pyrazine (**1c**, 14 mmol) in DMF (30 ml) was added dropwise. Cooling was removed and the product was stirred for 8 h at 20ºC and then refluxed for 10 min. After cooling to room temperature it was poured onto crushed ice. The aqueous solution was neutralized with sodium carbonate, extracted with ethyl acetate and dried over 3 Å sieve. Solvent was removed and the residue was recrystallized from acetone.

1-Ethylidene-2,6-diformyl-1,2-dihydropyrrolo[1,2-*a*]pyrazine (3). Yield 19% (^{1}H NMR data). ^{1}H NMR Spectrum, δ, ppm (*J*, Hz): 1.63 (3H, d, *J* = 6.64, C=CH(C<u>H</u>$_3$); 4.17 (1H, q, *J* = 6.64, C=C<u>H</u>(CH_3)); 6.87 (1H, d, $J_{8,7}$ = 4.80, H-8); 7.53 (1H, d, $J_{7,8}$ = 4.80, H-7); 7.96 (1H, d, $J_{3,4}$ = 4.55, H-3); 9.36 (1H, d, $J_{4,3}$ = 4.55, H-4); 9.88 (1H, s, 2-CHO); 9.93 (1H, s, 6-CHO).

1-(1-Methyl-2-oxoethylidene)-1,2-dihydropyrrolo[1,2-*a*]pyrazine (4). Yield 5.5% (^{1}H NMR data). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.29 (3H, s, CH_3); 6.89 (1H, d, $J_{4,3}$ = 5.56, H-4); 7.19 (1H, $J_{8,7}$ = 4.55, H-8); 7.35 (1H, d, $J_{7,8}$ = 4.55, H-7); 8.65 (1H, d, $J_{3,4}$ = 5.56, H-3); 8.78 (1H, br. s, H-6); 9.85 (1H, s, CHO).

6-Formyl-1-isopropylpyrrolo[1,2-*a*]pyrazine (5). Phosphorus oxychloride (210 mmol) was added dropwise with stirring and cooling to dry DMF (540 mmol). The product was stirred for 30 min at 0ºC and then a solution of 1-isopropylpyrrolo[1,2-*a*]pyrazine (**1d**, 13 mmol) in DMF (30 ml) was added dropwise. Cooling was removed and the product was stirred for 24 h at 20ºC and then poured onto crushed ice. The aqueous solution was neutralized with sodium carbonate, extracted with ethyl acetate and dried over 3 Å sieve. Solvent was removed and the residue was recrystallized from hexane. Yield 72%; mp 110-113ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.44 (6H, d, *J* = 6.90, CH(C<u>H</u>$_3$)$_2$); 3.51 (1H, sept, *J* = 6.90, C<u>H</u>(CH_3)$_2$); 6.87 (1H, d, $J_{8,7}$ = 4.70, H-8); 7.47 (1H, d, $J_{7,8}$ = 4.70, H-7); 7.93 (1H, d, $J_{3,4}$ = 4.70, H-3); 9.26 (1H, d, $J_{4,3}$ = 4.70, H-4); 9.87 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 21.09 (CH(<u>C</u>H$_3$)$_2$); 32.96 (<u>C</u>H(CH$_3$)$_2$); 104.27, 118.30, 124.36, 125.05, 130.90, 131.70, 161.63, 179.50 (CHO). Mass spectrum, *m/z* (I_{rel}, %): 188 $[M]^+$ (80.01), 173 (100), 160 (40.10). Found, %: C 70.46; H 5.99; N 14.71. $C_{11}H_{12}N_2O$. Calculated, %: C 70.21; H 6.38; N 14.89.

2,6-Diformyl-1-(1-methylethylidene)- 1,2-dihydropyrrolo[1,2-*a*]pyrazine (6) was prepared similarly to compound **5** at 0-20ºC and a reaction time of 2 days in 66% yield. If stirred for 5 h at 20ºC and then refluxed for 10 min the yield is 34%. Mp 76-78ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.64 (6H, s, C=C(CH$_3$)$_2$); 6.74 (1H, d, $J_{8,7}$ = 4.7, H-8); 7.49 (1H, d, $J_{7,8}$ = 4.70, H-7); 7.95 (1H, d, $J_{3,4}$ = 4.5, H-3); 9.39 (1H, d, $J_{4,3}$ = 4.5, H-4);

9.74 (1H, s, 2-CHO); 9.89 (1H, s, 6-CHO). ^{13}C NMR spectrum, δ, ppm: 20.84 (C=C($\underline{C}$H$_3$)$_2$); 53.90 (C=$\underline{C}$(CH$_3$)$_2$); 105.67, 119.31, 124.65, 125.48, 130.18, 130.80, 179.63 (6-CHO); 210.31 (2-CHO). Mass spectrum, *m/z* (I_{rel}, %): 216 $[M]^+$ (6.03), 188 (100), 173 (56.13), 160 (8.01). Found, %: C 67.02; H 5.76; N 12.92. $C_{12}H_{12}N_2O_2$. Calculated, %: C 66.67; H 5.56; N 12.96.

2-Formyl-1-methyl-1-[(pyrrolo[1,2-*a*]pyrazin-1-yl)methyl]- 1,2-dihydropyrrolo[1,2-*a*]pyrazine (7). Phosphorus oxychloride (2 mmol) was added dropwise with stirring and cooling to dry DMF (5 mmol). The product was stirred for 30 min at 0ºC and then a solution of 1-methylpyrrolo[1,2-a]pyrazine (**1e**, 2 mmol) in DMF (3 ml) was added dropwise. Cooling was removed and the product was stirred for 2 h at 20ºC and then poured onto crushed ice. The aqueous solution was neutralized with sodium carbonate, extracted with benzene and dried over 3 Å sieve. Solvent was removed and the residue was chromatographed on a Silpearl silica gel column using the system benzene–ethyl acetate (1:1). Yield 6% (^{1}H NMR data). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.15 (3H, s, 1-CH$_3$); 3.19 (1H, d, $J_{9,10}$ = 13.70, H-9(10)); 3.52 (1H, d, $J_{9,10}$ = 13.70, H-9(10)); 6.13, 6.53, 6.78, 6.89, 7.73, 8.15 (6H); 6.82 (1H, d, $J_{4,3}$ = 6.46, H-4); 7.45 (1H, d, $J_{3',4'}$ = 4.7, H-3'); 7.71 (1H, d, $J_{4',3'}$ = 4.70, H-4'); 7.73 (1H, d, $J_{3,4}$ = 6.46, H-3); 9.55 (1H, s, CHO).

1,6-Dimethylpyrrolo[1,2-*a*]pyrazine Hydrochloride (8). Phosphorus oxychloride (14 mmol) was added dropwise with stirring and cooling to dry DMF (34 mmol). The product was stirred for 30 min at 0ºC and then a solution of 1,6-dimethylpyrrolo[1,2-*a*]pyrazine (**1f**, 6.7 mmol) in DMF (3 ml) was added dropwise. Cooling was removed and the product was stirred for 2 h at 20ºC. The precipitate was filtered off, washed with absolute ether, dried and stored in a desiccator. Yield 49%; mp 203-204ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.66 (1H, s, 6-CH$_3$); 3.07 (1H, s, 1-CH$_3$); 7.07 (1H, d, $J_{8,7}$ = 4.5, H-8); 7.44 (1H, d, $J_{7,8}$ = 4.50, H-7); 7.53 (1H, d, $J_{3,4}$ = 5.67, H-3); 7.90 (1H, d, $J_{4,3}$ = 5.67, H-4).

1-Acetyl-6-methylpyrrolo[1,2-*a*]pyrazine (9). Phosphorus oxychloride (15 mmol) was added dropwise with stirring and cooling to a solution of 1-ethyl-6-methylpyrrolo[1,2-*a*]pyrazine (**1g**, 3 mmol) in dry DMF (5 ml). Cooling was removed and the product was stirred for 8 h at 20ºC and then poured onto crushed ice. The aqueous solution was neutralized with sodium carbonate, extracted with benzene and dried over 3 Å sieve. Solvent was removed and the residue was chromatographed on a Silpearl silica gel column in the system benzene-ethyl acetate (1:1). Yield 4%; mp 183-184ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.51 (1H, s, COC$\underline{H}_3$); 2.74 (1H, s, 6-CH$_3$); 6.82 (1H, d, $J_{7,8}$ = 3.82, H-7); 7.51 (1H, d, $J_{8,7}$ = 3.82, H-8); 7.65 (1H, d, $J_{3,4}$ = 4.60, H-3); 7.74 (1H, d, $J_{4,3}$ = 4.60, H-4). Mass spectrum, *m/z* (I_{rel}, %): 174 $[M]^+$ (89.29), 146 (15.42), 132 (100), 104 (9.81), 90 (8.21), 76 (16.02). Found, %: C 69.03; H 5.74; N 15.88. $C_{10}H_{10}N_2O$. Calculated, %: C 68.97; H 5.75; N 16.09.

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