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LETTERS TO THE EDITOR

UNEXPECTED TANDEM CONDENSATION OF 2-FURONITRILES WITH DIETHYLENETRIAMINE

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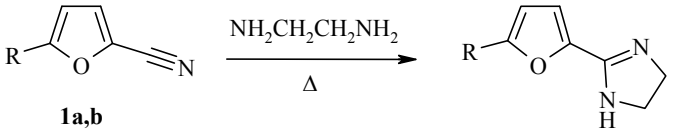
Pyrrolo[1,2-*a*]pyrazines have a broad spectrum of biological activity [1, 2]. The method widely used for synthesis of 1,6-dialkyl-substituted pyrrolo[1,2-*a*]pyrazines is based on the reaction of substituted 2-acylfurans with ethylenediamine [3].

We proposed that exchange of the starting 2-acylfurans and ethylenediamine for the corresponding 2-furonitriles and diethylenetriamine respectively permit the preparation of more complex structures. Reaction of 2-furonitriles with ethylenediamine, however, gave only the 2-(2-furyl)-4,5-dihydro-1H-imidazoles **2a,b**.

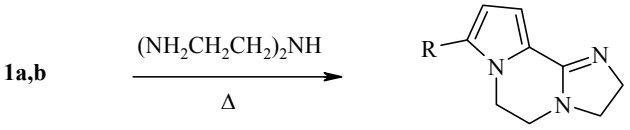


1a,b

2 a (72%), **b** (75%)

1, 2 a R = H, **b** R = Me

The exchange of ethylenediamine for diethylenetriamine unexpectedly led to the preparation of tricyclic structures via refluxing a mixture of the 2-furonitrile (**1a**) or 5-methyl-2-furonitrile (**1b**) with diethylenetriamine for 10 h to give the corresponding 2,3,5,6-tetrahydroimidazo[2,1-*c*]pyrrolo[1,2-*a*]pyrazine **(3a**) or its 8-methyl analog **3b** in 32 and 35% yields respectively.



1a,b

1, **3 a** R = H, **b** R = Me

3 a (32%), **b** (35%)

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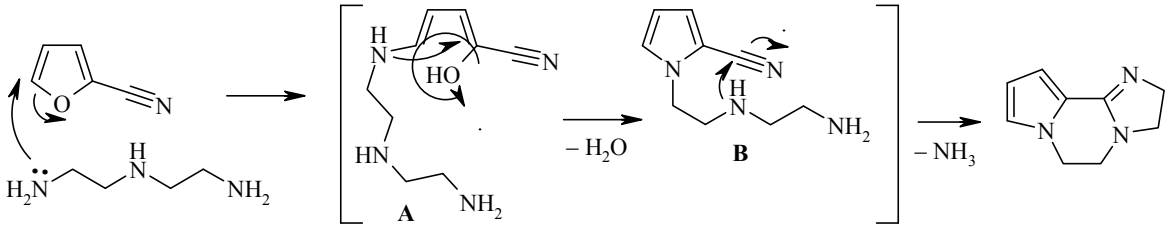
We propose the following tandem mechanism for formation of compounds **3a,b**. Initial attack of a terminal nitrogen atom of the diethylenetriamine at atom C(5) of the furan ring leads to formation of the open intermediate **A**, subsequent dehydration and ring closing of a pyrrole ring giving the intermediate **B** which then forms a pyrazine and finally an imidazole ring.



^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 spectrometer (400 and 100 MHz respectively) using $CDCl_3$ at temperatures of 23 and 25ºC and with TMS as internal standard. Mass spectra were taken on a Kratos MS-90 instrument with an ionization energy of 70 eV.

2-(2-Furyl)-4,5-dihydro-1H-imidazole (2a). Ethylenediamine (5 ml, 0.112 mol) was added to 2-furonitrile (4.7 ml, 0.048 mol). The reaction mixture was heated for 4 h, cooled to room temperature, the precipitated solid filtered off, and the mother liquor evaporated *in vacuo*. The precipitates were combined, washed with petroleum ether (40-70 ml), and dried in air. Yield 4.76 g (72%); mp 180ºC (ethylenediamine). The spectroscopic data agreed with that reported in [4].

2-(5-Methyl-2-furyl)-4,5-dihydro-1H-imidazole (2b) was prepared similarly to compound **2a**. Yield 6 g (75%); mp 132ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.30 (3H, s, 5-CH_3); 3.69 (4H, s, H-4',5'); 4.75 (1H, br. s, NH); 6.02 (1H, m, H-4); 6.76 (1H, d, $J_{3,4}$ = 3.1, H-3). ^{13}C NMR spectrum, δ, ppm: 13.64 (5-CH_3); 50.01 (C-4',5'); 107.82 (C-4); 112.57 (C-3); 144.03 (C-5); 154.12 (C-2); 156.75 (C-6). Mass spectrum, *m/z* (I_{rel}, %): 150 $[M]^+$ (70.89), 149 (34.40), 121 (100), 107 (21.89), 106 (36.45), 94 (6.38), 78 (22.42), 66 (65.07), 51 (76.30), 43 (69.43). Found, %: C 64.11; H 6.90; N 18.48. $C_8H_{10}N_2O$. Calculated, %: C 63.98; H 6.71; N 18.65.

2,3,5,6-Tetrahydroimidazo[2,1-*c*]pyrrolo[1,2-*a*]pyrazine (3a). Diethylenetriamine (21.6 ml, 0.2 mol) was added to 2-furonitrile (**1a)**, (9.38 g, 0.1 mol). The reaction mixture was heated for 10 h, poured into ice, water was added, neutralized with Na_2CO_3 to weakly alkaline reaction, and extracted with benzene. The benzene extracts were dried over $CaCl_2$ and solvent was evaporated *in vacuo*. The residue was distilled *in vacuo*. Yield 7.8 g (32%); bp 200ºC (15 mm Hg), mp 65ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.28 (2H, t, $J_{3,4}$ = 8.8, 2H-3); 3.33 (2H, t, $J_{5,6}$ = 5.7, 2H-5); 3.81 (2H, t, $J_{2,3}$ = 8.8, 2H-2); 4.17 (2H, t, $J_{6,5}$ = 5.7, 2H-6); 6.20 (1H, dd, $J_{9,10}$ = 3.8, $J_{9,8}$ = 2.5, H-9); 6.71 (1H, dd, $J_{8,9}$ = 2.5, $J_{8,10}$ = 1.3, H-8); 6.84 (1H, dd, $J_{10,9}$ = 3.8, $J_{10,8}$ = 1.3, H-10). ^{13}C NMR spectrum, δ, ppm: 44.29 (C-6); 46.03 (C-5); 51.85 (C-3); 53.26 (C-2); 109.88 (C-9); 110.01 (C-10); 121.65 (C-8); 122.31 (C-11); 159.38 (C-12). Mass spectrum, *m/z* (I_{rel}, %): 161 $[M]^+$ (69.54), 160 (78.10), 133 (22.48), 119 (8.97), 106 (35.47), 92 (15.53), 79 (21.94), 78 (24.77), 65 (21.44); 42 (100). Elemental analysis is given for the hydrate of compound **3a**. Found, %: C 57.65; H 7.25; N 22.37. $C_9H_{11}N_3 \cdot 1.5H_2O$. Calculated, % C 57.43; H 7.45, N 22.32.

8-Methyl-2,3,5,6-tetrahydroimidazo[2,1-*c*]pyrrolo[1,2-*a*]pyrazine (3b) was prepared similarly to compound **3a** from 5-methyl-2-furonitrile (**1b**). Yield 1.85 g (35%); bp 207ºC (7 mm Hg), mp 105ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.26 (3H, s, CH_3); 3.25 (2H, t, $J_{3,2}$ = 8.7, 2H-3); 3.31 (2H, t, $J_{5,6}$ = 5.2, 2H-5); 3.79 (2H, t, $J_{2,3}$ = 8.7, 2H-2); 4.00 (2H, t, $J_{6,5}$ = 5.2, 2H-6); 5.94 (1H, d, $J_{10,9}$ = 3.8, H-10); 6.74 (1H, d, $J_{9,10}$ = 3.8, H-9). ^{13}C NMR spectrum, δ, ppm: 11.82 (CH_3); 41.40 (C-6); 46.08 (C-5); 51.91 (C-3); 53.34 (C-2); 108.59 (C-9); 109.39 (C-10); 120.87 (C-8); 130.66 (C-10*a*); 157.67 (C-4*a*). Mass spectrum, *m/z* (I_{rel}, %): 175 $[M]^+$ (37.24), 174 (54.78), 147 (19.45), 133 (24.51), 121 (37.30), 106 (20.12), 92 (12.40), 78 (18.17), 56 (100), 42 (55.18). Found, %: C 63.81; H 6.62; N 18.71. $C_{10}H_{13}N_3$. Calculated, %: C 63.98; H 6.71; N 18.65.

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