Pergamon

Tetrahedron 54 (1998) 9393–9400

TETRAHEDRON

Unambiguous Synthesis of 1-Methyl-3-hydroxypyrazoles

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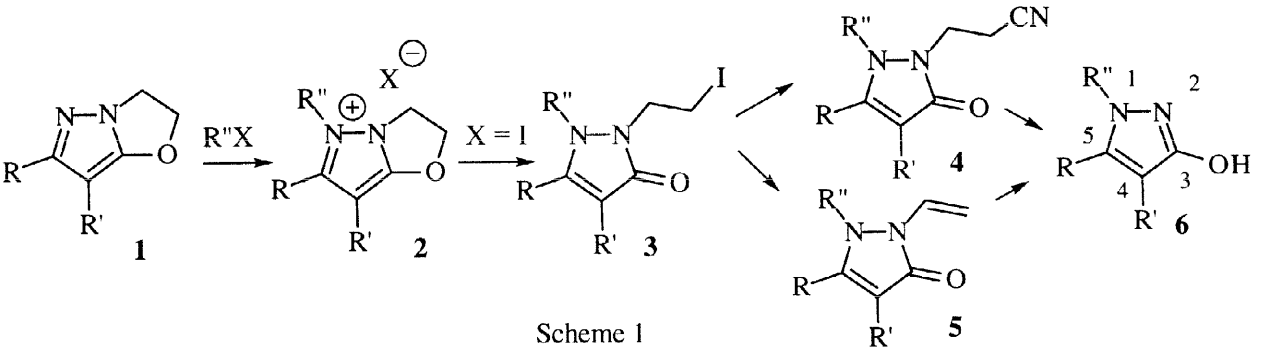
Received 31 March 1998; accepted 10 June 1998

Abstract: 2,3-Dihydropyrazolo[3,2-*b*]oxazoles were used as intermediates in a new method for preparation of N1-methyl-3-hydroxypyrazoles. Synthesis of this bicyclic system was achieved either by alkylation of 3-hydroxypyrazole with 1,2-dibromoethane or, with better yields, by cyclization of 1-tosyl-2-(2-hydroxyethyl)pyrazol-3-ones *via* a nitrogen to oxygen transfer of the tosyl group. Alkylation with methyl trifluoromethanesulfonate followed by dihydrooxazole ring-opening with sodium iodide, led to the 1-methyl-2-(2-iodoethyl)pyrazoles. Removal of the iodoethyl chain on N2 to give the target 3-hydroxypyrazoles was achieved either *via* a cyanation and then a decyanoethylation reaction or *via* an elimination of hydrogen iodide, followed by an iodine-based oxidation of the resulting vinylic derivative. Using the latter method, 1-methyl-3-hydroxypyrazoles were obtained in 58-73% yields from the corresponding 2,3-dihydropyrazolo[3,2-*b*]oxazoles. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

The method of choice for preparation of 1-alkyl-3-hydroxypyrazoles from N-alkyl hydrazines is quite dependent on the molecule targeted.[1-3] The classical condensation between N-alkyl hydrazines and β-ketoesters most often leads to 2-alkyl-3-hydroxypyrazoles and sometimes to a mixture of isomers.[2] Moreover, N-alkylation of 3-hydroxypyrazoles usually, though not always,[4] proceeds poorly. Indeed, depending on the substrate, O-alkylated derivatives along with N-1, N-2, C-4 and even bis-alkylated materials can be obtained.[5] For example, synthesis of 1,5-dimethyl-3-hydroxypyrazole from 5-methyl-3-hydroxypyrazole was reported with a 25 % yield only.[6] In order to develop an unambiguous method for the preparation of 1-alkyl-3-hydroxypyrazoles, we have investigated the use of 2,3-dihydropyrazolo[3,2-*b*]oxazoles **1** as depicted below :



Scheme 1

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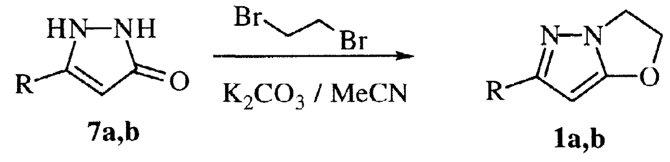
PII: S0040-4020(98)00579-1

In a first step, alkylation of the bicyclic derivatives **1**, which can be regarded as N2- and O-protected 3-hydroxypyrazoles, leads to the iminium salts **2**. Nucleophilic ring-opening of the oxazole then deprotects the oxygen to give **3**. The iodoethyl derivatives **3** provide opportunity to remove the N2 substituent, either by substitution with cyanide to give **4** or by elimination reaction to give **5**. Indeed, either base-triggered decyanoethylation[7-12] or vinyl removal[13-22] *via* hydrolysis or oxidation have been reported for some nitrogen heterocycles. In our case this leads to the target 1-alkyl-3-hydroxypyrazoles **6**.

RESULTS AND DISCUSSION

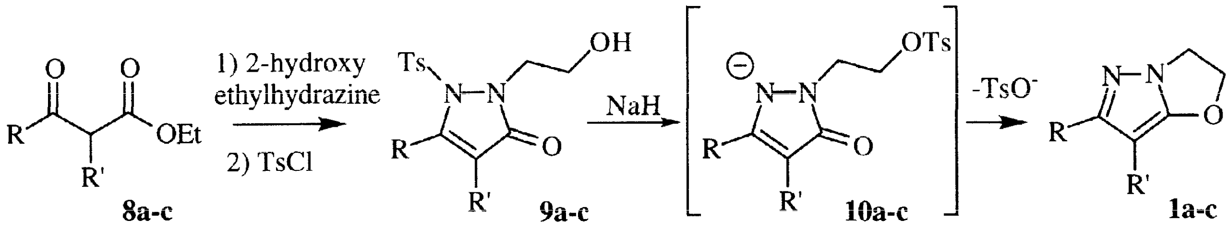
Preparation of the 2,3-dihydropyrazolo[3,2-*b*]oxazoles[23] **1a,b** was first done *via* alkylation of 3-hydroxypyrazoles **7a-b** with 1,2-dibromoethane (Scheme 2). The 5-phenyl derivative **1a** could be obtained in 58% yield from **7a**, however, a similar reaction with 5-methyl-3-hydroxypyrazole **7b** led to only 28% of compound **1b**. ^1H NMR spectrum of the crude reaction mixture showed the presence of other alkylated species, which were not isolated and characterized.



a : R = Ph; **b** : R = Me

Scheme 2

In a second approach, we prepared the pyrazole ring, already bearing the proper substituent on N2, *via* the condensation of 2-hydroxyethylhydrazine and β-ketoesters **8a-c** (Scheme 3). Tosylation of the crude reaction mixture led to the stable derivatives **9a-c** in 60-70% yields. As reported[24-25] for two other classes of heterocycles, treatment with a strong base led to a transfer of the tosyl group from nitrogen to oxygen, and these intermediates (**10a-c**) subsequently underwent cyclization. In the present case, treatment of **9a-c** with sodium hydride gave 2,3-dihydropyrazolo[3,2-*b*]oxazoles **1a-c** in a 75-85 % yield.

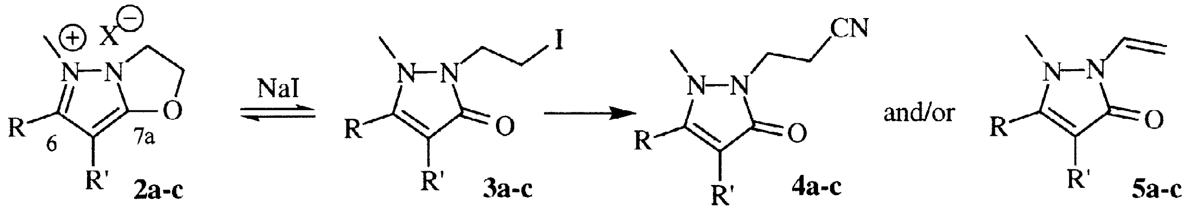


a : R, R' = Ph, H; **b** : R, R' = Me, H; **c** : R, R' = Me, Et

Ts = Tosyl

Scheme 3

Quaternization of **1b** was first attempted with methyl iodide in a sealed flask. NMR spectra showed the reaction mixture to contain the expected salt **2b** (X = I) and the iodoethyl derivative **3b** (Scheme 4). Isolation of **3b** was achieved after chromatography in 20% yield. However, slight heating of **3b** (40° C) in solution led to recyclization to **2b** (X = I). In a second approach, alkylation of **1a-c** was accomplished with methyl trifluoromethanesulfonate at room temperature.



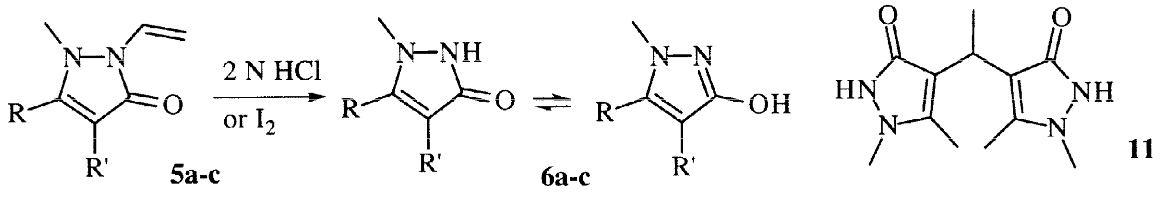
a : R, R' = Ph, H; **b** : R, R' = Me, H; **c** : R, R' = Me, Et

Scheme 4

This led quantitatively to **2a-c** (X = $CF_3SO_3^-$), as determined by NMR spectroscopy of the reaction mixtures (two methylene signals at 4.8 and 5.3 ppm compared to 4.1 and 4.9 ppm before alkylation). The dihydrooxazole ring was then opened by addition of sodium iodide. The resulting iodoethyl compounds **3a-c** could be isolated in 60-80 % yields, but these compounds, especially **3c**, had a tendency to revert to their bicyclic salts. Reaction of the iodoethyl derivatives **3a,b** with potassium cyanide gave only low yields of **4a,b** and no cyanoethyl derivative could be isolated when starting from **3c**. At best, from **3a,b**, using tetraethylammonium cyanide[26], we were able to obtain the cyanoethyl derivatives **4a,b** in 47 and 30% yields, respectively, along with variable amounts of the vinyl derivatives **5a,b** and unidentified materials. The low yields obtained in the cyanation steps are probably caused by the easy reversion to the cyclized species, containing potential electrophilic centers (i.e. carbon 6 and 7a of **2**). Preparation of **4c** could only be achieved (16% yield) when reacting the bicyclic salt **2c** (X = $CF_3SO_3^-$) with tetraethylammonium cyanide.

On the other hand, the preparation of the vinyl derivatives **5a-c** was more successful. Following the treatment of **2a-c** with sodium iodide, one equivalent of toluenesulfonic acid was added to shift the equilibrium from **2** towards **3** by protonation of **3**. Then treatment of the reaction mixture with an excess of potassium *tert*-butoxide led to compounds **5a-c** in a 77-90% yield from **1a-c**.

Removal of the cyanoethyl group from **4a-c** was achieved using sodium methanolate in methanol and led to the target compounds **6a-c** in 45-75 % yields. Removal of the vinyl group from **5a-c** with hydrochloric acid (Scheme 5) gave mixed results. Hydrolysis of **5c** led to **6c** in 83% yield, whereas hydrolysis of **5a** led to **6a** in 40% yield only. Moreover, acidic hydrolysis of **5b** led to only 25% of **6b** along with compound **11** arising from a C4 alkylation reaction. We then adapted an iodine-based oxidative method[17] for the hydrolysis of **5a,b**. Thus, addition of iodine to a hot solution of **5a,b** in THF/water (9:1) led to **6a,b** in 76 and 82% yields, respectively. It is important to mention that although the reaction also led to iodinated species, these were reduced[27] in the course of the treatment, by the addition of an excess of sodium sulfite and heating.



Scheme 5

In the course of this work, we were able to demonstrate the complex chemistry of pyrazolones. Our attempts to prepare **1a,b** from pyrazolones **7a,b** revealed the difference of reactivity seen in the course of alkylation reactions[5]. Study of the chemical behaviour of the iodinated derivatives **3a-c** disclosed the propensity of **3c** to revert back to the bicyclic derivative **2c** as opposed to the stability of derivative **3a**. Finally isolation of compound **11** proved the highly versatile nature of 3-hydroxypyrazoles, which can behave as acids, bases and in some cases, enamines. The synthetic route we present here, starts from substituted β-ketoesters and, through the bicyclic derivatives **1a-c**, leads to the vinyl compounds **5a-c**. Using an oxidative method for the final deprotection, this route offers a general and unambiguous method for the preparation of 1-methyl-3-hydroxypyrazoles **6a-c** in 58-73% yields from 2,3-dihydropyrazolo[3,2-*b*]oxazoles **1a-c**. Extension of this method to other strong alkylating agents instead of methyl trifluoromethanesulfonate seems possible, though this has not yet been investigated.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer. Unless otherwise stated $CDCl_3$ was the solvent used. Shifts are given in ppm (δ) with respect to the TMS signal and coupling constants (*J*) are given in Hertz. Column chromatography was performed on Merck silica gel 60 (0.060 - 0.200 mm). When necessary, solvents were dried using activated 3 Å or 4 Å molecular sieves[28]. Activation of the molecular sieves was done by using a plastic-free domestic microwave oven (irradiation in a quartz beaker of 100-200 g of new molecular sieve until partial melting, i.e. from 1 to 8 min by periods of 1 min alternated with cooling). **CAUTION**: due to the remain of traces of solvents, microwave irradiation of molecular sieve previously used can result in a serious explosion.

3-Hydroxy-5-phenylpyrazole **7a**: Ethyl benzoylacetate (40 ml; 0.11 mol) in EtOH (100 ml) was added dropwise to hydrazine hydrate (11.2 ml; 0.235 mol) in refluxing EtOH (150 ml) over one hour. The suspension was heated for an additional hour and left to cool. Filtration and drying of the precipitate led to **7a** (25 g; 67 %) as a peach-coloured solid. M.p. = 243°C (lit[29] = 242-243°C). ^{1}H (DMSO): 5.88 (s, 1H, CH-4); 7.29-7.4 (m, 3H, Ar); 7.44-7.67 (m, 2H, Ar). ^{13}C: 86.8 (CH-4); 124.6, 127.6, 128.7 (CH Ar); 130.5 (C Ar); 143.3 (C-5); 160.9 (C-3). *m/z* (EI) = 160. Anal. ($C_9H_8N_2O$): Calc, C: 67.48, H: 5.03, N: 17.49; found, C: 67.49, H: 5.10, N: 17.60.

Preparation of **1a-b** *via* bis-alkylation of 3-hydroxypyrazoles : In a typical procedure, 3-hydroxypyrazole **7a,b** (66.2 mmol), dibromoethane (13.7 g; 72.8 mmol) and K_2CO_3 (32.6 g; 265 mmol) in dry acetonitrile (500 ml) were refluxed for 15 hours. The reaction mixture was concentrated, the residue was diluted with water and extracted with ether. The organic phase was dried ($MgSO_4$), evaporated to dryness and chromatographed (CH_2Cl_2/MeOH from 99:1 to 97:3) to give **1a** and **1b** in 56 and 28% yield, respectively (for characterization see preparation of **1a-c** *via* cyclization of **9a-c** below).

Preparation of **9a-c**: Under an inert atmosphere, one of the β-ketoesters **8a-c** (62 mmol) in toluene (100 ml) was added dropwise to 90% 2-hydroxyethylhydrazine (5.3 g; 62 mmol) in boiling toluene (100 ml) and refluxed for 3 hours. The excess of water was removed with a Dean-Stark apparatus and the oily suspension was cooled to room temperature. Dry acetonitrile (200 ml) and dry triethylamine were added (8.6 ml; 62 mmol) followed by addition of tosylchloride (11.8 g; 62 mmol). The solution was stirred for 20 min and evaporated to dryness. The residue was dissolved in ethyl acetate, washed with water, dried ($MgSO_4$) and concentrated to dryness. This was chromatographed (CH_2Cl_2 then CH_2Cl_2/MeOH 98:2) to give **9a-c**.

2-(2-Hydroxyethyl)-5-phenyl-1-tosylpyrazol-3-one **9a**: Obtained as an oil that solidified upon standing (58 %). M.p. = 84-86°C. ^{1}H: 2.46 (s, 3H, CH_3); 3.84 (m, 2H, CH_2N); 3.97 (m, 2H, CH_2O); 6.09 (s, 1H, CH-4); 7.35 (m, 5H, Ar); 7.64 (m, 2H, Ts); 7.80 (m, 2H, Ts). ^{13}C: 21.8 (CH_3); 49.1 (CH_2N); 61.2 (CH_2O); 92.3 (CH-4); 125.2 (CH Ar); 128.3 (CH Ar); 128.6 (CH Ar and CH Ts); 130.2 (CH Ts); 130.9 (C Ts); 132.5 (C Ar); 143.8 (C Ts); 146.8 (C-5); 150.1 (C-3). *m/z* (EI) = 358.

2-(2-Hydroxyethyl)-5-methyl-1-tosylpyrazol-3-one **9b**: Obtained as a solid (68 %). M.p. = 85°C. ^{1}H: 2.14 (s, 3H, CH_3); 2.46 (s, 3H, CH_3 Ts); 3.77 and 3.86 (m, 4H, CH_2N and CH_2O); 5.55 (s, 1H, CH-4); 7.36 (d, 2H, J = 8.5 Hz, Ts); 7.76 (d, 2H, J = 8.5 Hz, Ts). ^{13}C: 14.3 (CH_3); 21.8 (CH_3 Ts); 48.6 (CH_2N); 61.3 (CH_2O); 94.5 (CH-4); 128.6 (CH Ts); 130.0 (C Ts); 130.1 (CH Ts); 131.1 (C Ts); 146.6 (C-5); 147.9 (C-3). *m/z* (EI) = 296. Anal. ($C_{13}H_{16}N_2SO_4$): Calc, C: 52.69, H: 5.44, N: 9.45; found, C: 52.67, H: 5.35, N: 9.51.

4-Ethyl-2-(2-hydroxyethyl)-5-methyl-1-tosylpyrazol-3-one **9c**: Obtained as an oil (73 %). ^{1}H: 0.93 (t, 3H, J = 7.6, CH_3); 2.02 (q, 2H, J = 7.6, CH_2); 2.07 (s, 3H, CH_3); 2.46 (s, 3H, CH_3 Ts); 3.81 (s, 4H, CH_2N and CH_2O); 7.37 (d, 2H, J = 8.1 Hz, Ts); 7.79 (d, 2H, J = 8.5 Hz, Ts). ^{13}C: 13.0 (CH_3); 13.8 (CH_3); 15.2 (CH_2); 21.8 (CH_3 Ts); 48.8 (CH_2N); 61.5 (CH_2O); 109.7 (C-4); 128.6 (CH Ts); 130.2 (CH Ts); 131.8 (C Ts); 139.9 (CTs); 146.6 (C-5); 148.8 (C-3). *m/z* (EI) = 324.

Preparation of **1a-c** *via* cyclization of **9a-c**: In a typical procedure, under an inert atmosphere, compound **9a-c** (21 mmol) was dissolved in dry acetonitrile (200 ml), 60 % sodium hydride (0.9 g; 22.5 mmol) was added and the suspension was stirred overnight. The solution was evaporated to dryness and chromatographed (CH_2Cl_2/MeOH from 99:1 to 97:3) to give **1a-c**.

*2,3-Dihydro-6-phenylpyrazolo[3,2-*b*]oxazole* **1a** obtained as a solid (82%). A small sample was recrystallized (heptane). M.p. = 104 °C (lit[23] = 102.5-103°C). ^{1}H: 4.32 (t, 2H, J = 7.9, NCH_2); 5.03 (t, 2H, J = 7.9, OCH_2); 5.70 (s, 1H, CH-7); 7.26-7.42 (m, 3H, CHAr); 7.72-7.74 (m, 2H, CHAr). ^{13}C: 45.3 (NCH_2); 75.0 (OCH_2); 77.9 (CH-7); 125.3 (CHAr); 127.9 (CHAr); 128.6 (CHAr); 134.2 (C-6); 156.8 (C-7a). *m/z* (EI) = 186. Anal. ($C_{11}H_{10}N_2O$): Calc, C: 70.95, H: 5.41, N: 15.04; found, C: 70.93, H: 5.39, N: 15.09.

*2,3-Dihydro-6-methylpyrazolo[3,2-*b*]oxazole* **1b**: The oil obtained was distilled in a Kugelrohr apparatus (10 mmHg - 200 °C) to give **1b** (81%, crystallize upon standing). M.p. = 45-46°C (lit[23] = 45.5-46 °C). ^{1}H: 2.15 (s, 3H, CH_3); 4.12 (t, 2H, J = 8.1, CH_2); 4.90 (t, 2H, J = 8.1, CH_2); 5.10 (s, 1H, CH-7). ^{13}C: 15.0 (CH_3); 44.8 (CH_2); 74.5 (CH_2); 79.7 (CH-7); 154.4 (C-6); 159.3 (C-7a). *m/z* (EI) = 124. Anal. ($C_6H_8N_2O$): Calc, C: 58.05, H: 6.50, N: 22.57; found, C: 57.98, H: 6.70, N: 22.64.

*7-Ethyl-2,3-dihydro-6-methylpyrazolo[3,2-*b*]oxazole* **1c**: The oil obtained was distilled in a Kugelrohr apparatus (10 mmHg - 200 °C) to give **1c** (75%, crystallize upon standing). M.p. = 68-69°C. ^{1}H: 1.09 (t, 3H, J = 7.5, CH_3); 2.13 (s, 3H, CH_3); 2.26 (q, 2H, J = 7.5, CH_2); 4.13 (t, 2H, J = 8.1, NCH_2); 4.91 (t, 2H, J = 8.1, OCH_2). ^{13}C: 13.3 (CH_3); 14.1 (CH_3); 15.4 (CH_2); 45.1 (CH_2); 74.5 (CH_2); 94.7 (C-7); 153.2 (C-6); 156.9 (C-7a). *m/z* (EI) = 152. Anal. ($C_8H_{12}N_2O$, 3/4 H_2O): Calc, C: 57.99, H: 8.21, N: 16.91; found, C: 57.99, H: 8.06, N: 17.13.

Preparation of **3b** using methyl iodide: 2,3-Dihydro-6-methylpyrazolo[3,2-*b*]oxazole **1b** (1.67 g; 13 mmol) and methyl iodide (1.6 ml; 26 mmol) in acetonitrile (20 ml) were heated in a sealed flask for 15-20 hours at 100°C. Following removal of the solvent, the residue was chromatographed (CH_2Cl_2/MeOH 95:5) to give **3b** (20%). Note: Concentration of the fractions obtained should be done under vacuum without heat as recyclization was observed on TLC and NMR when heating.

Preparation of **3a-c** using methyl trifluoromethanesulfonate *via* **2a-c** followed by addition of sodium iodide: Under a dry atmosphere, pyrazolo[3,2-*b*]oxazoles **1a-c** (2.5 mmol) were dissolved in dry acetonitrile (15 ml), methyl trifluoromethanesulfonate (0.31 ml; 2.7 mmol) was added and the solution was stirred for 2 hours to give **2a-c**. Dry sodium iodide (0.72 g; 5 mmol) was then added and the solution was stirred overnight. The solvent was removed *in vacuo* and the residue chromatographed (CH_2Cl_2/MeOH from 97:3 to 94:6) to give **3a-c**.

2,3-Dihydro-5-methyl-6-phenylpyrazolo[5,1-b]oxazol-5-ium trifluoromethanesulfonate **2a**: ^{1}H: 3.86 (s, 3H, NCH_3); 4.80 (t, 2H, J = 8.4, NCH_2); 5.30 (t, 2H, J = 8.4, OCH_2); 5.86 (s, 1H, CH-7); 7.49 (m, 5H, CHAr). ^{13}C : 35.7 (NCH_3); 46.6 (NCH_2); 78.0 (OCH_2); 86.4 (CH-7); 126.6 (CAr); 129 (CHAr); 129.4 (CHAr); 131.6 (CHAr); 156.1 (C-6); 161.0 (C-7a).

*5,6-Dimethyl-2,3-dihydro-pyrazolo[5,1-*b*]oxazol-5-ium trifluoromethanesulfonate* **2b**: ^{1}H: 2.36 (s, 3H, CH_3); 3.91 (s, 3H, NCH_3); 4.64 (t, 2H, J = 8.2, CH_2); 5.27 (t, 2H, J = 8.2, CH_2); 5.68 (s, 1H, CH-7).

*5,6-Dimethyl-2,3-dihydro-7-ethylpyrazolo[5,1-*b*]oxazol-5-ium trifluoromethanesulfonate* **2c**: ^{1}H: 1.09 (t, 3H, J = 7.6, CH_3); 2.32 (s, 5H, CH_2C, CH_3); 3.77 (s, 3H, NCH_3); 4.58 (t, 2H, J = 8.1, NCH_2); 5.23 (t, 2H, J = 8.1, OCH_2). ^{13}C: 10.7 (CH_3); 13.0 (CH_3); 19.2 (CH_2); 34.4 (NCH_3); 46.6 (NCH_2); 77.3 (CH_2); 101.2 (C-7); 152.0 (C-6); 160.2 (C-7a).

2-(2-Iodoethyl)-1-methyl-5-phenylpyrazol-3-one **3a**: Obtained as an oil (87 %). ^{1}H: 3.11 (s, 3H, CH_3N); 3.31 (t, 2H, J = 7.6, CH_2I); 4.19 (t, 2H, J = 7.6, CH_2N); 5.64 (s, 1H, CH-4); 7.38-7.51 (m, 5H, ArH). ^{13}C: -0.4 (CH_2I); 37.2 (CH_3N); 44.7 (CH_2N); 99.4 (CH-4); 128.4 (CHAr); 128.8 (CAr); 129.1 (CHAr); 130.5 (CHAr); 160.4 (C-5); 166.7 (C-3). *m/z* (EI) = 328.

1,5-Dimethyl-2-(2-iodoethyl)pyrazol-3-one **3b**: Obtained as an oil (61 %). ^{1}H: 2.08 (s, 3H, CH_3); 3.14 (t, 2H, J = 5, CH_2); 3.23 (s, 3H, CH_3); 4.10 (t, 2H, J = 5, CH_2); 5.22 (s, 1H, CH-4, note : ex. in D_2O). ^{13}C: -0.5 (CH_2I); 12.8 (CH_3); 33.9 (CH_3N); 44.6 (CH_2); 97.5 (CH-4); 154.6 (C-5); 166.9 (C-3).*m/z* (EI) = 266.

1,5-Dimethyl-4-ethyl-2-(2-iodoethyl)pyrazol-3-one **3c**: Obtained as an oil (70%) contaminated with small amounts of **2c** (even if no heat was applied while concentrating to dryness the far more polar cyclization product **2c** could still be seen on TLC and in NMR spectra). ^{1}H: 1.05 (t, 3H, J = 7.5, CH_3); 2.06 (s, 3H, CH_3); 2.24 (q, 2H, J = 7.5, CH_2); 3.04 (s, 3H, NCH_3); 3.18 (t, 2H, J = 7.7, ICH_2); 4.06 (t, 2H, J = 7.7, NCH_2). ^{13}C: -0.2 (CH_2I); 10.7 (CH_3); 13.9 (CH_3); 15.5 (CH_2); 34.7 (CH_3N); 44.4 (CH_2N); 111.6 (C-4); 151.4 (C-5); 167.0 (C-3). *m/z* (EI) = 294.

Preparation of 2-(2-cyanoethyl)pyrazol-3-ones **4a,b**: Under a dry atmosphere, pyrazolo[3,2-*b*]oxazoles **1a,b** (2.5 mmol) were dissolved in dry acetonitrile (15 ml), methyl trifluoromethanesulfonate (0.31 ml; 2.7 mmol) was added and the solution was stirred for 2 hours. Dry sodium iodide (0.72 g; 5 mmol) was added and the solution was stirred overnight. Triethylammonium cyanide (o.5 g; 32 mmol) was added and the solution was stirred for another 10 hours. The solvents were removed *in vacuo* and the residue was chromatographed to give **4a,b**. From **1c** the procedure above failed to give any isolable amount of **4c**. When omitting the sodium iodide treatment of **1c** compound **4c** could be isolated in 16% yield.

2-(2-Cyanoethyl)-1-methyl-5-phenylpyrazol-3-one **4a**: Elution with CH_2Cl_2/MeOH from 98:2 to 97:3 gave **4a** as an oil (47%). ^{1}H: 2.73 (t, 2H, J = 6.1, CH_2-CN); 3.18 (s, 3H, CH_3N); 4.13 (t, 2H, J = 6.1, CH_2N); 5.80 (s, 1H, CH-4); 7.44-7.52 (m, 5H, HAr). *m/z* (EI) = 227.

2-(2-Cyanoethyl)-1,5-dimethylpyrazol-3-one **4b**: Elution with MeOH/ethyl acetate 12:88 gave first **5b** (25 %) and then **4b** as an oil (30%). ^{1}H: 2.13 (s, 1H, CH_3); 2.61 (t, 2H, J = 6.4, CH_2-CN); 3.2 (s, 3H, CH_3N); 4.00 (t, 2H, J = 6.4, CH_2N); 5.23 (s, 1H, CH-4). *m/z* (EI) = 165.

2-(2-Cyanoethyl)-1,5-dimethyl-4-ethylpyrazol-3-one **4c**: Elution with CH_2Cl_2/MeOH 97:3 gave **4c** as an oil (16%). ^{1}H: 1.06 (t, 3H, J = 7.5, CH_3); 2.08 (s, 1H, CH_3); 2.24 (q, 2H, J = 7.5, CH_2); 2.59 (t, 2H, J = 6.5, CH_2-CN); 3.08 (s, 3H, CH_3N); 3.96 (t, 2H, J = 6.5, CH_2N).

Preparation of 1-methyl-2-vinylpyrazol-3-ones **5a-c**: In a typical procedure, under a dry atmosphere, the relevant pyrazolo[3,2-*b*]oxazoles **1a-c** (8.4 mmol) were dissolved in dry acetonitrile (100 ml), methyl trifluoromethanesulfonate (1.04 ml; 9.2 mmol) was added and the solution was stirred for 2 hours. Dry sodium iodide (2.5 g; 16 mmol) was added followed by toluenesulfonic acid (1.6 g; 8.4 mmol). The suspension obtained was stirred for 24 hours and NMR monitoring showed a complete conversion into the iodinated derivatives **3a-c**. *tert*-BuOK (2.35 g; 21 mmol) was then added and the suspension stirred for one hour before removing the solvents under vacuum. Chromatography of the residue gave **5a-c**.

1-Methyl-5-phenyl-2-vinylpyrazol-3-one **5a**: Elution with first heptane/ethyl acetate 1:1 then heptane/ethyl acetate 1:2 gave **5a** as an oil (77 %). ^{1}H: 2.99 (s, 3H, NCH_3); 4.72 (d, 1H, J = 9.4, $=CH_2$); 4.85 (d, 1H, J = 16.0, $=CH_2$); 5.68 (s,1H, CH-4); 6.90 (dd, 1H, J = 9.4 and 16.0, =CH); 7.42 (s, 5H, HAr). ^{13}C: 40.1 (CH_3N); 98.1 (CH-4); 100.7 (CH_2); 126.1 (CH); 128.2 (CHAr); 128.8 (CAr); 129.1 (CHAr); 130.8 (CHAr); 164.2 (C-5); 165.2 (C-3). *m/z* (EI) = 200.

1,5-Dimethyl-2-vinylpyrazol-3-one **5b**: Elution with first heptane/ethyl acetate 1:1 then CH_2Cl_2/MeOH 92:8 gave **5b** as an oil (90 %). ^{1}H: 2.16 (s, 3H, CH_3); 3.12 (s, 3H, NCH_3); 4.73 (d, 1H, J = 9.3, $=CH_2$); 4.68 (d, 1H, J = 16.9, $=CH_2$); 5.35 (s,1H, CH-4); 6.83 (dd, 1H, J = 9.3 and 16.9, =CH). ^{13}C: 12.9 (CH_3); 36.1 (CH_3N); 98.4 (CH-4); 99.6 ($=CH_2$); 126.5 (=CH); 159.4 (C-5); 165.9 (C-3). *m/z* (EI) = 138.

1,5-Dimethyl-4-ethyl-2-vinylpyrazol-3-one **5c**: Elution with heptane/ethyl acetate 1:1 gave **5c** as an oil (81 %). ^{1}H: 1.05 (t, 3H, J = 7.4, CH_3); 2.09 (s, 3H, CH_3); 2.23 (q, 2H, J = 7.4, CH_2); 2.98 (s, 3H, NCH_3); 4.63 (d, 1H, J = 9.4, $=CH_2$); 4.68 (d, 1H, J = 16, $=CH_2$); 6.87 (dd, 1H, J = 9.4 and 16, =CH). ^{13}C: 10.8 (CH_3); 13.5 (CH_3); 15.4 (CH_2); 37.0 (CH_3N); 97.0 (CH_2); 113.5 (C-4); 126.4 (CH); 155.4 (C-5); 165.8 (C-3). *m/z* (EI) = 166.

Preparation of **6a-c** *via* decyanoethylation: Sodium (81 mg; 3.52 mmol) was dissolved in dry MeOH (30 ml). A solution of 1-methyl-2-(2-cyanoethyl)-3-oxopyrazole **4a-c** (1.76 mmol) in dry MeOH (10 ml) was added and the mixture refluxed for 1-15 hours. The solvent was removed *in vacuo* and the residue was chromatographed (CH_2Cl_2/EtOH from 93:7 to 9:1) to give **6a-c** in 49, 75 and 45 % yields, respectively.

Preparation of **6a-c** by acidic hydrolysis of **5a-c** and isolation of **11**: In a typical procedure, 1-methyl-2-vinyl-3-oxopyrazoles **5a-c** (2 mmol) were stirred overnight in 2 N hydrochloric acid (20 ml). The solvent were removed in vacuo and the residue was chromatographed (CH_2Cl_2/MeOH 95:5) to give **6a-c** in 50, 25 and 82% yields, respectively (for characterization see preparation of **6a-c** *via* iodine-based oxidation of **5a,b** below). Compound **11** was isolated in 20 % yield.

1,5,1',5'-Tetramethyl-1,2,1',2'-tetrahydro-4-4'-ethane-1,1'-diyl-bispyrazol-3-one **11**: M.p. > 250°C. ^{1}H (DMSO + CF_3CO_2D): 1.39 (d, 3H, J = 7.3, CH_3); 2.13 (s, 6H, CH_3); 3.50 (s, 6H, NCH_3); 3.64 (q, 1H, J = 7.5, CH). ^{13}C: 9.8 (CH_3); 19.2 (CH_3); 23.8 (CH); 34.5 (CH_3N); 107.6 (C-4); 144.5 (C-5); 158.4 (C-3). *m/z* (EI) = 250. Anal. ($C_{12}H_{18}N_4O_2$): Calc, C: 57.58, H: 7.25, N: 22.38; found, C: 57.42, H: 7.33, N: 22.77.

Preparation of **6a,b** via iodine-based oxidation of **5a,b**: following the guidelines of the reported procedure[17], 1-methyl-2-vinyl-3-oxopyrazole **5a,b** (2 mmol) was refluxed in 50 ml of THF/water 9:1. Iodine (0.53 g; 2.1 mmol) was then added and the solution was heated for 90 min before adding sodium sulfite (0.56 g; 4.5 mmol) in water (10 ml). The reflux was resumed for another 90 min, the solution was concentrated to dryness and the residue chromatographed (CH_2Cl_2/MeOH from 99:1 to 97:3) to give **6a,b** in 76 and 82% yields, respectively.

3-Hydroxy-1-methyl-5-phenylpyrazole **6a**: M.p. (water) = 160-161°C (lit[30] = 161°C). ^{1}H: 3.71 (s, 3H, CH_3); 5.71 (s, 1H, CH=); 7.39-7.48 (m, 5H, ArH). ^{13}C (DMSO) : 36.6 (CH_3); 90.4 (CH-4); 128.2, 128.6 (CHAr); 130.3 (CAr); 143.5 (C-5); 159.8 (C-3).

1,5-Dimethyl-3-hydroxypyrazole **6b**: M.p. (water) = 173°C; (lit[6] = 172-173 °C). ^{1}H (DMSO): 2.10 (s, 3H, CH_3); 3.46 (s, 3H, NCH_3); 5.23 (s,1H, CH-4). ^{13}C: 10.7 (CH_3); 34.8 (CH_3N); 89.7 (CH-4); 138.7 (C-5); 159.4 (C-3). *m/z* (EI) = 112.

1,5-dimethyl-4-ethyl-3-hydroxypyrazole **6c**: Obtained as a solid (82 %) *via* acidic hydrolysis. Recrystallization (water) of a small amount gave **6c**. M.p. = 146°C. ^{1}H: 1.07 (t, 3H, J = 7.4, CH_3); 2.07 (s, 3H, CH_3); 2.30 (q, 2H, J = 7.4, CH_2); 3.55 (s, 3H, NCH_3); 9.3 (s(l), 1H, NH). ^{13}C : 9.5 (CH_3); 15.0 (CH_3); 15.4 (CH_2); 34.7 (N-CH_3); 104.1 (C-4); 136.9 (C-5); 159.4 (C-3). *m/z* (EI) = 140. Anal. ($C_7H_{12}N_2O$): Calc: C: 59.98, H: 8.63, N: 19.98; found, C: 59.91, H: 8.36, N: 20.08.

ACKNOWLEDGMENTS

This work was supported by grants from the Lundbeck Foundation and EEC (BIO2-CT93-0243).

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