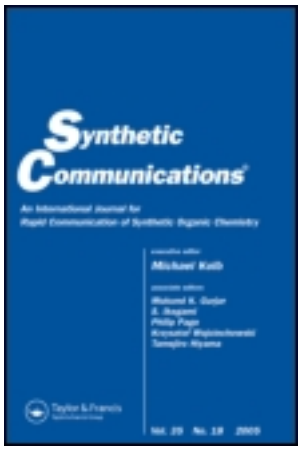

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Potassium Cyanate as an Amino-dehydroxylating Agent: Synthesis of Aminooxypyrrole Mono, Dicarboxylic Acid Esters, and Carbonitrile

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INTRODUCTION

In the vast area of heterocyclic chemistry, the search for new small polyfunctionalized heterocyclic rings constitutes a key step towards the synthesis of larger systems. Amongst these intermediate heterocycles, ortho amino esters are electrophilic and nucleophilic centre containing reagents that have been widely used for further cyclization reactions such as the annelation of a pyridine,[1] pyrimidine,[2] diazepine,[3] benzox-

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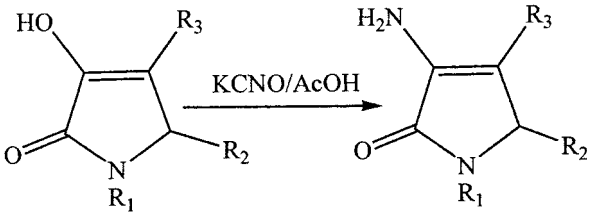
azine or benzothiazine,[4] benzodiazepine,[5] benzoxazepines,[6] and pyrazine[7] ring. Thus, aiming at preparing new heterobicyclic derivatives as potential Xanthine Oxidase inhibitors, we were particularly interested in synthesizing new 4-amino-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylic acid esters.

RESULTS

During the preparation of new potential inhibitors of xanthine oxidase, we have incidentally found that potassium cyanate can be used as a reagent for the amino-dehydroxylation of various hydroxypyrroles such as **1a–d**, **3a–d**, and **5a–d** (Sch. 1 and Table 1).

The preparation of the 4-hydroxy-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylic acid esters **1a–d**, 4-hydroxy-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylic acid esters **3a–d**, and 4-hydroxy-5-oxo-2,5-dihydro-1*H*-pyrrole-3-carbonitrile **5a–d** followed methods previously described in the Lit.[8–10] When subjected to reaction with potassium cyanate in refluxing acetic acid and water the hydroxypyrroles **1a–d**, **3a–d**, and **5a–d** gave the corresponding aminopyrroles **2a–d**, **4a–d**, and **6a–d** in 50 to 82% yields. The best yields were obtained when refluxing the hydroxypyrroles in a 5/1 (v/v) mixture of water and acetic acid. The aminopyrrole carboxylic acid esters **2a–d** and carbonitriles **6a–d** have been described before and were prepared by aminodehydroxylation of their respective hydroxypyrroles with ammonium formate in refluxing ethanol[11] or 2-ethoxyethanol.[12] On the other hand, this is the first preparation of the 4-amino-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylic acid esters **4a–d** (see Table 2 for NMR data). The derivatives **4a–d** couldn't be prepared in satisfactory yield with ammonium salts in refluxing ethanol, 2-ethoxyethanol, or



1a-d
3a-d
5a-d

2a-d
4a-d
6a-d

Scheme 1.

Table 1. Percentage yields for the amino-dehydroxylation of the 4-hydroxypyrroles.

Reactant	Product	R_1	R_2	R_3	Yield (%)
1a	**2a**	CH_3	H	COOEt	65
1b	**2b**	$(CH_3)_2CHCH_2$	H	COOEt	52
1c	**2c**	Benzyl	H	COOEt	76
1d	**2d**	Phenyl	H	COOEt	82
3a	**4a**	CH_3	COOEt	COOEt	59
3b	**4b**	$(CH_3)_2CHCH_2$	COOEt	COOEt	50
3c	**4c**	Benzyl	COOEt	COOEt	65
3d	**4d**	Phenyl	COOEt	COOEt	72
5a	**6a**	CH_3	H	CN	63
5b	**6b**	$(CH_3)_2CHCH_2$	H	CN	51
5c	**6c**	Benzyl	H	CN	62
5d	**6d**	Phenyl	H	CN	69

acetic acid. Moreover, small amounts (up to 8–10%) of **2a–d** were obtained together with **4a–d** when **3a–d** was refluxed in acetic acid or 2-ethoxyethanol.

To the best of our knowledge, the present communication is the first report of the use of cyanate salts for a direct conversion of an enol to an enamine. This procedure provides an alternative route to the standard ones using hexamethyldisilazane[13] (HMDS), high-pressure ammonia,[14] or ammonium salts.[11,12,15] A possible mechanism for this reaction might involve an in situ hydrolysis of potassium cyanate to ammonium acetate. The current method can be applied to molecules containing many different types of functional and protecting groups and might be suitable in cases where the methods using ammonium salts[11,12,15] fail or give unsatisfactory results as shown for the derivatives **4a–d**.

EXPERIMENTAL

Yields expressed are for isolated pure compounds (flash chromatography). Their characterization was obtained by a combination of IR, NMR, MS, microanalysis, and/or direct comparison to authentic material prepared with ammonium acetate. Infrared spectra were recorded on a FTIR-8300 Shimadzu spectrometer in KBr with absorptions in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM

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LA-400 spectrometer. Mass spectra were recorded on a Kratos MS25 spectrometer.

General Procedure

A solution of **1a–d**, **3a–d**, or **5a–d** (2 mmol) and potassium cyanate (1 equiv.) in 5 mL acetic acid and 25 mL water was refluxed for 3 h. After cooling the solution to room temperature, an equivalent of potassium cyanate was added and the solution refluxed for 3 h. This operation was repeated until the reaction was complete as monitored by TLC. The solvents were evaporated and the residual solid stirred in water. The aqueous solution was made alkaline by addition of sodium hydrogenocarbonate, the organics were extracted with ethylacetate and the organic layer washed with brine and water and dried over magensium sulfate. After removal of ethyl acetate, the crude product was purified using flash chromatography (hexane/ethyl acetate ranging from 2/1 to 1/1 ratio) to give the corresponding aminopyrroles **2a–d**, **4a–d**, or **6a–d**.

4-Amino-1-methyl-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylic acid esters 4a. White crystals, m.p. 111°C. IR: 3441 and 3319 (νNH_2), 1733, 1700 and 1688 ($\nu C{=}O$). ^{1}H NMR ($CDCl_3$) δ: 5.76 (br, 2H, NH_2), 4.64 (s, 1H, CH), 4.25 (tq, $J_{H\text{-}H}$=7.3 and 3.7 Hz, 2H, OCH_2), 4.23 ($J_{H\text{-}H}$=7.3 and 3.7Hz, 2H, OCH_2), 3.01 (s, 3H, CH_3N), 1.29 (t, $J_{H\text{-}H}$= 7.3 Hz, 3H, CH_3), 1.27 (t, $J_{H\text{-}H}$=7.3 Hz, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 168.6 (CO), 165.6 (CO), 164.3 (CO), 147.1 (C4), 98.4 (C3), 62.6 (CH_2O), 61.9 (CH_2O), 59.9 (C2), 28.3 (CH_3N), 14.4 (CH_3), 14.1 (CH_3). MS *m*/*e* (%): 256 (M+, 13), 183 (100), 153 (5), 137 (98), 111 (64). Anal. calcd. for $C_{11}H_{16}N_2O_5$: C, 51.56; H, 6.29; N, 10.93. Found: C, 51.73; H, 6.24; N, 10.70.

4-Amino-1-isobutyl-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylic acid esters 4b. Light yellow crystals m.p. 78°C, IR: 3442 and 3317 (νNH_2), 1738, 1701 and 1689 ($\nu C{=}O$), ^{1}H NMR ($CDCl_3$) δ: 5.91 (br, 2H, NH_2), 4.73 (s, 1H, CH), 4.25 (tq, $J_{H\text{-}H}$=7.3 and 3.4 Hz, 2H, OCH_2), 4.23 ($J_{H\text{-}H}$ = 7.3 and 3.4 Hz, 2H, OCH_2), 3.58 (dd $J_{H\text{-}H}$=13.9 and 9.0 Hz, 1H, NCH_2), 2.84 (dd $J_{H\text{-}H}$=13.9 and 6.4 Hz, 1H, NCH_2), 1.98 (m, 1H, CH), 1.29 (t, $J_{H\text{-}H}$=7.3 Hz, 3H, CH_3), 1.27 (t, $J_{H\text{-}H}$= 7.3 Hz, 3H, CH_3), 0.94 (d, $J_{H\text{-}H}$=6.8 Hz, 3H, CH_3), 0.86 (d, $J_{H\text{-}H}$= 6.6 Hz, 3H, CH_3) ^{13}C NMR ($CDCl_3$) δ: 168.6 (CO), 166.1 (CO), 164.4 (CO), 147.1 (C4), 98.5 (C3), 61.8 (CH_2O), 61.4 (CH_2O), 60.0 (C2), 49.2 (CH_2N), 27.3 (CH), 20.1 (CH_3), 19.7 (CH_3), 14.4 (CH_3), 14.1 (CH_3). MS *m*/*e* (%): 298 (M+, 15), 225 (100), 179, (56), 111 (5), 137 (98), 109 (22).

Anal. calcd. for $C_{14}H_{22}N_2O_5$: C, 56.36; H, 7.43; N, 9.39. Found: C, 56.31; H, 7.34; N, 9.44.

4-Amino-1-benzyl-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylic acid esters 4c. White crystals, m.p. 102°C. IR: 3418 and 3320 (νNH_2), 1747, 1707 and 1696 ($\nu C{=}O$). ^1H NMR ($CDCl_3$) δ: 5.68 (br, 2H, NH_2), 5.03 (d, $J_{H\text{-}H}$=14.9 Hz, 1H, $1CH_2Ph$), 4.56 (s, 1H, CH), 4.19 ($J_{H\text{-}H}$=7.0 and 3.7 Hz, 2H, OCH_2), 4.16 (d, $J_{H\text{-}H}$=14.9 Hz, 1H, $1CH_2Ph$), 4.10 ($J_{H\text{-}H}$ = 7.1 and 3.7 Hz, 2H, OCH_2), 1.25 (t, $J_{H\text{-}H}$=7.0 Hz, 3H, CH_3), 1.23 (t, $J_{H\text{-}H}$=7.1 Hz, 3H, CH_3) ^{13}C NMR ($CDCl_3$) δ: 168.6 (CO), 165.6 (CO), 164.4 (CO), 148.8 (C4), 135.5 (Ph), 128.7 (Ph), 128.5 (Ph), 128.0 (Ph), 99.0 (C3), 61.8 (CH_2O), 60.3 (CH_2O), 60.0 (C2), 45.7 (CH_2N), 14.3 (CH_3), 14.0 (CH_3). MS *m*/*e* (%): 332 (M+, 16), 259 (100), 213 (67), 187, (18), 177 (35), 149 (19), 135 (16), 106 (786). Anal. calcd. for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43. Found: C, 61.51; H, 6.00; N, 8.42.

4-Amino-1-phenyl-5-oxo-2,5-dihydro-1*H*-pyrrole-2,3-dicarboxylic acid esters 4d. Light red crystals, m.p. 98°C. IR: 3441 and 3319 (νNH_2), 1746, 1720 and 1699 ($\nu C{=}O$). ^1H NMR ($CDCl_3$) δ: 5.68 (br, 2H, NH_2), 5.03 (d, $J_{H\text{-}H}$=14.9 Hz, 1H, $1CH_2Ph$), 4.56 (s, 1H, CH), 4.19 ($J_{H\text{-}H}$=7.0 and 3.7 Hz, 2H, OCH_2), 4.16 (d, $J_{H\text{-}H}$=14.9 Hz, 1H, $1CH_2Ph$), 4.10 ($J_{H\text{-}H}$=7.1 and 3.7 Hz, 2H, OCH_2), 1.27 (t, $J_{H\text{-}H}$=7.0 Hz, 3H, CH_3), 1.25 (t, $J_{H\text{-}H}$=7.1 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ: 168.6 (CO), 165.6 (CO), 164.4 (CO), 148.8 (C4), 135.5 (Ph), 128.7 (Ph), 128.5 (Ph), 128.0 (Ph), 99.0 (C3), 61.8 (CH_2O), 60.3 (CH_2O), 60.0 (C2), 45.7 (CH_2N), 14.3 (CH_3), 14.0 (CH_3) MS *m*/*e* (%): 318 (M+, 18), 245 (100), 199 (79), 171 (9), 143 (9), 104 (19), 77 (32). Anal. calcd. for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.23; H, 5.60; N, 8.71.

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