Synthesis of Cyanopyrroles

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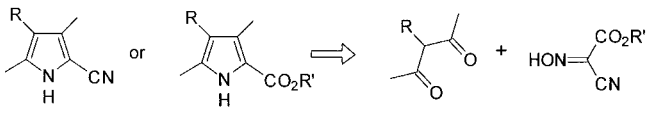
Abstract: Regioselective synthesis of α-cyanopyrroles (vs. α-alkoxycarbonylpyrroles) using oximinocyanoacetate esters in a Knorr-type reductive condensation with β-diketones can be directed by the presence of water. Thus, methyl oximinocyanoacetate was reacted with pentane-2,4-dione in hot acetic acid in the presence of zinc dust to give exclusively 3,5-dimethylpyrrole-2-carbonitrile when the acetic acid was wet; whereas, in glacial acetic acid only methyl 3,5-dimethylpyrrole-2-carboxylate was isolated (~40% yield).

Key words: α-cyanopyrroles, oximinocyanoacetate, Knorr-type reaction

Over forty years ago, Kleinspehn described for the first time how ethyl oximinocyanoacetate could be used in a Knorr-type reductive condensation to synthesize α-cyanopyrroles. Thus, after mixing pentane-2,4-dione, ethyl oximinocyanoacetate and anhydrous sodium acetate in ~12% aqueous acetic acid, addition of zinc dust at 95–105 °C afforded a 35% crude yield of 3,5-dimethylpyrrole-2-carbonitrile. A similar reaction using 3-ethylpentane-2,4-dione gave 4-ethyl-3,5-dimethylpyrrole-2-carbonitrile in 45% crude yield. These two α-cyanopyrroles had been described some 20–30 years earlier, prepared by Fischer et al.[2,3] by cyanation of the corresponding α-free pyrroles. The Kleinspehn modification offered a simple and direct way to prepare α-cyanopyrroles that was different from the then known procedures.[4] Interestingly, Kleinspehn noted that the order of addition of reactants affected the course of the reaction: when ethyl oximinocyanoacetate was added to a mixture of zinc dust in a hot acetic acid containing pentane-2,4-dione, a mixture of ethyl 3,5-dimethylpyrrole-2-carboxylate and 3,5-dimethylpyrrole-2-carbonitrile was obtained, but when the zinc dust was added slowly with stirring to a hot solution of the two organic reactants, only the cyanopyrrole was obtained.



1a	**2ac**	**3a**	**4** R' = Me
1a	**2ad**	**3a**	**5** R' = Et
1b	**2bc**	**3b**	**4** R' = Me
1b	**2bd**	**3b**	**5** R' = Et

a: R = H; **b**: R = $CH_2CH_2CO_2Me$ **c**: R' = Me **d**: R' = Et

Scheme 1

Subsequently, Clezy et al.[5] repeated the Kleinspehn procedure to afford ethyl 2-cyano-3,5-dimethylpyrrole-4-propanoate in moderate yield, with the corresponding ethyl pyrrole-2-carboxylate isolated as a minor byproduct. Although other methods are now available to prepare α-cyanopyrroles, e.g. by displacement of an α-bromo[6] or by a Barton–Zard reaction using isocyanoacetonitrile and α-acetoxynitroalkanes,[7] the former requires strong electron-withdrawing groups at the β and α' positions, and the latter affords an α′-free pyrrole. Since our interests lay in preparing directly 2-cyanopyrroles with substituents at pyrrole ring positions 3, 4 and 5, we reinvestigated Kleinspehn's reaction.

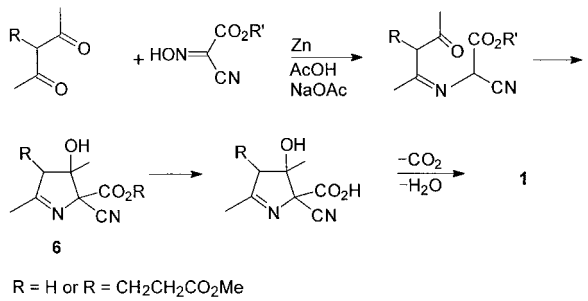
For synthesis of cyanopyrroles, we used either methyl or ethyl cyanoacetate (**4** and **5**, respectively) and either pentane-2,4-dione **(3a)** or 3-[2-(methoxycarbonyl)ethyl]pentane-2,4-dione **(3b)** as synthons in Scheme 1. As is customary for Knorr-type pyrrole syntheses, zinc dust was the reducing agent and acetic acid was the solvent. We found that regioselectivity in the product formation depended on the presence of water in the acetic acid solvent. For reactions carried out in glacial acetic acid, the cyanopyrrole was not observed in the crude solid obtained after quenching the reaction with water. However, when water was present in the reaction solvent, as in 1:1 acetic acid/water, the α-cyanopyrrole was found in the crude solid obtained after quenching the reaction with water, but the α-(m)ethoxycarbonylpyrrole was not observed (Table). By varying the reaction temperature and time, we noted that with longer reaction times, the product yields were altered. Thus in 1:1 acetic acid/water, the yield of cyanopyrrole decreased when the reaction time was extended from 0.5 to 4 h but no α-(m)ethoxycarbonylpyrrole was found. When the temperature was lowered from 80 °C to 50 °C, no pyrrole products were isolated. For purposes of making α-cyanopyrroles, there appears to be no advantage in using **5** or **4**. As the ratio of acetic acid to water increases, e.g. to 2:1, a mixture of α-cyano and α-(m)ethoxycarbonylpyrroles is obtained. In glacial acetic acid, only the latter is formed. Of course, a better synthesis of the latter is to use (m)ethyl oximinoacetoacetate or di(m)ethyl oximinomalonate as synthons in place of **4** or **5**.[8,9]

Just how water acts to control the product distribution is not entirely clear. We speculate that it becomes most important after the dihydroisopyrrole intermediate **6** is formed (Scheme 2). The presence of water in the reaction might lead to hydrolysis of the alkoxycarbonyl group (CO_2R') to the acid, which after decarboxylation and dehydration converts **6** to **1**. When water is absent, a differ-

Table Influence of Reaction Temperature and the Presence of Water on the Regioselectivity of the Pyrrole-Forming Condensation of Methyl (**4**) or Ethyl Oximinocyanoacetate (**5**) with Pentane-2,5-dione (**3a**) and 3-(Methoxycarbonylethyl)pentane-2,4-dione (**3b**)[a]

Reactants		Reaction Conditions			Yield (%) Product[a]			
Dione	Oxime	Solvent	Temp (°C)	Time (h)	**1a**	**2a**	**1b**	**2b**
3a	**4**	AcOH/H_2O (1:1)	80	0.5	38	0	–	–
3a	**4**	AcOH/H_2O (1:1)	80	4	25	0	–	–
3a	**4**	AcOH/H_2O (1:1)	50	4	13	0	–	–
3a	**4**	AcOH	80	0.5	0	0	–	–
3a	**4**	AcOH	80	4	0	28	–	–
3a	**4**	AcOH	50	4	0	<1	–	–
3b	**4**	AcOH/H_2O (1:1)	80	0.5	–	–	23	0
3b	**4**	AcOH/H_2O (1:1)	80	4	–	–	0	0
3b	**4**	AcOH/H_2O (1:1)	50	4	–	–	21	0
3b	**4**	AcOH	80	4	–	–	0	32
3b	**4**	AcOH	50	4	–	–	0	23
3a	**5**	AcOH/H_2O (1:1)	80	0.5	26	0	–	–
3a	**5**	AcOH/H_2O (2:1)	80	0.5	4	10	–	–
3a	**5**	AcOH	80	4	0	37	–	–
3b	**5**	AcOH/H_2O (1:1)	80	0.5	–	–	27	0
3b	**5**	AcOH	80	0.5	–	–	0	16
3b	**5**	AcOH	50	4	–	–	0	12
3b	**5**	AcOH	50	11	–	–	0	40

[a] See Scheme 1 for structures; **2a** = **2ac** and **2b** = **2bc** when **4** is used; when **5** is used **2a** = **2ad** and **2b** = **2bd**.



Scheme 2

ent course is followed, where presumably acetate ion attacks the CN group in preference to the (m)ethoxycarbonyl group followed by elimination.

IR spectra were recorded on Perkin–Elmer 1600 FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Unity 500 MHz spectrometer or a General Electric QE-300 spectrometer using $CDCl_3$ as solvent and TMS as an internal standard. GC-MS analyses were carried out on a Hewlett–Packard GC-MS Model 5890A ion selective detector equipped with a DB-1 (100% dimethylpolysiloxane) column. Mps are uncorrected. Combustion analyses were carried out by the Desert Analytics Laboratory in Tucson, Arizona. All reagents and solvents were from Fisher Chemicals or ACROS Organics and were used without further purification.

Methyl Oximinocyanoacetate [Methyl 2-Cyano-2-(hydroxyimino)acetate] (4)

Into a 500-mL three-neck round bottom flask equipped with a mechanical stirrer and a long stem funnel were placed glacial AcOH (100 mL) and NaOH pellets (12 g). Stirring was begun, and over 10 min the pellets dissolved, bringing the mixture just barely to reflux. Methyl cyanoacetate (50.0 g, 0.50 mol) was added to the hot solution and rinsed with glacial AcOH (5 mL). Slow dropwise addition of a solution of $NaNO_2$ (80 g, 1.16 mol) in water (100 mL) was begun immediately. The addition was complete in 1–1.5 h. Stirring was continued while the reaction temperature dropped to r.t. After stirring at r.t. for 3 h, a precipitate began to form. Then the mixture was diluted with water (100 mL) and allowed to stand at 10 °C for 3 h. The solid was collected by suction filtration and dried in air to give a white product (64.47 g, 97%); mp 120–122 °C (lit.[10] mp 124 °C).

IR (KBr): ν = 3547, 3448 (O–H), 2990 (C–H), 2233 (CN), 1728 (C=O), 1654, 1434, 1314, 1067, 853, 768 cm^{-1}.

^{1}H NMR (300 MHz, D_2O): δ = 3.886 (s, 3H, CH_3), 4.8 (br, *H*DO).

^{13}C NMR (75 MHz, D_2O): δ = 53.662 (*C*H$_3$), 111.611 (*C*N), 127.267 (*C*=N), 162.706 (*C*=O).

GC-MS (t_R 5.4 min): *m/z* = 128 ($M^{+\bullet}$), 111 (M – OH), 97 (M – OCH_3), 69 (M – CO_2CH_3).

Ethyl Oximinocyanoacetate [Ethyl 2-Cyano-2-(hydroxyimino)acetate] (5)

Ethyl cyanoacetate (119.7 g 1.06 mmol) was treated with $NaNO_2$ (150 g, 2.17 mmol) as described earlier[11] to give **5** as white needles (130 g, 92%); mp 128–130 °C (lit.[11] mp 131–133 °C).

IR (KBr): ν = 3600, 3248 (O–H), 3008, 2851 (C–H), 2239 (CN), 1732 (C=O), 1636, 1594, 1452, 1319, 1062, 820, 763, 513 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.407 (t, 3H, *J* = 6.84 Hz, CH_2CH_3), 4.436 (q, 2H, *J* = 6.84 Hz, CH_2CH_3), 4.833 (br, 1H, O*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.909 (CH_2CH_3), 63.58 (CH_2CH_3), 109.25, 109.46(*C*N), 126.46, 128.71 (*C*=N), 161.83 (*C*=O).

GC-MS (t_R 7.2 min): *m/z* = 142 ($M^{+\bullet}$), 125 (M – OH), 114 (M – CH_2CH_2), 97 (M – OCH_2CH_3), 69 (M – $CO_2CH_2CH_3$).

Synthesis of α-Cyanopyrroles or α-(M)ethoxycarbonylpyrroles; General Procedure

Equal molar amounts of oxime (**4** or **5**) and β-diketone (**3a** or **3b**) (10 mmol each) were dissolved in glacial AcOH (20 mL) or aq AcOH (20 mL). The solution was warmed to a designated temperature on an oil bath or a water bath. Into the rapidly stirred solution, zinc dust (2.5 g-atoms) was added in small portions so that the tem-

perature of the mixture was kept at 3–5 °C above the bath temperature. After all the zinc dust was added, the mixture was stirred on the same bath for a time listed in the Table. (For reactions in aq AcOH, excess zinc dust became small pearls at the end of the reaction.) The mixture was poured into water (100 mL), and the precipitated pyrrole was collected by suction filtration and washed with water. The product was crystallized once from 70% aq MeOH for spectroscopic analyses.

3,5-Dimethylpyrrole-2-carbonitrile (1a)
Following the general procedure, in AcOH/H_2O (1:1) at 80 °C and a 30 min reaction time, **3a** (1.0 g, 0.01 mol) gave 0.46 g (38%) of **1a** by reaction with **4** (1.3 g, 0.01 mol), and a 26% yield by reaction with **5** (1.4 g, 0.01 mol); mp 75–76 °C (lit.[1] mp 75–76.5 °C).

IR (KBr): ν = 3268 (N–H), 2919 (C–H), 2212 (CN), 1499, 1384, 1264, 800 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.199 (s, 3H, CH_3), 2.248 (s, 3H, CH_3), 5.791 (s, 1H, 4-H), 9.450 (br, 1H, N-*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.59, 13.09, 97.10, 109.25, 115.55, 132.87, 134.29.

GC-MS (t_R 12.0 min): *m/z* = 120 ($M^{+\bullet}$), 119 (M – H), 105 (M – CH_3), 92, 65.

Methyl 3,5-Dimethylpyrrole-2-carboxylate (2ac)
Following the general procedure, in glacial AcOH at 80 °C and a 4 h reaction time, **3a** (1.0 g, 0.01 mol) and **4** (1.3 g, 0.01 mol) gave 0.43 g (28%) of **2ac**; mp 94–96 °C (lit.[12] no mp reported).

IR (KBr): ν = 3292 (N–H), 2956 (C–H), 1684 (C=O), 1474, 1458, 1283, 1224, 1109, 802 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.245 (s, 3H, CH_3), 2.300 (s, 3H, CH_3), 3.824 (s, 3H, CH_3), 5.796 (s, 1H, *J* = 2.3 Hz, 4-H), 8.758 (br, 1H, N-*H*).

GC-MS (t_R 8.2 min): *m/z* = 153 ($M^{+\bullet}$), 138 (M – CH_3), 122 (M – OCH_3), 94 (M – CO_2CH_3), 66.

Ethyl 3,5-Dimethylpyrrole-2-carboxylate (2ad)
Following the general procedure, in glacial AcOH, at 50 °C and a 4 h reaction time, **3a** (1.0 g, 0.01 mol) and **5** (1.4 g, 0.01 mol) gave 0.62 g (37%) of **2ad**; mp 125–126 °C (lit.[3] mp 125 °C).

IR (KBr): ν = 3296 (N–H), 2981, 2929 (C–H), 1658 (C=O), 1454,1272, 1218, 1121, 1105, 1026, 801 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.350 (t, 3H, *J* = 6.84 Hz, CH_2CH_3), 2.248 (s, 3H, CH_3), 2.305 (s, 3H, CH_3), 4.294 (q, 2H, *J* = 6.84 Hz, CH_2CH_3), 5.793 (s, 1H, *J* = 2.3 Hz, 4-H), 8.760 (br, 1H, N-*H*).

GC-MS (t_R 9.4 min): *m/z* = 167 ($M^{+\bullet}$), 138 (M – CH_2CH_3), 122 (M – OCH_2CH_3), 94 (M – $CO_2CH_2CH_3$), 66.

Methyl 2-Cyano-3,5-dimethylpyrrole-4-propanoate (1b)
Following the general procedure, in AcOH/H_2O (1:1) solvent β-diketone **3b** (1.9 g, 0.01 mol) was reacted with **4** (1.3 g, 0.01 mol) at 80 °C for 30 min to give 0.47 g (23%) of **1b**; mp 73–74 °C; reaction of **3b** with **5** gave a 27% yield of **1b**.

IR (KBr): ν = 3310 (N–H), 2959 (C–H), 2199 (CN), 1708 (C=O), 1432, 1370, 1303,1256, 1209 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.151 (s, 3H, CH_3), 2.208 (s, 3H, CH_3), 2.440 (t, 2H, *J* = 7.5 Hz, propanoic CH_2), 2.691 (t, 2H, *J* = 7.5 Hz, propanoic CH_2), 3.669 (s, 3H, CH_3), 8.645 (br, 1H, N–*H*).

^{13}C NMR (500 MHz, $CDCl_3$): δ = 10.02, 11.48, 19.53, 34.55, 51.64, 97.07, 115.10, 118.73,131.11, 131.19, 173.42.

GC-MS (15.8 min): *m/z* = 206 ($M^{+\bullet}$), 174 (M – $HOCH_3$), 133 (M – $CH_2CO_2CH_3$).

Anal. Calcd for $C_{11}H_{14}N_2O_4$ (206.2): C, 64.06; H, 6.84; N, 13.58. Found: C, 63.79; H, 6.70; N, 13.59

Methyl 2-Methoxycarbonyl-3,5-dimethylpyrrole-4-propanoate (2bc)
Following the general procedure, in glacial AcOH solvent, **3b** (1.9 g, 0.01 mol) was reacted with **4** at 50 °C for 4 h to give 0.55 g (23%) of **2bc;** mp 106–107 °C (lit.[6] mp 108 °C).

IR (KBr): ν = 3311 (N–H), 2948 (C–H), 1736, 1664 (C=O), 11500, 1451, 1418, 1372, 1298, 1269, 1218, 1178, 1091, 991, 774, 582 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 2.215 (s, 3H, CH_3), 2.267 (s, 3H, CH_3), 2.427 (t, 2H, *J* = 7.5 Hz, propanoic CH_2), 2.704 (t, 2H, *J* = 7.5 Hz, propanoic CH_2), 3.661 (s, 3H, CH_3), 3.819 (s, 3H, CH_3), 8.666 (br, 1H, N-*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.47, 11.42, 19.59, 34.88, 50.88, 51.54, 116.79, 120.02, 127.07, 129.90. 161.99, 173.50.

GC-MS (t_R 15.2 min): *m/z* = 239 ($M^{+\bullet}$), 208 (M^+ – OCH_3), 180 (M^+ – CO_2CH_3), 166 (M^+ – $CH_2CO_2CH_3$), 134.

Methyl 2-Ethoxycarbonyl-3,5-dimethylpyrrole-4-propanoate (2bd)
Following the general procedure, in glacial AcOH solvent, **3b** (1.9 g, 0.1 mol) was reacted with **5** (1.4 g, 0.01 mol) at 50 °C for 11 h to give 1.0 g (40%) of **2bd**; mp 103–104 °C (lit.[6] mp 104 °C).

IR (KBr): ν = 3304 (N–H), 2949 (C–H), 1735, 1661 (C=O), 1508, 1438, 1267, 1171, 1093, 1025, 777 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.337 (t, 3H, *J* = 7.32 Hz, CH_2CH_3), 2.209 (s, 3H, CH_3), 2.263 (s, 3H, CH_3), 2.419 (t, 2H, *J* = 8.30 Hz, propanoic CH_2), 2.699 (t, 2H, *J* = 8.30 Hz, propanoic CH_2), 3.661 (s, 3H, CH_3), 4.280 (q, 2H, *J* = 7.32 Hz, CH_2CH_3), 8.638 (br, 1H, N-*H*).

GC-MS (t_R 16.4 min): *m/z* = 253 ($M^{+\bullet}$), 208 (M – OCH_2CH_3), 180 (M – $CO_2CH_2CH_3$ or M – $CH_2CO_2CH_3$), 134.

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