N-Acylpyrroles as Acylating Agents. Synthesis of β-Keto Esters

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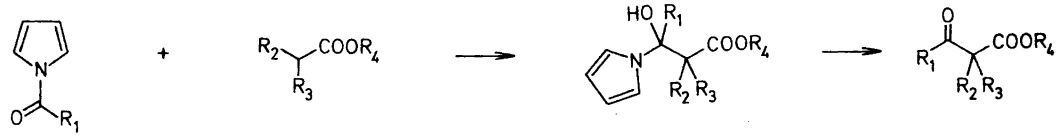
The reaction between lithium ester enolates and *N*-acylpyrroles gives isolable pyrrolyl carbinols (**3**) in almost quantitative yields. Heating or treatment of these with basic reagents affords β-keto esters in good to excellent yields.

Several condensation techniques are available for the preparation of β-keto esters.[1-5] For the α-acylation of ordinary esters one can prepare the lithium ester enolate using two equiv. of base and then acylate with an acyl chloride.[6] We report here on the use of *N*-acylpyrroles (**1**) as acylating agents. Unlike acyl chlorides, the *N*-acylpyrroles do not lead directly to β-keto esters and so the second equivalent of base is not needed. Instead, the tetrahedral intermediates obtained by reaction of the lithium ester enolates with **1** are stable in tetrahydrofuran at −78 °C and can be protonated with acetic acid at low temperature to give pyrrolyl carbinols (**3a–e**) in almost quantitative yields. In these experiments the esters **2** were used in excess, but it is also possible to obtain an excellent result when **1** is used in excess. When compound **3d** was prepared in this latter manner the yield based on ethyl acetate was ca. 95 %. As found by NMR, **3b** and **3e** are mixtures of diastereomers (2:7 and 1:5 ratios, respectively). Three of the pyrrolyl carbinols (**3c–e**) were obtained in crystalline form (**3d**, 81 %). The yield of crystalline **3e** was lower (38 %) owing to the presence of two diastereomers. The pyrrolyl carbinols (**3**) are stable in the crystalline state for several months at 22 °C and as a syrup for several months at −20 °C.



1 **2** **3** **4**

		Product (yield/%)[a]	Product (yield/%)
R^1=Me	R^2=R^3=H; R^4=Bu^t	**3a** (>95)	**4a**
	R^2=H; R^3=Bu; R^4=Et	**3b** (~95)	**4b** (82)[a,c]
	R^2=R^3=Me; R^4=Et	**3c** (~95)	**4c** (90)[b,c]
R^1=Et	R^2=R^3=H; R^4=Et	**3d** (>95)	**4d** (100)[b,d]
R^1=Pr^i	R^2=H; R^3=Bu; R^4=Et	**3e** (>95)	**4e** (92)[b,e]

[a]Determined by ^{1}H NMR; based on **1**. [b]Based on **3**.
Method of conversion **3** → **4**: [c]distillation at ca. 110 °C, [d]K_2CO_3, 50 °C, 6 h, [e]CH_3CN–H_2O, 77 °C, 6 h.

The transformation of **3** to **4** can be carried out in various ways, generally by heating and/or the use of basic reagents. Heating in aqueous acetonitrile (2.5–33 h) produces β-keto esters **4** in yields of from 90 to ca. 100 % yield. Heat treatment of **3b** (ca. 110 °C) under reduced pressure leads to the distillation of **4b**; the overall yield, based on **1**, was 82 %. The pyrrolyl carbinol **3c** was more stable and showed only about 50 % conversion after 24 h at the same temperature. However, on heating at 180–190 °C **4c** distilled (90 %). The most efficient conversion occurred when **3d** (neat) was treated with anhydrous potassium carbonate at 50 °C (100 %). Finally, it should be pointed out that extensive conversion to **4** can be obtained even at low temperature and with short reaction times. A cold (−75 °C) solution of the lithium salt precursor of **3b** was added to an insufficient amount of dilute hydrochloric acid so that the resulting aqueous phase had pH >9. After warming to 0 °C (ca. 15 min) and subsequently acidifying the mixture, **3b** and **4b** were obtained in the ratio 1:6 (^{1}H NMR).

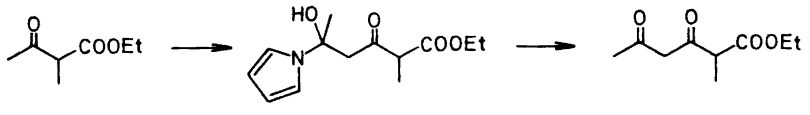
The new technique for synthesising β-keto esters has also been utilised to prepare a β,δ-diketo ester (**6**). Ethyl 2-methyl-3-oxo-butanoate was dilithiated[7] and allowed to react with *N*-acetylpyrrole, giving **5** in 89 % yield. This pyrrolyl carbinol was more difficult to convert to its corresponding keto ester than were the compounds **3**. Use of 1,4-diazabicyclo[2.2.2]octane in toluene (100 °C) gave mainly the undesired retroaldol cleavage, and only 25 % of **6** was obtained. However, when **5** was treated in aqueous acetonitrile under reflux the conversion into **6** was almost quantitative. The structure of the reaction product was evident from its ^{1}H and ^{13}C NMR spectra, which showed that there was ca. 85 % of the enol form. The literature ^{1}H NMR data for **6** are not compatible with either the keto or the enol form or any mixture of them, and these data must therefore be rejected.[8] On the other hand, there is good agreement between our ^{1}H NMR spectrum and values given for the methyl ester analogue of **6**, which was present in the enol form to the extent of 80 %.[9]

Several nucleophilic additions to the carbonyl group of *N*-acylpyrroles have been reported, but those involving organolithium or Grignard reagents were performed so as to give tertiary alcohols rather than ketones.[10] The syntheses of β-keto esters described here represent the first efficient C-acylations using *N*-acylpyrroles. Similar reactions have been obtained with *N,O*-dialkylhydroxamic acids[11,12], but these compounds are probably less electrophilic than the *N*-acylpyrroles. Other derivatives of carboxylic acids seem to give less stable tetrahedral intermediates.[12]

Experimental

Tetrahydrofuran (THF) was distilled over $LiAlH_4$. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM FX-100 spectrometer. Internal tetramethylsilane (TMS) was used as reference for ^{1}H spectra of $CDCl_3$ solutions, and the solvent signal (δ 3.40) for samples in CD_3OD. Unless otherwise stated, ^{13}C NMR shifts are relative to the solvent signal (CD_3OD, 49.30 ppm). DC-Fertigplatten Kieselgel 60 F_{254} plates (Merck) were used in the TLC analyses. Gas chromatography was performed on a OV-101 fused silica capillary column (25 m) mounted in a HP 5830 A instrument.

1-(2-methyl-1-oxopropyl)pyrrole. Pieces of potassium (3.12 g, 80 mmol) were added to a stirred solution of pyrrole (6.72 g, 100 mmol) in dry THF (120 ml, N_2 atmosphere) followed by heating under reflux (4 h). The temperature was then lowered to ca. −75 °C and 2-methylpropanoyl chloride (8.00 g, 75 mmol) in THF (75 ml) was added within a period of 1 min. The mixture was allowed to attain 22 °C overnight and was then washed with saturated aqueous sodium chloride. After drying (Na_2SO_4) and concentration of the organic phase, the residue was distilled to yield 8.73 g (85 %) of the *N*-acylpyrrole, b.p. 85–86 °C (1.6 kPa). GLC purity, 98 %; ^{1}H NMR (CD_3OD): δ 7.49 and 6.39 (t, 2 H, *J* 2.5 Hz), 3.47 (m, 1 H, *J* 6.8 Hz), 1.28 (d, 6 H, *J* 6.8 Hz).



5 **6**

1-(1-Oxopropyl)pyrrole was prepared similarly (79 %), b.p. 76–80 °C (1.6 kPa); lit.[13] b.p. 192–194 °C.

1-(1-Oxoethyl)pyrrole was prepared from *N*-acetylimidazole and pyrrole.[14]

Typical condensation. Ethyl 3-hydroxy-3-(1-pyrrolyl)pentanoate (**3d**). Butyllithium (42 mmol) in hexane (30 ml, 1.6 M) was added (10 min, N_2 atmosphere) to a cooled (−10 °C) and stirred solution of diisopropylamine (4.85 g, 48 mmol) in THF (40 ml). After stirring for an additional 15 min, the temperature was lowered to ca. −75 °C and a solution of ethyl acetate (4.22 g, 48 mmol) in THF (30 ml) was added over a period of 30 min. Stirring was continued for 30 min and then 1-(1-oxopropyl)pyrrole (3.70 g, 30 mmol) in THF (30 ml) was added (10 min). After 2 h at ca. −75 °C, acetic acid (9 ml) was added at such a rate that the temperature did not exceed −60 °C. The reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$; the pH of the resulting aqueous phase was ca. 8. The organic phase was separated, sodium chloride was added to the aqueous phase and this was then extracted with ether (2 × 50 ml). The organic phases were combined and dried (Na_2SO_4), and the solvents evaporated to give a crude product (6.70 g) which was about 95 % pure (^{1}H NMR). After filtration through a 1 cm silica gel column (ether/light petroleum, 1:1), **3d** was crystallised from ether/light petroleum (1:9). Three crops afforded in all 5.11 g (81 %), m.p. 44–45 °C; ^{1}H NMR: δ 6.95 (t, 2 H, $J \approx 2.3$ Hz), 6.14 (t, 2 H, $J \approx 2.3$ Hz), 4.14 (q, 2 H, J 7.0 Hz), 3.11 and 3.04 (AB spectrum, 2 H, J 15.4 Hz), 2.14 (m, 2 H), 1.24 (t, 3 H, J 7.0 Hz), 0.87 (t, 3 H, J 7.3 Hz). ^{13}C NMR: 172.3, 118.9, 109.0, 87.9, 62.1, 46.1, 35.7, 14.6, 8.0 ppm.

tert-*Butyl 3-hydroxy-3-(1-pyrrolyl)butanoate* (**3a**). ^{1}H NMR: 6.99 (t, 2 H, $J \approx 2.2$ Hz), 6.14 (t, 2 H, $J \approx 2.2$ Hz), 2.95 (s, 2 H), 1.90 (s, 3 H), 1.43 (s, 9 H). ^{13}C NMR: 171.1, 118.8, 109.1, 85.3, 82.5, 49.9, 28.9, 28.4 ppm.

Ethyl 2-butyl-3-hydroxy-3-(1-pyrrolyl)butanoate (**3b**) was obtained as a 2:7 mixture of stereoisomers. ^{13}C NMR of major (minor) component: 175.2 (174.7), 119.0 (118.9), 109.2 (108.9), 87.6 (87.2), 61.9 (61.6), 59.1 (60.0), 31.1 (31.5), 28.8 (28.8), 24.5 (25.1), 23.5 (23.8), 14.8 (14.6), 14.4 (14.4) ppm. ^{1}H NMR of major isomer: δ 6.98 (t, 2 H, $J \approx 2.3$ Hz), 6.14 (t, 2 H, $J \approx 2.3$ Hz), 4.20 (q, 2 H, $J \approx 7$ Hz), 3.03 (dd, 1 H, $J \approx 11$ and 2 Hz), 2.0–0.8 (m, 15 H, including a 3 H singlet at δ 1.90).

Ethyl 2,2-dimethyl-3-hydroxy-3-(1-pyrrolyl)butanoate (**3c**) was crystallised from light petroleum, m.p. 35–36 °C. ^{1}H NMR: δ 6.90 (t, 2 H, $J \approx 2.3$ Hz), 6.05 (t, 2 H, $J \approx 2.3$ Hz), 4.12 (q, 2 H, $J \approx 7$ Hz), 1.94 (s, 3 H), 1.30 (t, 3 H, $J \approx 7$ Hz), 1.29 (s, 3 H), 1.24 (s, 3 H). ^{13}C NMR: 177.6, 120.2, 108.1, 89.7, 62.2, 53.5, 25.9, 22.3, 22.2, 14.5 ppm.

Ethyl 2-butyl-3-hydroxy-4-methyl-3-(1-pyrrolyl)-pentanoate (**3e**) was obtained as a 1:5 mixture of stereoisomers. The major isomers crystallised from light petroleum/ether (4:1), m.p. 32–34 °C; ^{1}H NMR: δ 6.91 (t, 2 H, $J \approx 2.2$ Hz), 6.14 (t, 2 H, $J \approx 2.2$ Hz), 4.26 (q, 2 H), 3.28 (dd, 1 H, J 1.5 and 11 Hz), 2.5–0.8 (m, 19 H, including a 3 H triplet at 1.35 and two 3 H doublets at 0.96 and 0.92). ^{13}C NMR: 175.8, 119.6, 108.2, 91.8, 62.2, 54.7, 39.2, 31.2, 27.8, 23.7, 17.7, 17.2, 14.7, 14.5 ppm.

Ethyl 2-butyl-3-oxobutanoate (**4b**). The THF solution of the lithium salt of **3b**, prepared from *N*-acetylpyrrole (30 mmol) and ethyl hexanoate (33 mmol) according to the general technique described above, was allowed to reach −50 °C and then poured into hydrochloric acid (1 M, 80 ml). Normal extraction and drying followed by distillation at 105–115 °C (1.6 kPa) gave pure **4b** (82 %); lit.[15] b.p. 112–117 °C/16 mmHg. ^{1}H NMR ($CDCl_3$): δ 4.18 (q, 2 H), 3.38 (t, 1 H), 2.22 (s, 3 H), 2.0–1.7 (m, 2 H), 1.5–1.1 (m, 7 H, including a t at 1.28), 0.90 (t, 3 H); lit.[16] data for **4b** (neat) differ only slightly. ^{13}C NMR ($CDCl_3$, TMS): 203.2, 170.0, 61.3, 60.0, 29.6, 28.7, 28.0, 22.5, 14.2, 13.8 ppm.

Ethyl 3-oxopentanoate (**4d**). A mixture of **3d** (100 mg, 0.474 mmol) and 1,4-diazabicyclo[2.2.2]octane (25 mg, 0.222 mmol) in toluene (10 ml) was heated at 100 °C (2.5 h). The solution was cooled, diluted with ether (30 ml) and washed with hydrochloric acid and brine. After drying (Na_2SO_4) and concentration, a residue was obtained (80 mg) which consisted (^{1}H NMR) of **4d**, toluene and pyrrole in the molar ratios 78:20:2; yield of **4d**, 95 %. ^{1}H NMR ($CDCl_3$): δ 4.20 (q, 2 H), 3.44

(s, 2 H), 2.57 (q, 2 H), 1.28 (t, 3 H), 1.09 (t, 3 H). The enol form (ca. 7 %) showed a singlet at δ 4.94; these values are in good agreement with those measured[17] in CCl_4. ^{13}C NMR ($CDCl_3$, TMS): 203.3, 167.3, 61.3, 49.0, 36.3, 14.1, 7.5 ppm.

Alternative preparation of **4d**. A mixture of **3d** (210 mg, 1.00 mmol) and ground anhydrous potassium carbonate (30 mg) was heated (50 °C, 6 h) in a flame-dried flask equipped with a drying tube. The residue (234 mg) was dissolved in $CDCl_3$ (ca. 1 ml) and the solution analysed by ^1H NMR. Only pyrrole and **4d** were detected in a molar ratio of 0.86:1, corresponding to a ca. 100 % yield of **4d**.

Ethyl 2-butyl-4-methyl-3-oxopentanoate (**4e**). A mixture of **3e** (280 mg, 1.00 mmol), acetonitrile (10 ml) and hydrochloric acid (0.01 M, 5 ml) was heated under reflux for 6 h. After cooling, saturated aqueous sodium chloride (5 ml) and ether (20 ml) were added and the mixture shaken. The organic phase was dried (Na_2SO_4) and concentrated to give an oily residue (210 mg). ^1H NMR showed the presence of only pyrrole and **4e** in a molar ratio of 7:32, corresponding to a 92 % yield of **4e**. ^1H NMR ($CDCl_3$, TMS): δ 4.17 (q, 2 H), 3.59 (t, 1 H), 2.79 (septet, 1 H), 1.84 (m, 2 H), 1.5–0.8 (16 H, including a t at 1.25, dd at 1.11 and t at 0.89). ^{13}C NMR ($CDCl_3$, TMS): 209.2, 170.0, 61.2, 57.2, 40.7, 29.8, 28.1, 22.6, 18.4, 18.1, 14.2, 13.9 ppm.

Ethyl 5-hydroxy-2-methyl-3-oxo-5-(1-pyrrolyl)hexanoate (**5**). A solution of lithium diisopropylamide (42 mmol), prepared as above, was cooled to −40 °C and a solution of ethyl 2-methyl-3-oxobutanoate (2.88 g, 20 mmol) in THF (30 ml) was added over a period of 10 min. The reaction mixture was allowed to reach 0 °C, kept at this temperature for 1 h, and then cooled to −78 °C. A solution of *N*-acetylpyrrole (2.40 g, 22 mmol) in THF was added over a period of 30 min. After 1.5 h (−78 °C) a solution of acetic acid (6 ml) in THF (30 ml) was added and the mixture was allowed to attain 0 °C. Aqueous sodium hydrogencarbonate (0.4 M) was added until the mixture had pH ca. 7.5. The aqueous phase was separated; the organic phase was washed twice with this sodium hydrogen carbonate solution, then with 0.1 M hydrochloric acid and finally with aqueous sodium chloride. The THF was replaced with diethyl ether, and the solution was dried (Na_2SO_4) and the solvent evaporated. Further evaporation (30 min, ca. 0.13 kPa) gave a residue (4.80 g) which consisted (^1H NMR) of **5** (as a 1:1 diastereomeric mixture), ethyl 2-methyl-3-oxobutanoate and *N*-acetylpyrrole in the molar ratios 24.5:1:2.5, which corresponds to a purity of 94 %; estimated yield, 89 %. ^1H NMR (CD_3OD): δ 6.98 (m, 4 H), 6.15 (m, 4 H), 4.22 (q, 4 H), 3.7–2.9 (contains solvent peak), 1.90 (s, 3 H), 1.88 (s, 3 H), 1.6–1.0 (m, 12 H, including a triplet centered at 1.24). ^{13}C NMR ($CDCl_3$, TMS): 205.2, 204.9, 171.7, 118.4, 118.2, 108.9, 108.6, 85.2, 85.0, 62.3, 54.7, 54.6, 54.2, 54.1, 28.6, 28.1, 14.3, 12.7 ppm.

Ethyl 2-methyl-3,5-dioxohexanoate (**6**). Crude **5** (2.00 g, 7.43 mmol of **5**) was heated under reflux (33 h) in a mixture of water (80 ml) and acetonitrile (160 ml). The mixture was cooled to 25 °C, saturated with sodium chloride and extracted with ether (2 × 80 ml). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated (2.0 kPa, 35 °C, 1 h). The residue (1.74 g) consisted (^1H NMR) of **6**, ethyl 2-methyl-3-oxobutanoate, *N*-acetylpyrrole and pyrrole in the molar ratios 24:3:3:4.5, which corresponds to a ca. 100 % yield of **6**. Distillation (65–70 °C, 0.13 kPa) afforded 0.92 g of **6** (90 % purity, 60 % yield). ^1H NMR ($CDCl_3$, E = enol, K = keto): δ 15.2 (broad s, E), 5.59 (s, 1 H, E), 4.20 (q, 2.5 H, K+E), 3.73 (s, 0.3 H, K), 3.62 (weak q, E), 3.38 (q, 1 H, K), 2.25 (s, 0.55 H, K), 2.08 (s, 3.2 H, E), 1.5–1.1 (m, 8.0 H, including a large d at 1.40 and a large t at 1.27). ^{13}C NMR ($CDCl_3$, solvent signal at 77.17 ppm as reference): 192.6, 189.1, 170.7, 98.8, 61.5 (K), 61.2, 56.3 (K), 53.2 (K), 49.3, 30.4 (K), 23.9, 14.0, 13.8, 12.2 (K) ppm.

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