Reaction of Ethyl 7-Aminoindole-2-carboxylate with β-Diketone and β-Oxo Ester Compounds†

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Reaction of ethyl 7-aminoindole-2-carboxylate has been investigated: 1*H*-pyrrolo[3,2-*h*]quinoline and 6-hydroxy-1*H*-pyrrolo-[3,2-*h*]quinoline derivatives are obtained with β-diketones and β-oxo esters, respectively.

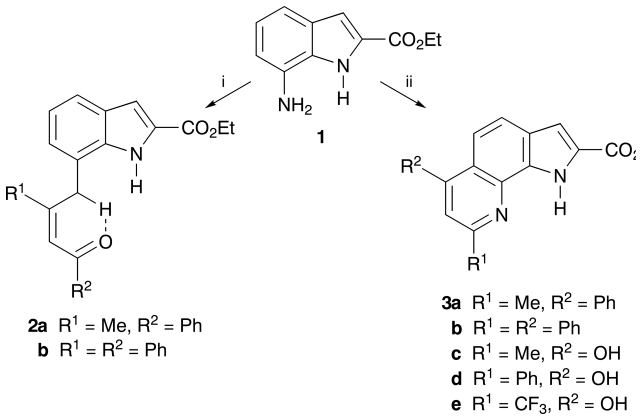
It has been reported recently that the reaction of 7-aminoindoles with acetylacetone gives 1*H*-pyrrolo[3,2-*h*]quinolines,[1] corresponding to a Combes synthesis.[2]

In this paper, we report the synthesis of 1*H*-pyrrolo-[3,2-*h*]quinoline and 6-hydroxy-1*H*-pyrrolo[3,2-*h*]quinoline derivatives (**3**) by condensation of ethyl 7-aminoindole-2-carboxylate (**1**) with β-diketones and β-oxo-esters, respectively.

The starting material (**1**) was prepared from 7-nitroindole-2-carboxylic acid, which was purchased from Janssen Chimica. Esterification followed by catalytic hydrogenation on Pd–charcoal gave the amino compound **1** in 71% yield.[3]

The reaction of the amine **1** with β-diketones (R^1 = Me, Ph, R^2 = Ph) in 1:1.2 ratio gave the crotonic derivatives **2** in the presence of catalytic amounts of toluene-*p*-sulfonic acid (*p*-TSA) at 80 °C.[4] The ^{1}H NMR spectra exhibit a singlet at 5.83 (R^1 = Me) and 6.21 (R^1 = Ph) ppm for the vinylic protons. When the reaction temperature was raised to 220 °C, the quinolinic derivatives **3a,b** were isolated as the major products together with minor amounts of **2a,b**[5] (Scheme 1).

To prove that the indole nitrogen was not sufficiently nucleophilic to react with the carbonyl groups of crotonic and acrylic compounds, we carried out the Conrad–Limpach reaction[6] of amine **1** with the appropriate β-oxo esters. Under acid catalysis at 80 °C, only anils **2** (R^1 = Me, Ph, R^2 = OEt) and 6,7,8,9-tetrahydro-1*H*-pyrrolo[3,2-*h*]-quinoline **4** (Scheme 2) were isolated.[7] However, at 160 °C, 6-hydroxy-1*H*-pyrrolo[3,2-*h*]quinoline derivatives **3c–e**[8–10] (R^1 = Me, Ph, CF_3, R^2 = OH) were obtained. The structural assignment of compounds **3** and **4** was based on IR, NMR and mass spectroscopic data.



Scheme 1 *Reagents and conditions*: i, $R^1COCH_2COR^2$, *p*-TSA, 80 °C; ii, $R^1COCH_2CO_2Me$, Et, *p*-TSA, 160 °C

Experimental

Mps are uncorrected and were measured with a Digital Melting Point Apparatus. IR spectra were recorded on a Perkin Elmer 1310 spectrophotometer, and NMR spectra with a Bruker AC 300 P (300 MHz for ^{1}H and 75 MHz for ^{13}C) spectrometer (shifts in ppm relative to TMS). Mass spectra were performed with a Varian Mat 311 spectrometer (C.R.M.P.O. Rennes).

Reaction of Ethyl 7-Aminoindole-2-carboxylate (**1**) *with β-Diketones*.—(a) A mixture of **1** (0.2 g), β-diketone (1.17 mmol, 1.2 equivalents) and *p*-TSA 0.02 g) was heated to 80 °C for 90 min. After cooling the products were purified by chromatography on silica gel using CH_2Cl_2 as eluent to yield compound **2**.

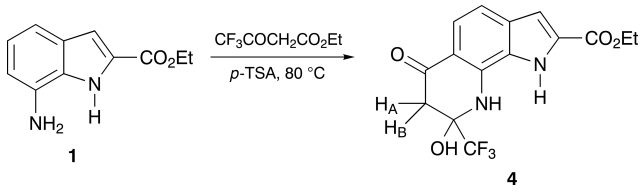
Ethyl 7-[N-(1-*methyl*-3-*oxo*-3-*phenylbut*-1-*enylamino*]*indole*-2-*carboxylate* (**2a**). Starting from benzoylacetone the reaction leads to **2a**. Yield 60%; mp 160 °C (ether); ν_{max}/cm^{-1} (KBr) 3240 (NH), 1710 (C=O ester), 1600 (C=O chelated); δ_H ($CDCl_3$) 1.33 (t, 3 H, ^3J 7.1 Hz), 1.77 (s, 3 H), 4.37 (q, 2 H, ^3J 7.1 Hz), 5.83 (s, 1 H, vinyl) 7.96 and 7.42 (dd and m, 5 H, R^2 = Ph) 7.07 (dd, 1 H, J_o 7.5, J_m 1.0 Hz), 7.12 (t, 1 H, J_o 7.5 Hz), 7.29 (d, 1 H, *J* 2.0 Hz), 7.61 (dd, 1 H, J_o 7.5, J_m 1.0 Hz); *m*/*z* 348 (M^+) (Found: 348.147. $C_{21}H_{20}N_2O_3$ requires 348.147).

Ethyl 7-[N-(1,3-*diphenyl*-3-*oxoprop*-1-*enyl*)*amino*]*indole*-2-*carboxylate* (**2b**). Starting from dibenzoylmethane the reaction leads to **2b**. Yield 65%; mp = 179 °C (ether); ν_{max}/cm^{-1} (KBr) 3200 (NH), 1720 (C=O ester), 1610 (C=O chelated). δ_H ($CDCl_3$) 1.41 (t, 3 H, *J* 7.2 Hz), 4.42 (q, 2 H, *J* 7.2 Hz), 6.21 (s, 1 H, vinyl), 6.55 (dd, 1 H, J_o 7.6, J_m 2.0 Hz), 6.84 (t, 1 H, J_o 7.6 Hz), 7.34–8.01 (m, 12 H, R^1, R^2 = Ph and H_3, H_4); *m*/*z* 410 (M^+) (Found: 410.165. $C_6H_{22}N_2O_3$ requires 410.163).

(b) A mixture of ethyl 7-aminoindole-2-carboxylate (**1**) (0.5 g), β-diketone (2.45 mmol) and a catalytic amount of *p*-TSA (0.04 g) was heated to 220 °C for 90 min. After cooling, the reaction products were separated by chromatography on silica gel using dichloromethane as eluent to yield compound **3** as the first fraction.

Ethyl 8-*methyl*-6-*phenyl*-1H-*pyrrolo*[3,2-h]*quinoline*-2-*carboxylate* **3a**, starting from benzoyl acetone. Yield 38%; mp 151 °C (ether); ν_{max}/cm^{-1} 1670 (C=O ester); δ_H ($CDCl_3$) 1.40 (t, 3 H, ^3J 7.1 Hz), 2.68 (s, 3 H), 4.40 (q, 2 H, ^3J 7.1 Hz), 7.30 (s, 1 H) 7.48 (m, 4 H), 7.61 (dd, 1 H, J_o 7.5, J_m 1.0 Hz), 7.63 (d, 2 H, J_o 7.5 Hz), 8.15 (d, 1 H, J_o 7.4 Hz), 10.40 (broad s, NH); δ_C ($CDCl_3$) 14.43, 1958, 60.92, 109.70, 116.53, 119.30, 121.34, 124.82, 126.05, 126.91, 127.38, 128.70, 129.11, 133.64, 138.0, 139.47, 145.17, 155.28, 161.61; *m*/*z* 330 (M^+) (Found: 330.137. $C_{21}H_{18}N_2O_2$ requires 330.137).

Ethyl 6,8-*diphenyl*-1H-*pyrrolo*[3,2-h]*quinoline*-2-*carboxylate* **3b**, starting from dibenzoymethane. Yield 34%; mp 114–116 °C (ether); ν_{max}/cm^{-1} (KBr) 1670 (C=O ester); δ_H ($CDCl_3$) 1.41 (t, 3 H, ^3J 7.2 Hz), 4.42 (q, 2 H, ^3J 7.1 Hz), 7.32 (s, 1 H), 7.50 (m, 9 H), 7.61 (d, 1 H, J_o 9.0 Hz), 7.79 (s, 1 H), 8.19 (d, 2 H, J_o 8.4 Hz), 10.70 (broad s, NH); δ_C ($CDCl_3$) 14.42, 61.0, 109.70, 118.38, 119.0, 121.72, 123.46, 126.21, 127.20, 127.50, 128.33, 128.53, 128.78,



Scheme 2

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1997, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

129.28, 129.55, 133.45, 138.77, 138.84, 139.36, 149.53, 155.34, 161.65; m/z 392 (M^+) (Found: 392.150. $C_{26}H_{20}N_2O_2$ requires 392.152).

Reaction of Ethyl 7-Aminoindole-2-carboxylate (**1**) *with β-Oxo Esters*.—A mixture of ethyl 7-aminoindole-2-carboxylate (**1**) (0.5 g), β-oxo-ester (1.5 equiv., 3.7 mmol) and a catalytic amount of *p*-TSA (0.04 g) was heated at 160 °C for 1 h. After cooling, the precipitate was filtered off and recrystallized from dimethylformamide.

Ethyl 6-hydroxy-8-methyl-1H-pyrrolo[3,2-h]*quinoline-2-carboxylate* (**3c**), starting from ethyl acetoacetate. Yield 45%; mp 151–153 °C (DMF); ν_{max}/cm^{-1} (KBr) 3200 (OH), 4.15 (q, 2 H, ^3J 7.5 Hz), 6.71 (s, 1 H), 7.09, (s, 1 H), 7.51 (d, 1 H, J_o 7.5 Hz), 7.57 (d, 1 H, J_o 7.5 Hz); m/z 270 (M^+) (Found: 270.100. $C_{15}H_{14}N_2O_3$ requires 270.10.

Ethyl 6-hydroxy-8-phenyl-1H-pyrrolo[3,2-h]*quinoline-2-carboxylate* (**3d**), starting from ethyl benzoylacetate. Yield 43%; mp 284 °C (DMF, dec.); ν_{max}/cm^{-1} (KBr) 3200 (OH), 1700 (C=O); δ_H ([$^2H_6$]DMSO/TFA) 1.04 (t, 3 H, ^3J 7.4 Hz), 4.10 (q, 2 H, ^3J 7.4 Hz), 7.02 (m, 2 H), 7.26 (m, 3 H), 7.44 (m, 4 H); δ_C ([$^2H_6$]DMSO/TFA) 14.27, 65.33, 106.23, 116.40, 125.34, 12602, 129.02, 130.80, 131.58, 131.80, 132.25, 133.31, 134.74, 155.68, 165.12; m/z = 332 (M^+) (Found: 332.115. $C_{20}H_{16}N_2O_3$ requires 332.116).

Ethyl 6-hydroxy-8-trifluoromethyl-1H-pyrrolo[3,2-h]*quinoline-2-carboxylate* (**3e**), starting from ethyl trifluoromethylacetoacetate. Yield 46%; mp 320–322 °C (DMF); ν_{max}/cm^{-1} (KBr) 3300 (OH), 1710 (C=O); δ_H ([$^2H_6$]DMSO/TFA) 1.12 (t, 3 H, ^3J 7.5 Hz), 4.16 (q, 2 H, ^3J 7.4 Hz), 7.04 (s, 1 H), 7.10 (s, 1 H), 7.32 (d, 1 H, J_o 8.2 Hz), 7.44 (d, 1 H, J_o 8.8 Hz), 10.53 (broad s, NH); m/z 324 (M^+) (Found: 324.073. $C_{15}H_{11}N_2O_3F_3$ requires 324.072).

Reaction of Ethyl 7-Aminoindole-2-carboxylate (**1**) *with Ethyl Trifluoromethylacetoacetate*.—A mixture of amine **1** (1.47 mmol), ethyl trifluoromethylacetoacetate (1.5 equiv.) and a catalytic amount of *p*-TSA (0.03 g) was heated at 80 °C for 1 h. After cooling, the precipitate was filtered off and recrystallized from ethanol.

Ethyl 8-hydroxy-8-trifluoromethyl-6,7,8,9-tetrahydro-1H-pyrrolo-[3,2-h]*quinolin-6-one-2-carboxylate* (**4**). Yield 40%; mp 230 °C (EtOH); ν_{max}/cm^{-1} (KBr) 3310 (NH), 1700 (C=O ester), 1630 (C=O ketone); δ_H ([$^2H_6$]DMSO) 1.42 (t, 3 H, ^3J 7.1 Hz), 3.03 and 3.14 (d, H_A, H_B, J_{AB} 16.8 Hz), 4.39 (q, 2 H, ^3J 7.2 Hz), 6.45 (broad s, OH), 7.12 (s, 1 H), 7.36 (d, 1 H, J_o 8.5 Hz), 7.43 (d, 1 H, J_o 8.3 Hz), 10.36 (broad s, NH), 11.45 (broad s, NH); δ_C ([$^2H_6$]DMSO) 14.37, 60.86, 72.55, 108.00, 115.03, 116.25, 119.01, 123.81, 125.80, 129.0, 129.37, 161.72, 167.71; m/z 342 (M^+) (Found: 342.092. $C_{15}H_{13}N_2O_4F_3$ requires 342.082).

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