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A New Two Step Route to 1-Hydroxy-9*H*-3-Carbazolecarboxylic Acid Derivatives from 3-Formylindole. Application to the Synthesis of Mukonine

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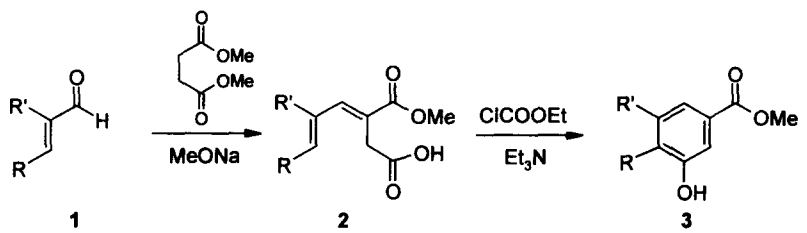
Abstract: Carbazole alkaloid mukonine **6b** was prepared from 3-formylindole in three steps (32% overall yield). The key step was the base-promoted cyclization of a mixed anhydride of mono ester mono acid **5**

INTRODUCTION

Recently,[1] we have improved a known[2] two step procedure to synthesise 4-substituted-3-hydroxybenzoic acid derivatives starting from 3-substituted- 2,3-unsaturated aldehydes **1** and dimethyl succinate. This synthetic route allowed us to obtain 4-aryl and heteroaryl 3-hydroxybenzoates **3** in good yields (Scheme 1) *via* the key intermediate **2**, and to prepare p,p'-oligophenyls by an iterative sequence.



Scheme 1

A further development of the research induced us to investigate this kind of intramolecular cyclization on aldehydic derivatives showing the double bond as a part of a ring, which could be both carbocyclic and heterocyclic (Scheme 2). This study was aimed to apply the two step procedure as an "aromatic annulation method" for the synthesis of ring fused structures.

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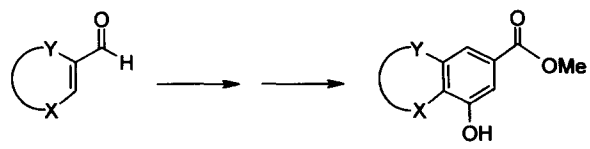
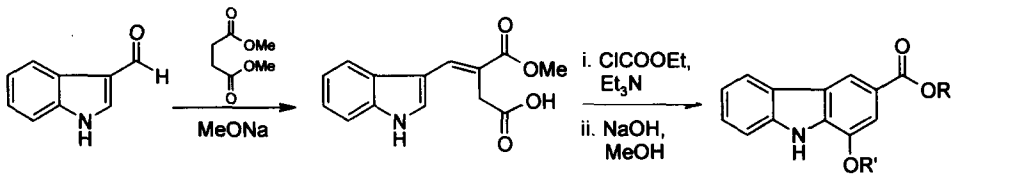


X = CH_2, Y= heteroatom or X= heteroatom, Y= CH_2

Scheme 2

Preliminary work was performed using 3-formylindole (**4**) as a starting material, in order to provide a new synthetic approach to 1-hydroxy-9*H*-3-carbazolecarboxylic acid derivatives **6** (Scheme 3).



4 **5**

6a R = Me, R' = H
6b R = Me, R' = Me mukonine
6c R = H , R' = Me mukoeic acid

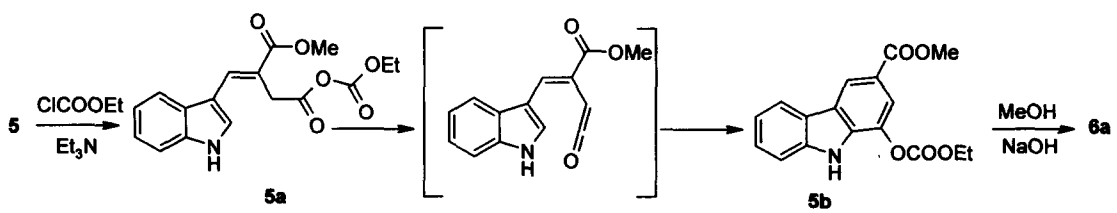
Scheme 3

These latter substrates show great interest, as they are structurally related to a well-known class of natural alkaloids.[3] Thus, we report herein on the synthesis of one of these carbazole alkaloids, mukonine (**6b**)[4], from which murrayanine, murrayafoline A, and O-demethylmurrayanine can be prepared by common functional group manipulations.

RESULTS AND DISCUSSION

Reaction of 3-formylindole[5] with dimethyl succinate and sodium methylate in methanol afforded compound **5** through a Stobbe condensation.[6] This classic synthetic approach to mono ester mono acid derivatives was preferred to the use of triphenyl-(α-carbethoxy-β-carboxy-ethyl)phosphonium betaine.[7] In fact, this phosphorane reacted with **4** very slowly, providing **5** in poor yields.

The mono ester mono acid **5** reacted with 1 eq. of ethyl chloroformate in presence of triethylamine to give the mixed anhydride **5a**, that was unstable in basic condition towards a cyclization process (Scheme 4).



5a **5b**

Scheme 4

A slight excess of base allowed the complete conversion of the starting substrate **5a** into the aromatic derivative **5b** in a few minutes at room temperature. We assumed that the key cyclization step possibly proceeded through a 1,6 electrocyclic reaction[8] involving a ketene intermediate[9], as in the case of aromatic annulation described by Ramage *et al.*[2]

Mukonine **6b**[9] was obtained by quantitative methylation of **6a** with diazomethane in methylene chloride; then, it could be easily converted into mukoeic acid[4] **6c** upon saponification in ethanolic sodium hydroxide.

This annulation route affording mukonine from 3-formylindole and dimethyl succinate showed interesting advantages, when it was compared with the known synthetic methods, as for the high overall yields (32 % -3 steps), the easy availability of the reagents and the simplicity of the involved operative procedures. A classical modification of the Fischer indole synthesis gave **6b** in four steps through reactions performed in rather vigorous conditions.[4] A more recent approach to mukonine was based on an electrophilic aromatic substitution with tricarbonylcyclohexadienylium iron[10] (or molybdenum)[11] tetrafluoroborate, followed by an oxidative cyclization to create the central ring (15 % - 3 steps).

Furthermore, our cyclization method could be considered a general procedure to prepare carbazole alkaloids by creating ring C onto the suitable indole derivative.[3] It was formally complementary to the one which affords 1-oxygenated carbazoles from indole-2-carboxylates[12] in four steps, taking advantage of a key intramolecular electrophilic substitution to build ring C.

In conclusion, we have shown that our annulation route is a synthetic useful approach to 1-hydroxy-9*H*-3-carbazolecarboxylic acid derivatives **6,** which can be suitably manipulated *via* unexceptional organic reactions to give carbazole alkaloids structurally related to mukonine.

EXPERIMENTAL

^{1}H NMR spectra were recorded in $CDCl_3$ solutions at room temperature unless otherwise stated, on a Bruker AC-250 spectrometer (250 MHz ^{1}H). The chemical shift scale was based on internal tetramethylsilane. All reactions were monitored by TLC analyses using Merck Kieselgel 60 F_{254} plates. Melting points were measured on a Reichert melting point apparatus, equipped with a Reichert microscope and are uncorrected.

(E)-4-(1H-3-indolyl)-3-(methoxycarbonyl)-3-butenoic acid (5)

Sodium methylate (2.0 g, 0.038 mol) in methanol (30 mL) was added to 3-formylindole[5] (5.0 g, 0.035 mol) and dimethyl succinate (5.5 g, 0.038 mol). The heterogeneous phase was concentrated under reduced pressure in 1 h at 45°C The residue was treated with 5% HCl (60 ml), extracted with ethyl acetate, and the dried (Na_2SO_4) organic phase concentrated under reduced pressure to give an amorphous solid which was chromatographed on a silica gel column, using ethyl acetate-methanol 4:1 as eluent, to afford unreacted 3-formylindole (1.5 g), and **5** (4.0 g, 42 %):^{1}H NMR (DMSO d_6) δ 3.56 (2H, s), 3.72 (3H, s), 7.15 (2H, m), 7.45 (1H, d J = 7.4 Hz), 7.68 (1H, d J = 7.4Hz), 7.9 (2H, m), 12.1 (1H, s); EI-MS *m/z* 259 (M^+), 227 (M^+- MeOH), 155, 115, 101; FT-IR (nujol): ν (cm^{-1}) 1680, 1735, 3398. Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 65.03; H, 5.09; N, 5.37.

Methyl 1-hydroxy-9H-3-carbazolecarboxylate (6a)

Ethyl chloroformate (2.6 g, 0.024 mol) was added to **5** (3.1 g, 0.011 mol) in THF (100 mL); then, triethylamine (3.4 g, 0.033 mol) was added dropwise. After 15 min the reaction mixture was diluted with water and extracted with diethyl ether. The residue, obtained upon concentration under reduced pressure, was treated with sodium hydroxide (0.44 g, 0.022 mol) in methanol (50 mL). The mixture was stirred at room temperature till the conversion into the phenolic derivative **6a** was complete and then treated with HCl 5%, and extracted with

diethyl ether. The organic phase was dried (Na_2SO_4), and concentrated *in vacuo*. The residue was chromatographed on a silica gel column, using hexane-ethyl acetate 3:1 as eluent, to afford **6a** (2.14 g, 81 %) as colourless crystals (hexane-ethyl acetate): m.p. 203-205°C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.00 (3H, s), 5.65 (1H, broad s), 7.25 (1H, m), 7.50 (2H, m), 7.62 (1H, d J = 1. 2 Hz), 8.10 (1H, d J = 7.9 Hz), 8.44 (2H, d J = 1.2 Hz + broad s); EI-MS *m/z* 241 (M^+), 210 (M^+- OMe), 196, 182 (M^+ - COOMe), 154; FT-IR (nujol): ν (cm^{-1}) 1655, 3355. Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.93; H, 4.71; N, 5.74.

Methyl 1-methoxy-9H-3-carbazolecarboxylate -Mukonine (6b)

A 0.5 M solution of diazomethane (5ml, 0.0025 mol) in diethyl ether was added dropwise to **6a** (0.3 g, 0.0012 moli) in methylene chloride (10 ml). After stirring 1 h at room temperature, the reaction mixture was treated with water (10 ml) and extracted with methylene chloride (30 ml). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed on a silica gel column, using hexane-ethyl acetate 4:1 as eluent, to afford **6b** (0.31 g, 97%) as a colourless solid: m.p. 193-195°C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.98 (3H, s), 4.04 (3H, s), 7.29 (1H, m), 7.47 (2H, m), 7.58 (1H, d J = 1.3 Hz), 8.10 (1H, d J = 7.8 Hz), 8.47 (1H, s), 8.54 (1H, broad s); EI-MS *m/z* 255 (M^+), 240 (M^+ - Me), 224 (M^+ - OMe), 212, 196, 181, 153. FT-IR (nujol): ν (cm^{-1}) 1698, 3321. Anal. Calcd for $C_{15}H_{13}NO3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.87; H, 5.19; N, 5.33.

1-Methoxy-9H-3-carbazolecarboxylic acid - Mukoeic acid (6c)

Sodium hydroxide.(0.2 g, 5 mmoli) in ethanol (10 ml) was added to **6a** (0.2 g, 0.78 mmoli) in ethanol (5 ml). After stirring 1 h at 50°C, the reaction mixture was treated with 5% HCl (30 ml) and extracted with ethyl acetate. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed on a silica gel column, using hexane-ethyl acetate 1:1 as eluent, to afford **6c** (0.175 g, 92%) as a colourless solid, m.p. 239-241°C (lit.[4] 242°C); FT-IR (nujol): ν (cm^{-1}) 3425, 1690. Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.89; H, 4.53; N, 5.63.

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