Facile Syntheses of Ethyl 2-Alkylindole-3-carboxylates: Reinvestigation of an Earlier Synthesis of Ethyl 3-Methyl-indole-2-carboxylates

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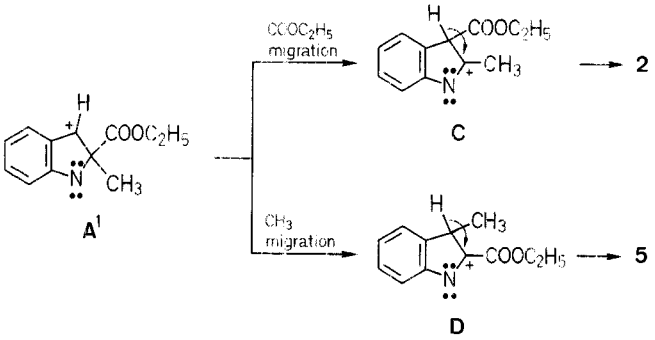
A convenient, general synthesis of ethyl 2-alkylindole-3-carboxylates has been described from the easily accessible *o*-nitroarylaldehydes. In an alternate approach the same *o*-nitroarylaldehydes have been converted to ethyl 3-alkylindole-2-carboxylates.

Indole-2-carboxylates and -3-carboxylates are of interest as intermediates for the synthesis of alkaloids and various heterocyclic compounds.[1,2] Several methods have therefore been reported for the synthesis of these compounds.[3] Some of the newly developed methods for 2-substituted indole-3-carboxylic

acids and their esters utilize either preformed indoles,[4] 2-nitrophenylacetic esters,[5] or 2-iodoaniline.[6] Recently[3] we have reported a good method for the synthesis of ethyl indole-2-carboxylates 3, which are unsubstituted at the 3-position. The method used involved deoxygenation of ethyl 2-nitrocinnamates.

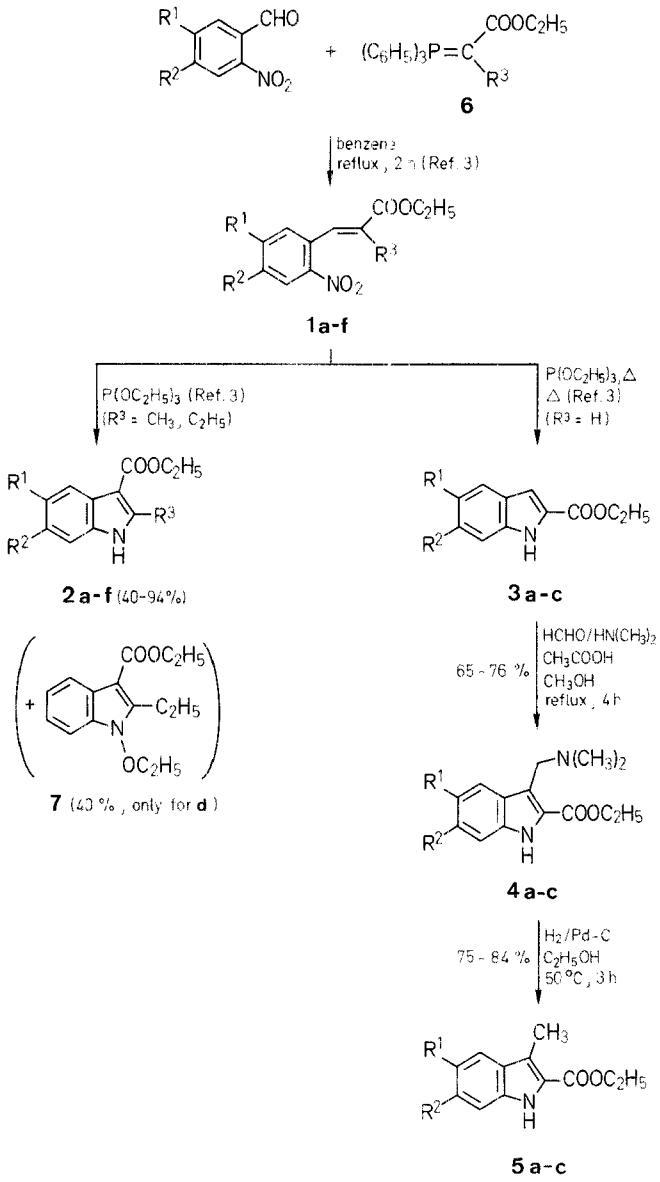
In an extension of this method it was reported[3] that deoxygenation of ethyl 2-nitro(α-methyl)cinnamates **1a–c** had afforded the corresponding 3-methylderivatives **5a–c**. This was based on the belief that for the cation **A**[1] (Scheme A) the methyl group should migrate in preference to the $-COOC_2H_5$ group. This was supported by the literature report, that deoxygenation of β,β-disubstituted ω-nitrostyrenes provided 2,3-disubstituted indoles, in which the group having the better migratory aptitude migrates.[7]



Scheme A

By careful analysis of the ^{1}H-NMR, it is now clear that the deoxygenation products in fact have structures **2a–c** rather than **5a–c**. Thus, in case of the ethyl indole-2-carboxylates **3a–c**, the H at C-4 resonates at $\delta = 7.68$, 7.05, and 6.93 ppm respectively. However, in case of the deoxygenation products (m.p. 129–31 °C, 185–6 °C, and 210–12 °C) obtained from **1a–c**, respectively, this signal appears at $\delta = 8.00$, 7.50, and 7.38 respectively. It has now been realised that this downfield shift in positions of ^{1}H-NMR signals can be explained if the deoxygenation products are assigned structures **2a–c** rather than the originally proposed structures **5a–c** (Scheme **B**). The elemental analysis, IR data and mode of formation were also in agreement with these structures.

These structures were also supported by ^{13}C-NMR data. Thus, the ^{13}C-NMR spectrum of **3a** as compared to **5a** and **2a**, shows that the chemical shifts of **5a** are similar to that of **3a**. This suggests that **5a** must have the $-COOC_2H_5$ group at C-2. Since the chemical shifts of **2a** are similar to those reported[8] for 3-acetylindole, it is obvious that in **2a** the carbonyl must be at C-3.



1, 2	R^1	R^2	R^3
a	H	H	CH_3
b	OCH_3	OCH_3	CH_3
c	$-OCH_2O-$		CH_3
d	H	H	C_2H_5
e	OCH_3	OCH_3	C_2H_5
f	$-OCH_2O-$		C_2H_5

3–5	R^1	R^2
a	H	H
b	OCH_3	OCH_3
c	$-OCH_2O-$	

Scheme B

Table 1. ^{13}C-NMR ($CDCl_3$) Spectral Data for **2a**, **3a** and **5a**

Compound	δ (ppm)
2a	14.07 ($Ar-CH_2$), 14.51 (CH_3), 59.48 (CH_2), 110.55 (C-7), 121.17 (C-6), 121.58 (C-5), 122.22 (C-4), 127.20 (C-8), 134.58 (C-9), 144.09 (C-2), 166.46 (CO)[a]
3a	14.88 (CH_3), 61.06 (CH_2), 108.68 (C-3), 111.96 (C-7), 120.75 (C-6), 122.59 (C-5), 125.29 (C-4), 127.54 (C-2, C-8), 137.10 (C-9), 162.34 (CO)
5a	9.94 ($Ar-CH_3$), 14.48 (CH_3), 60.72 (CH_2), 111.69 (C-7), 119.90 (C-6), 120.78 (C-5), 123.51 (C-3), 124.52 (C-4), 128.60 (C-2, C-8), 136.03 (C-9), 162.37 (CO)

[a] C-3 is merged between 121 and 122 ppm.

These conclusions were supported by unambiguous synthesis of compounds **5a–c**. The products obtained using the new method were quite different (mp, IR, ^{1}H-NMR, TLC) from the deoxygenation products obtained from **1a–c**. The unambiguous synthesis involves conversion of **3a–c** to **4a–c** by Mannich reaction. Subsequent reduction of **4a–c** with hydrogen in presence of palladium on carbon gave ethyl 3-methylindole-2-carboxylates **5a–c**. As expected, these products, **5a–c**, showed the signals for the H at C-4 at $\delta = 7.60$, 6.96, and 6.95 ppm, respectively.

These results clearly demonstrate that in the cation *A'* (Scheme **A**), the –COOEt group migrates in preference to the methyl group. This is probably due to the fact that cation *C* would be

more stable than *D*. In order to decide whether –COOEt would migrate in preference to other alkyl groups, it was decided to study the reactions of other ethyl *o*-nitrocinnamates.

The ethyl *o*-nitrocinnamates **1d–f**, required for this purpose, were synthesized by reacting the corresponding 2-nitrobenzaldehydes with phosphorane **6**. Heating a mixture of 5 equivalents of triethyl phosphite with nitroesters **1d–f** at 170 °C gave ethyl indole-3-carboxylates **(2d–f)** in good yields. The formation of indoles **2d–f** rather than **5** also supports that the $COOC_2H_5$ group migrates in preference to the C_2H_5 group.

The present work has thus demonstrated the following. (i) In ion **A**[1], ester group migrates in preference to alkyl groups. (ii) *o*-Nitroarylaldehydes can be converted in two steps to ethyl 2-alkylindole-3-carboxylates. (iii) Alternatively, the same aldehydes can be converted in four steps to ethyl 3-alkylindole-2-carboxylates. Thus, from a single easily available aldehyde two different important indole carboxylic esters could be readily obtained.

Ethyl *o*-Nitrocinnamates 1a-f:

The synthesis of esters **1a–c** is described previously.[3] The esters **1d–f** are synthesized similarly from the corresponding *o*-nitrobenzaldehydes. Thus, *o*-nitrobenzaldehydes (1 mmol) are refluxed in benzene (10 ml) with phosphorane **6**, for 2 h to give esters **1d–f** (Table 2).

Ethyl 2-Alkylindole-3-carboxylates 2a–f; General Procedure:

The appropriate ethyl *o*-nitrocinnamate **1** is reacted with triethyl phosphite as described previously[3] to give ethyl 2-alkylindole-3-carboxylates **2**. In case of **1d**, along with the expected product **2d**, compound **7** is also obtained in 40% yield. All these products are recrystallized from hexane/chloroform (Table 2).

Table 2. Compounds **1**, **2**, **4**, **5** and **7** Prepared[a]

Product No.	Yield (%)	m.p. (°C) or b.p. (°C)/torr	Molecular Formula[b] or Lit. Data	IR (Nujol) ν(cm^{-1})
1d	98	47	$C_{13}H_{15}NO_4$ (249.3)	1700 (C=O)
1e	95	82	$C_{15}H_{15}NO_6$ (309.3)	1725 (C=O)
1f	96	93	$C_{14}H_{15}NO_6$ (293.27)	1725 (C=O)
2d	20	103	m.p. = 103 °C[6]	3240 (NH), 1650 (C=O)
2e	60	122–123	$C_{15}H_{19}NO_4$ (277.3)	3300 (NH), 1680 (C=O)
2f	70	186	$C_{14}H_{15}NO_4$ (261.3)	3250 (NH), 1650 (C=O)
4a	65	79–80	$C_{14}H_{18}N_2O_2$ (246.3)	3300 (NH), 1700 (C=O)
4b	76	134	$C_{16}H_{22}N_2O_4$ (306.4)	3300 (NH), 1650 (C=O)
4c	67	164	$C_{15}H_{18}N_2O_4$ (290.3)	3260 (NH), 1650 (C=O)
5a	84	127–128	m.p. = 132–133 °C[9]	3300 (NH), 1670 (C=O)
5b	75	166–168	m.p. = 166–168 °C[4]	3300 (NH), 1670 (C=O)
5c	76	143	$C_{13}H_{13}NO_4$ (235.2)	3290 (NH), 1650 (C=O)
7	40	170/2 mm	$C_{15}H_{19}NO_3$ (261.3)	1700 (C=O)

[a] The yield, m.p. and IR data for compounds **2a–c** are reported in Ref. 3.

[b] Satisfactory microanalyses obtained: C ±0.30, H ±0.25.

Table 3. ^{1}H-NMR Spectral Data for Compounds **2**, **4**, **5** and **7**[a]

Product No.	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm)
2d	1.34 (t, 3H, J = 7.5 Hz, CH_2CH_3); 1.47 (t, 3H, J = 7 Hz, OCH_2CH_3); 3.2 (q, 2H, J = 7.5 Hz, CH_2CH_3); 4.42 (q, 2H, J = 7 Hz, OCH_2CH_3); 7.1–7.4 (m, 3H$_{arom}$); 8.1 (m, 4-H$_{arom}$); 8.6 (br s, 1H, exchangeable with D_2O, NH)
2e	1.3 (t, 3H, J = 7.5 Hz, CH_2CH_3); 1.42 (t, 3H, J = 7 Hz, OCH_2CH_3); 3.12 (q, 2H, J = 7.5 Hz, CH_2CH_3); 3.78, 3.9 (2 × s, 3H each, 2 × OCH_3); 4.39 (q, 2H, J = 7 Hz, OCH_2CH_3); 6.75 (s, 1H, 7-H); 7.62 (s, 1H, 4-H); 8.72 (br s, 1H, exchangeable with D_2O, NH)
2f	1.3 (t, 3H, J = 7.5 Hz, CH_2CH_3); 1.42 (t, 3H, J = 7 Hz, OCH_2CH_3); 3.13 (q, 2H, J = 7.5 Hz, CH_2CH_3); 4.38 (q, 2H, J = 7 Hz, OCH_2CH_3); 5.91 (s, 2H, OCH_2O); 6.75 (s, 1H, 7-H); 7.52 (s, 1H, 4-H); 8.42 (br s, 1H, exchangeable with D_2O, NH)
4a	1.42 (t, 3H, J = 7 Hz, CH_2CH_3); 2.29 (s, 6H, 2 × CH_3); 3.95 (s, 2H, CH_2N); 4.42 (q, 2H, J = 7 Hz, CH_2CH_3); 7–7.4 (m, 3H$_{arom}$); 7.84 (m, 1H, 4-H); 9.0 (br s, 1H, exchangeable with D_2O, NH)
4b	1.4 (t, 3H, J = 7 Hz, CH_2CH_3); 2.3 (s, 6H, 2 × CH_3); 3.85 (s, 2H, CH_2N); 3.89 (s, 6H, 2 × OCH_3); 4.36 (q, 2H, J = 7 Hz, OCH_2CH_3); 6.71 (s, 1H, 7-H); 7.18 (s, 1H, 4-H); 8.9 (br s, 1H, exchangeable with D_2O, NH)
4c	1.4 (t, 3H, J = 7 Hz, CH_2CH_3); 2.3 (s, 6H, 2 × CH_3); 3.88 (s, 2H, CH_2N); 4.38 (q, 2H, J = 7 Hz, CH_2CH_3); 5.91 (s, 2H, OCH_2O); 6.74 (s, 1H, 7-H); 7.18 (s, 1H, 4-H); 8.95 (br s, 1H, exchangeable with D_2O, NH)
5a	1.4 (t, 3H, J = 7 Hz, CH_2CH_3); 2.6 (s, 3H, CH_3); 4.41 (q, 2H, J = 7 Hz, CH_2CH_3); 7.2 (m, 3H$_{arom}$); 7.6 (m, 1H, 4-H); 8.85 (br s, 1H, exchangeable with D_2O, NH)
5b	1.4 (t, 3H, J = 7 Hz, CH_2CH_3); 2.55 (s, 3H, CH_3); 3.89, 3.91 (s, 6H, 2 × OCH_3); 4.38 (q, 2H, J = 7 Hz, CH_2CH_3); 6.78 (s, 1H, 7-H); 6.96 (s, 1H, 4-H); 8.62 (br s, 1H, exchangeable with D_2O, NH)
5c	1.4 (t, 3H, J = 7 Hz, CH_2CH_3); 2.52 (s, 3H, CH_3); 4.4 (q, 2H, J = 7 Hz, CH_2CH_3); 5.94 (s, 2H, OCH_2O); 6.75 (s, 1H, 7-H); 6.95 (s, 1H, 4-H); 8.8 (br s, 1H, exchangeable with D_2O, NH)
7	1.23–1.6 (m, 9H, 3 × CH_2CH_3); 3.16 (q, 2H, J = 7.5 Hz, CH_2CH_3); 4.3 (q, 4H, J = 7 Hz, 2 × OCH_2CH_3); 7–7.3 (m, 3H$_{arom}$); 8.04 (m, 1H, 4-H)

[a] For ^{1}H-NMR spectral properties of compounds **2a–c** see Ref. 3.

Ethyl 3-Methylindole-2-carboxylates 5:

Ethyl 3-dimethylaminomethylindole-2-carboxylates **4a–c**: *General Procedure:*

To an ice-cold solution of dimethylamine (40%, 0.68 ml, 6 mmol) is added acetic acid (0.73 ml) followed by formaldehyde (37%, 0.44 ml, 6 mmol). Ethyl indole-2-carboxylate[3] (**3**; 2 mmol) in methanol (20 ml) is then added, and the resulting solution heated under reflux for 4 h. The solvent is concentrated to about 20% of its volume *in vacuo*, and the resulting mixture treated with 10 ml of water and washed with chloroform (20 ml). The aqueous layer is chilled, made basic with 20% NaOH (to pH 12), and extracted with dichloromethane (3 × 10 ml). The dichloromethane solution is dried with sodium sulfate and evaporated to give indoles **4**. Recrystallization from chloroform/petroleum ether provided analytical samples.

Ethyl-3-methylindole 2-carboxylates **5a–c**: *General Procedure:*

A mixture of indole (**4**; 1 mmol), 10% palladium on carbon (0.020 g), ethanol (15 ml), and two drops of perchloric acid is shaken in a Parr hydrogenator under hydrogen (70 psi) for 3 h at 50 °C. The mixture is filtered and concentrated *in vacuo* to give a solid residue, which is dissolved in chloroform (20 ml). The chloroform solution is washed with 10% sodium carbonate solution (20 ml), dried with sodium sulfate, and evaporated to yield indoles **5**. Recrystallization from chloroform/petroleum ether provided analytical samples.

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