Synthesis of 3-Alkyl-3-bromo-1-ethoxycarbonyl-1,3-dihydro-2*H*-indol-2-ones

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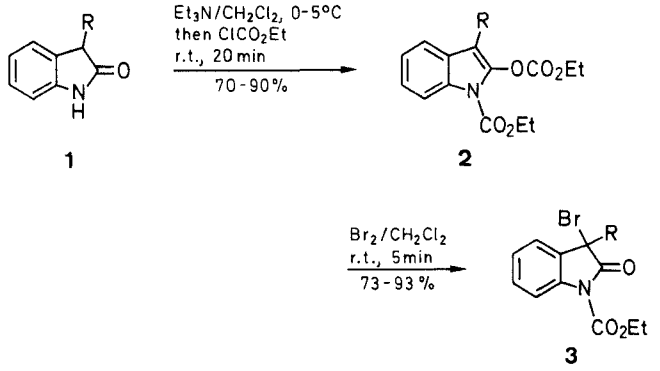
3-Alkyl-1,3-dihydro-2*H*-indol-2-ones **1** are converted to the corresponding 2-ethoxycarbonyloxy derivatives **2** by reaction with ethyl chloroformate in the presence of triethylamine. Bromination of **2** affords the title compounds in 73–93% yield.

During the course of our work on the synthesis of [*b*]annulated indole derivatives, we needed 3-alkyl-3-bromo-1-ethoxycarbonyl-1,3-dihydro-2*H*-indol-2-ones **3** as starting materials. These compounds, like the 3-alkyl-3-bromo-1,3-dihydro-2*H*-indol-2-ones,[1] are expected to undergo an easy replacement of the halogen by nucleophiles. Moreover, the carbonyl at the 2 position would be very reactive towards nucleophilic addition. To the best of our knowledge this class of compounds is not known in the literature. Acylation at the nitrogen atom of the 3-alkyl-3-bromo-1,3-dihydro-2*H*-indol-2-ones was not considered a promising synthetic entry to **3** because the synthesis of the former compounds is only possible, in moderate yield, by reaction of the scarcely accessible 3-alkylindoles with *N*-bromosuccinimide.[2]



1–3	R	1–3	R
a	Bn	**d**	*i*-Pr
b	Et	**e**	*c*-C_6H_{11}
c	Pr	**f**	CH(Me)Ph

Scheme

Table. Compounds **2** and **3** Prepared

Product	Yield (%)	mp (°C) (hexane)	Molecular Formula[a]	IR (Nujol or film), ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, J (Hz)
2a	89	81–82	$C_{21}H_{21}NO_5$ (367.4)	1788, 1749	1.37 (t, 3H, J = 7.1), 1.44 (t, 3H, J = 7.1), 3.97 (s, 2H), 4.31 (q, 2H, J = 7.1), 4.46 (q, 2H, J = 7.1), 7.17 (m, 2H), 7.26 (m, 6H), 8.07 (d, 1H, J = 8.1)
2b	90	36–37	$C_{16}H_{19}NO_5$ (305.3)	1771, 1746	1.23 (t, 3H, J = 7.6), 1.41 (t, 3H, J = 7.1), 1.43 (t, 3H, J = 7.1), 2.64 (q, 2H, J = 7.6), 4.36 (q, 2H, J = 7.1), 4.45 (q, 2H, J = 7.1), 7.28 (m, 2H), 7.49 (m, 1H), 8.06 (m, 1H)
2c	70	oil	$C_{17}H_{21}NO_5$ (319.3)	1786, 1749	0.95 (t, 3H, J = 7.3), 1.42 (m, 6H), 1.66 (sextet, 2H, J = 7.3), 2.59 (t, 2H, J = 7.3), 4.36 (q, 2H, J = 7.1), 4.45 (q, 2H, J = 7.1), 7.28 (m, 2H), 7.49 (m, 1H), 8.06 (d, 1H, J = 8.1
2d	87	oil	$C_{17}H_{21}NO_5$ (319.3)	1788, 1751	1.36 (d, 6H, J = 7.1), 1.42 (m, 6H), 3.14 (septet, 1H, J = 7.1), 4.36 (q, 2H, J = 7.1), 4.44 (q, 2H, J = 7.1), 7.27 (m, 2H), 7.57 (m, 1H), 8.07 (d, 1H, J = 7.8)
2e	72	58	$C_{20}H_{25}NO_5$ (359.4)	1788, 1748	1.35 (m, 2H), 1.41 (t, 3H, J = 7.1), 1.42 (t, 3H, J = 7.1), 1.70–1.90 (m, 8H), 2.74 (m, 1H), 4.36 (q, 2H, J = 7.1), 4.44 (q, 2H, J = 7.1), 7.27 (m, 2H), 7.58 (m, 1H), 8.07 (d, 1H, J = 7.8)
2f	88	49	$C_{22}H_{23}NO_5$ (381.4)	1784, 1746	1.37 (t, 3H, J = 7.1), 1.41 (t, 3H, J = 7.1), 1.72 (d, 3H, J = 7.3), 4.31 (q, 2H, J = 7.1), 4.36 (q, 1H, J = 7.3), 4.45 (q, 2H, J = 7.1), 7.15 (m, 2H), 7.26 (m, 4H), 7.34 (m, 2H), 8.06 (d, 1H, J = 8.9)
3a	87	oil	$C_{18}H_{16}BrNO_3$ (374.3)	1810, 1785, 1750	1.41 (t, 3H, J = 7.1), 3.72 (d, 1H, J = 13.5), 3.82 (d, 1H, J = 13.5), 4.41 (q, 2H, J = 7.1), 6.94 (m, 2H), 7.09 (m, 3H), 7.25 (m, 2H), 7.46 (m, 1H), 7.69 (d, 1H, J = 8.0)
3b	91	44–45	$C_{13}H_{14}BrNO_3$ (312.2)	1788, 1752	0.79 (t, 3H, J = 7.4), 1.46 (t, 3H, J = 7.1), 2.49 (m, 2H), 4.47 (q, 2H, J = 7.1), 7.24 (m, 1H), 7.39 (m, 2H), 7.91 (d, 1H, J = 8.2)
3c	73	50–51	$C_{14}H_{16}BrNO_3$ (326.2)	1789, 1752	0.86 (t, 3H, J = 7.2), 1.11 (m, 2H), 1.46 (t, 3H, J = 7.1), 2.44 (m, 2H), 4.47 (q, 2H, J = 7.1), 7.21 (m, 1H), 7.39 (m, 2H), 7.89 (d, 1H, J = 8.2)
3d	78	52	$C_{14}H_{16}BrNO_3$ (326.2)	1810, 1784, 1749	0.96 (d, 3H, J = 6.9), 1.25 (d, 3H, J = 6.9), 1.45 (t, 3H, J = 7.1), 2.65 (septet, 1H, J = 6.9), 4.46, 4.48 (2H, AB part of ABX_3 system, J_{AB} = 8.8, J_{AX} = 7.1), 7.21 (m, 1H), 7.36 (m, 1H), 7.44 (m, 1H), 7.91 (d, 1H, J = 8.2)
3e	93	oil	$C_{17}H_{20}BrNO_3$ (366.3)	1811, 1788, 1750	0.95 (m, 2H), 1.26 (m, 3H), 1.45 (t, 3H, J = 7.1), 1.69 (m, 4H), 2.10 (m, 1H), 2.25 (m, 1H), 4.47, 4.49 (2H, AB part of ABX_3 system, J_{AB} = 9.3, J_{AX} = 7.1), 7.19 (m, 1H), 7.35 (m, 1H), 7.42 (m, 1H), 7.89 (d, 1H, J = 8.1)
3f	84	oil[b]	$C_{19}H_{18}BrNO_3$ (388.2)	1811, 1787 1749	1.33 (t, 3H, J = 7.1), 1.82 (d, 3H, J = 7.2), 3.77 (q, 1H, J = 7.2), 4.31 (q, 2H, J = 7.1), 6.78–7.69 (m, 9H) (more abundant diastereoisomer) 1.45 (t, 3H, J = 7.1), 1.57 (d, 3H, J = 7.1), 3.76 (q, 1H, J = 7.1), 4.45 (q, 2H, J = 7.1), 6.78–7.69 (m, 9H)

[a] Satisfactory microanalyses obtained: C ±0.13, H ±0.12, N ±0.12. [b] A 2:1 mixture of diastereoisomers.

We report here that the reaction of 3-alkyl-1,3-dihydro-2*H*-indol-2-ones **1** with ethyl chloroformate in the presence of triethylamine gives the ethyl 3-alkyl-1-ethoxycarbonylindol-2-yl carbonate **2** in very good yield (Scheme, Table). Bromination of compounds **2** with bromine in dichloromethane at room temperature affords pure 3-alkyl-3-bromo-1-ethoxycarbonyl-1,3-dihydro-2*H*-indol-2-ones **3** in high yield (Scheme, Table).

In summary we have presented a simple and novel strategy for an easy access to the title compounds.

Melting points are determined on a Büchi apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 298 instrument, in Nujol mull for solids and as liquid film for oils. ^1H NMR were recorded on a Bruker AC 300 Spectrometer in $CDCl_3$ solution. Column chromatography was performed on Merck Kiesegel 60, 0.063–0.2 mm and on Florisil 0.150–0.250 mm. Evaporation was carried out under vacuum in a rotary evaporator.

Compounds **1a**,[3] **1b**,[4] **1c**,[4] **1d**,[5] **1e**,[3] and **1f**[6] were prepared according to literature procedures. A better yield for **1d** was obtained by $NaBH_4$ reduction of 3-isopropylidene-1,3-dihydro-2*H*-indol-2-one[7] as reported in Ref. 4.

Ethyl 3-Alkyl-1-ethoxycarbonylindol-2-yl Carbonate 2; General Procedure:

Compound **1** (10 mmol) was dissolved in CH_2Cl_2 (70 mL) and Et_3N (5.6 mL, 40 mmol) was added. The solution was cooled to 0–5 °C and ethyl chloroformate (2.9 mL, 30 mmol) in CH_2Cl_2 (10 mL) was added under stirring. After 20 min at r.t., the mixture was washed with water (2 × 40 mL). The organic layer was dried, (Na_2SO_4), filtered and evaporated. The residue was purified by column chromatography on silica gel (eluent: hexane/CH_2Cl_2, 1:1).

3-Alkyl-3-bromo-1-ethoxycarbonyl-1,3-dihydro-2*H*-indol-2-ones 3; General Procedure:

Compound **2** (10 mmol) was dissolved in CH_2Cl_2 (50 mL) and then Br_2 (0.57 mL, 11 mmol) in CH_2Cl_2 (10 mL) was added under stirring at r.t.. After 5 min the solution was evaporated and the residue purified by column chromatography on Florisil (eluent: hexane/Et_2O, 4:1).

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