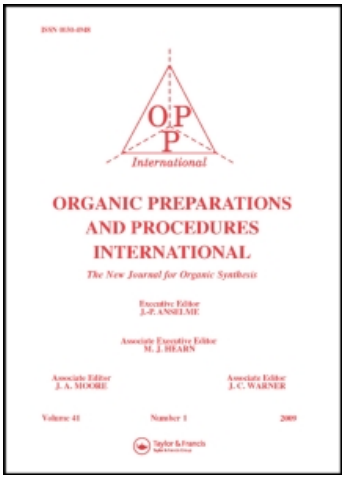

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SYNTHESIS OF 3-VINYLINDOLES FROM 3-ALKYLIDENEINDOL-2(3H)-ONES

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SYNTHESIS OF 3-VINYLINDOLES FROM 3-ALKYLIDENEINDOL-2(3H)-ONES

Submitted by (05/24/94)

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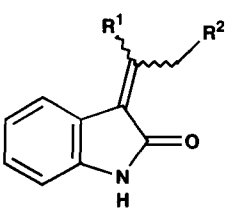
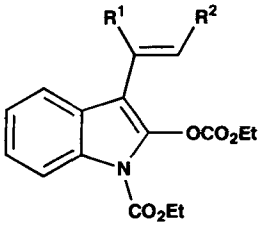
We recently described a new and facile entry to heterosubstituted-3vinylindoles from 3-[(1-hydroxy-2-substituted)ethylidene]indol-2(3H)-ones[1] and now report another entry to heterosubstituted-3-vinylindoles starting from 3alkylideneindol-2(3H)-ones (**1**).

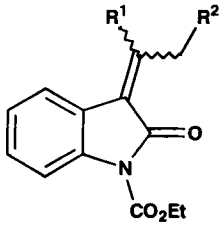
3-Alkylideneindol-2(3H)-ones are easily obtained by reaction of indol-2(3H)-one (oxindole) with carbonyl compounds.[2] When compounds **1** are treated with excess of ethyl chloroformate and triethylamine in dichloromethane, the corresponding ethyl 3-ethenyl-2-(ethoxycarbonyloxy)indole-1-carboxylates (**2**) are formed; derivatives **3** were also obtained as by-products. Compounds **3** afford compounds **2** by reaction with triethylamine and ethyl chloroformate. The stereochemistry of **2** has been assigned in analogy to that of ethyl-3-[(1-ethoxycarbonyloxy-2-substituted)ethenyl]-2-(ethoxycarbonyloxy) indole-1-carboxylates[1] and the ethyl-3-[2-aryl-1-ethoxycarbonyloxy)ethenyl]-2-(ethoxycarbonyloxy)indole-1-carboxylates.[3]



1a-k



2a-k



3a,b,d-g,k

a) R^1 = Ph, R^2 = H b) $R^1 = R^2 = -(CH_2)_4-$ c) R^1 = H, R^2 = Ph
d) R^1 = Me, R^2 = Ph e) $R^1 = CH_2Ph$, R^2 = Ph f) R^1 = Et, R^2 = Ph
g) R^1 = Me, R^2 = H f) $R^1 = CO_2Et$, R^2 = H k) $R^1 = R^2 = -(CH_2)_3-$

The stereochemistry of compounds **3a, d, f** could be assigned safely only by comparison with the corresponding isomers on the basis that methyl and benzylic methylene hydrogens are associated with lower-field signals when they lie on the same side of the 2-CO group. A mixture of compounds **3a, d, f** with their isomers was obtained by photochemical isomerization ($CDCl_3$, nmr test tube, HPK-125 W Philips high-pressure Hg-lamp, 10 min). Compound **3a** has E stereochemistry (CH_3 at δ 2.78 *vs* 2.64 in the Z isomer), **3d** has Z stereochemistry (CH_2Ph at δ 4.52 *vs* 4.10 in the E isomer) and **3f** has E stereochemistry (CH_2Ph at δ 4.10 *vs* 4.50 in the Z isomer).

TABLE 1. Ethyl 3-Ethenyl-2(ethoxycarbonyloxy)indole-1-carboxylates (**2**)

Starting Material	Products	Yield (%)	Eluent Ratio[a]	mp (°C) (solvent)[b]
1a	**2a**	70	1:1	oil
	3a	26		97-98
1b	**2b**	53	1:2	81-82[c]
	3b	10		62[c]
1c	**2c**	68		106-107
	2d	65	2:1	90-91
1d	**3d**	25		61[d]
1e	**2e**	55	2:1	94-95
	3e	35		75-76
1f	**2f**	35	1:1	74-75
	3f	56		94-95
1g	**2g**	9	1:1	oil
	3g	86		58-59
1h	**2h**	90	1:1	oil
1k	**2k**	18	1:1	81-83[c]
	3k	61		120-122[e]

a) Hexane-CH_2Cl_2. b) Crystallization solvent: hexane-ether unless otherwise noted. c) Pentane. d) Hexane. e) CH_2Cl_2-Et_2O.

TABLE 2. Elemental Analyses of Compounds **1-3**

Compd.	Molecular	Formula Calcd. (Found)		
		C	H	N
1c	$C_{16}H_{13}NO$	81.68 (81.52)	5.57 (5.64)	5.95. (5.88)
2a	$C_{22}H_{21}NO_5$	69.65 (69.46)	5.58 (5.71)	3.69 (3.59)
2b	$C_{20}H_{23}NO_5$	67.21 (67.18)	6.49 (6.39)	3.92 (3.88)
2c	$C_{22}H_{21}NO_5$	69.65 (69.77)	5.58 (5.42)	3.69 (3.74)
2d	$C_{23}H_{23}N0_5$	70.21 (70.23)	5.89 (5.91)	3.56 (3.60)
2e	$C_{29}H_{27}NO_5$	74.18 (74.31)	5.80 (5.71)	2.98 (2.93)
2f	$C_{24}H_{25}NO_5$	70.75 (70.82)	6.18 (6.22).	3.44 (3.49)
2g	$C_{17}H_{19}NO_5$	64.34 (64.31)	6.03 (6.10)	4.41 (4.45)
2h	$C_{19}H_{21}NO_7$	60.79 (60.85)	5.64 (5.70)	3.73 (3.69)
2k	$C_{19}H_{21}NO_5$	66.46 (66.53)	6.16 (6.19)	4.08 (4.20)
3a	$C_{19}H_{17}NO_3$	74.25 (74.40)	5.58 (5.42)	4.56 (4.34)
3b	$C_{17}H_{19}NO_3$	71.56 (71.41)	6.71 (6.80)	4.91 (4.83)
3d	$C_{20}H_{19}NO_3$	74.75 (74.62)	5.96 (6.02)	4.36 (4.29)
3e	$C_{26}H_{23}NO_3$	78.57 (78.44)	5.83 5.95)	3.52 (3.41)
3f	$C_{21}H_{21}NO_3$	75.20 (75.19)	6.31 (6.27)	4.18 (4.08)
3g	$C_{14}H_{15}NO_3$	68.56 (68.40)	6.16 (6.22)	5.71 (5.48)
3k	$C_{16}H_{17}NO_3$	70.83 (70.65)	6.32 (6.41)	5.16 (5.02)

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 298 instrument as nujol mull for solids and liquid film for oils. ^{1}H NMR spectra were recorded on a Bruker AC 300 in $CDCl_3$ solution if not otherwise stated. Column chromatography was performed on Merck Kieselgel 60, 0.063-0.2 mm. Melting points were determined on a Büchi apparatus and are uncorrected. Na_2SO_4 was used as drying agent. Evaporation was carried out under vacuum in a rotary evaporator. Compounds **1a**, [4] **1b**, [5] **1d**, [5] **1e**, [5] **1f**, [5] **1g**,[6] **1k**[5] were prepared according to literature procedure; ester **1h** was prepared by Fischer esterification on the corresponding acid[7].

3-(2-Phenylethylidene)indol-2(3H)-one 1c.- A solution of 2-morpholinostyrene[8] (4.73 g, 25 mmol) and indol-2(3H)-one (2.93 g, 22 mmol) in benzene (140 mL) and AcOH (10 mL) was refluxed for 1 hr. The residue from the solvents evaporation was taken-up with water (100 mL), neutralized with $NaHCO_3$ and extracted with CH_2Cl_2 (2 x 50 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was purified by SiO_2 column chromatography (eluent CH_2Cl_2-Et_2O 20:1) to give 3.5 g (67 %) of **1c** as a mixture of the two isomers. Silica gel column chromatography (eluent $CH_2Cl_2Et_2O$ 20:1) gives pure isomers: **E-1c**, mp 157-158° (CH_2Cl_2-Et_2O). IR 3150, 1702, 1642 cm^{-1}; ^{1}H NMR: δ 4.03 (2H, d, 7.7), 6.90 (1H, d, 7.8), 7.03 (1H, t, 7.6), 7.15 (1H, t, 7.7), 7.22-7.34 (6H, m), 7.64 (1H, d, 7.6), 8.25 (1H, bs); **Z-1c**, mp. 182-183° (CH_2Cl_2-Et_2O). IR 3150, 1698, 1639 cm^{-1}; ^{1}H NMR δ 4.39 (2H, d, 7.9), 6.84-7.03 (3H, m), 7.17-7.38 (7H, m), 8.02 (1H, bs).

TABLE 3. Spectroscopic Data of Compounds **2** and **3**

Product	IR (Nujol or film) ν, (cm^{-1})	^1H NMR ($CDCl_3$) δ, J (Hz)
2a	1785, 1750	1.30 (3H, t, 7.1), 1.44 (3H, t, 7.1), 4.24 (2H, q, 7.1), 4.48 (2H, q, 7.1), 5.51 (1H, s), 5.79 (1H, s), 7.11-7.39 (8H, m), 8.10 (1H, d, 8.4).
2b	1789, 1747	1.40 (3H, t, 7.1), 1.43 (3H, t, 7.1), 1.73 (4H, m), 2.22 (2H, m), 2.33 (2H, m), 4.35 (2H, q, 7.1), 4.45 (2H, q, 7.1), 5.98 (1H, m), 7.23 (1H, m), 7.29 (1H, m), 7.57 (1H, bd, 7.6), 8.07 (1H, bd, 8.0).
2c	1788, 1747	1.43 (3H, t, 7.1), 1.46 (3H, t, 7.1), 4.39 (2H, q, 7.1), 4.49 (2H, q, 7.1), 7.08 (1H, d, 16.6), 7.19 (1H, d, 16.6), 7.28 (1H, m), 7.36 (4H, m), 7.51 (2H, m), 7.88 (1H, m), 8.14 (1H, m).
2d	1779, 1740	1.39 (3H, t, 7.1), 1.46 (3H, t, 7.1), 2.27 (3H, d, 1.3), 4.36 (2H, q, 7.1), 4.49 (2H, q, 7.1), 6.77 (1H, bs), 7.20-7.39 (7H, m), 7.67 (1H, bd, 7.9), 8.12 (1H, bd, 8.0).
2e	1781 1752	1.34 (3H, t, 7.1), 1.42 (3H, t, 7.1), 4.11 (2H, bs), 4.26 (2H, q, 7.1), 4.43 (2H, q, 7.1), 7.01 (1H, bs), 7.09-7.39 (12H, m), 7.67 (1H, bd, 8.0), 8.05 (1H, bd, 7.8).
2f	1790 1750	1.03 (3H, t, 7.5), 1.38 (3H, t, 7.1), 1.46 (3H, t, 7.1), 2.70 (2H, q, 7.5), 4.34 (2H, q, 7.1), 4.49 (2H, q, 7.1), 6.67 (1H, s), 7.24-7.40 (7H, m), 7.60 (1H, d, 7.5), 8.13 (1H, d, 8.2).
2g	1788, 1751	1.40 (3H, t, 7.1), 1.44 (3H, t, 7.1), 2.14 (3H, s), 4.36 (2H, q, 7.1), 4.47 (2H, q, 7.1), 5.29 (1H, bs), 5.33 (1H, bs), 7.24-7.35 (2H, m), 7.64 (1H, d, 7.6), 8.10 (1H, d, 8.1).
2h	1775, 1738, 1715	1.28 (3H, t, 7.1), 1.40 (3H, t, 7.1), 1.46 (3H, t, 7.1), 4.26 (2H, q, 7.1), 4.36 (2H, q, 7.1), 4.48 (2H, q, 7.1), 6.05 (1H, d, 1.5), 6.67 (1H, d, 1.5), 7.27-7.45 (3H, m), 8.15 (1H, m).
2k	1770 1723	1.42 (3H, t, 7.2), 1.46 (3H, t, 7.2), 2.03 (2H, m), 2.55 (2H, m), 2.82 (2H, m), 4.39 (2H, q, 7.2), 4.48 (2H, q, 7.2), 6.24 (1H, m), 7.31 (2H, m), 7.75 (1H, m), 8.12 (1H, m).
3a	1750, 1732	1.48 (3H, t, 7.2), 2.78 (3H, s), 4.50 (2H, q, 7.2), 6.17 (1H, d, 7.9), 6.73 (1H, t, 7.7), 7.13(1H, t, 7.9), 7.26 (2H, m), 7.46 (3H, m), 7.87 (1H, d, 8.2).
3b	1759, 1732, 1720	1.43 (3H, t, 7.1), 1.66-1.87 (6H, m), 2.88 (2H, bt, 6.4), 3.32 (2H, bt, 6.5), 4.47 (2H, q, 7.1), 7.12 (1H, bt, 7.6), 7.26 (1H, bt, 7.5), 7.65 (1H, d, 7.8), 7.94 (1H, d, 8.1).
3d	1750, 1740	1.47 (3H, t, 7.1), 2.30(3H, s), 4.50(2H, q, 7.1), 4.52 (2H, s), 7.13-7.34 (7H, m), 7.58 (1H, d, 7.8), 7.98 (1 H, d, 8.2).
3e	1754, 1738	1.48 (3H, t, 7.1), 4.01(2H, s), 4.47(2H, s), 4.52(2H, q, 7.1), 7.01-7.33(12H, m), 7.51(1H, d, 7.8), 7.99 (1 H, d, 8.2).
3f	1750, 1725	1.13 (3H, t, 7.5), 1.46 (3H, t, 7.1), 2.96 (2H, q, 7.5), 4.10 (2H, s), 4.50 (2H, q, 7.1), 7.00-7.33 (7H, m), 7.48 (1H, d, 7.8), 7.98 (1H, d, 8.0).
3g	1748, 1726	1.46 (3H, t, 7.1), 2.41 (3H, s), 2.61 (3H, s), 4.48 (2H, q, 7.1), 7.16 (1H, bt, 7.6), 7.29 (1H, bt, 7.8), 7.58 (1H, d, 7.8), 7.96 (1H, d, 8.1).
3k	1738, 1702	1.48 (3H, t, 7.2), 1.88 (4H, m), 2.90 (2H, m), 3.15 (2H, m), 4.50 (2H, q, 7.2), 7.25 (2H, m), 7.48 (1H, m), 8.00 (1H, m).

Ethyl 3-Ethenyl-2(ethoxycarbonyloxy)indole-1-carboxylates (2). General Procedure.- To a solution of **1** (10 mmol) in CH_2Cl_2 (50 mL) was added ethyl chloroformate (2.9 mL, 30 mmol). After cooling at 0-5° triethylamine (5.6 mL, 40 mmol)in CH_2Cl_2 (15 mL) was added under stirring. After allowed to warmed up to room temperature overnight, the reaction mixture was washed with H_2O (2 x 50 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated. The products were purified by column chromatography on silica gel and crystallized (Table 1).

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A SAFE AND CONVENIENT PROCEDURE FOR THE SYNTHESIS OF POLYAMINES *via* AZIDE INTERMEDIATES

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In connection with our studies on molecular amplifiers for contrast enhancement in magnetic resonance imaging (MRI),[1] we required a safe, efficient synthesis of several functionalized polyamines including triamine **5** and diamine **7**. Triamine **5** has exhibited interesting chelation properties[2] and synthetic potential.[3] Procedures for the preparation of **5** from pentaerythritol (**1**) involve discrimination among four equivalent hydroxyl groups and introduction of the amino groups. In one recent synthesis,[4] the requisite discrimination was achieved by initial formation of a bicyclic