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2-Ethoxycarbonyloxy-3-ethynylindoles from Indol-2(3H)-ones.

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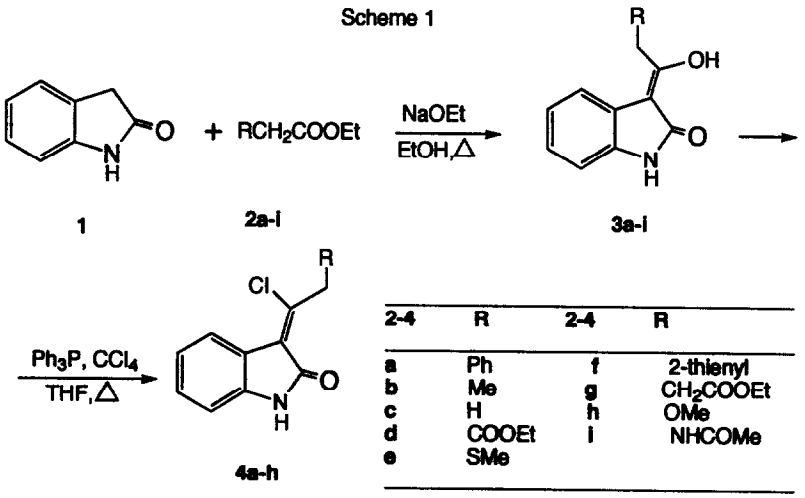
Abstract: The treatment of the 3-[(1-chloro-2-substituted)ethylidene]indol-2(3H)-ones **4**, prepared from indol-2(3H)-one **1**, with ethyl chloroformate and triethylamine gives the ethy 3-(ethynyl)-2-(ethoxy-carbonyloxy)indole-1-carboxylates **7**. Some dimeric derivatives of the intermediate allenes have been isolated.

The synthesis of 3-ethynylindoles has been previously achieved both from 3-acylindoles and by condensation of 3-iodoindoles with terminal acetylenes.[1] Palladium-catalyzed coupling of 3-iodoindoles with terminal acetylenes[2] and with ethoxy(tributylstannyl)acetylene[3] were also reported. Ethynylindoles were also obtained by flash vacuum pyrolysis of 5-(indol-3-yl-methylene)-2,2-dimethyl-1,3-dioxane-4,6-diones[4] and of 4-(indol-3-yl)methylene-5(4H)-isoxazolones.[5]

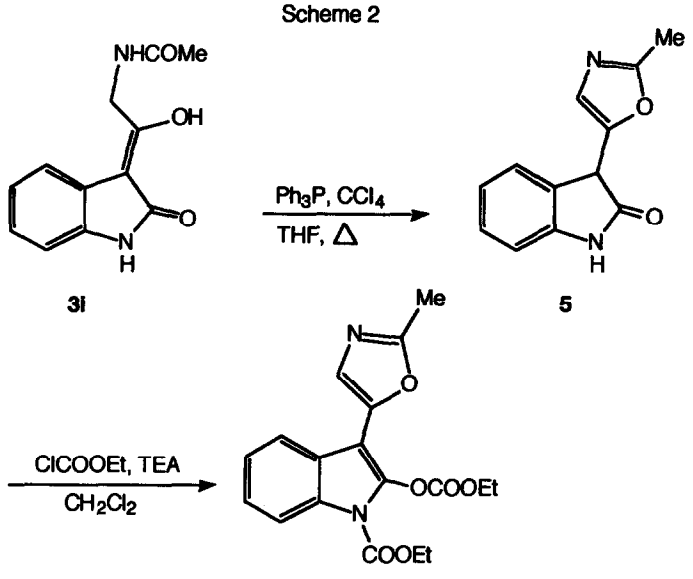
Scheme 1



2-4	R	2-4	R
a	Ph	f	2-thienyl
b	Me	g	CH_2COOEt
c	H	h	OMe
d	COOEt	i	NHCOMe
e	SMe		

We wish to report here a new synthesis of ethyl 2-ethoxycarbonyloxy-3-ethynylindoles-1-carboxylates **7** starting from indol-2(3H)-one **1**. The indol-2(3H)-one **1** is condensed with the ethyl esters **2a-i**, following the reported methods[6-9], to give the 3-[(1-hydroxy-2-substituted)ethylidene]indol-2(3H)-ones **3a-i**. From compounds **3a-h**, the corresponding chloroderivatives **4a-h** are prepared by reaction with Ph_3P/CCl_4 in anydrous THF.(Scheme 1, Table 1). Only by this route may these derivatives be obtained in resonable yields. Compounds **4a-h** are pure isomers, and the reported E stereochemistry has been assigned on the basis of the chemical shifts of the allylic hydrogens in comparison with the chemical shift of the same hydrogens in the Z isomers, obtained as an unseparable E/Z mixture by photochemical isomerization ($CDCl_3$, nmr test-tube, HPK-125 W Philips high-pressure Hg-lamp, pyrex, 15 min) (Table 2). Compounds **3i** does not afford the corresponding chloroderivative. Instead, the 3-oxazolylindol-2(3H)-one **5** is obtained, whose structure is confirmed by reaction with ethyl chloroformate and TEA, to give 1-ethoxycarbonyl-2-ethoxycarbonyloxy derivative **6** (Scheme 2, Table 1).

Scheme 2

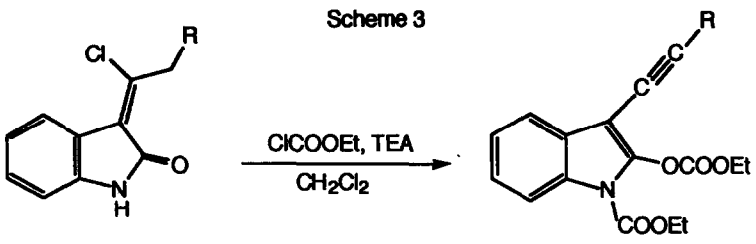


6

When the chloroderivatives **4a-f** are treated with excess of ethyl chloroformate, followed by reaction with triethylamine in dichloromethane, the corresponding ethyl 3-(ethynyl)-2-(ethoxycarbonyloxy)-indole-1-carboxylates **7a-f** are obtained (Scheme 3, Table 1), while from compound **4g** the corresponding allene **8** is isolated (Scheme 4, Table 1).

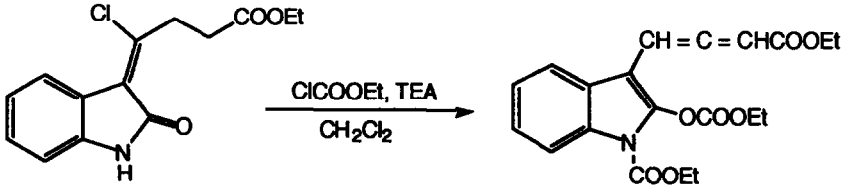
The formation of the ethynylindoles **7** occurs *via* initial dehydrohalogenation to the intermediate allenes, in equilibrium with the corresponding alkynes, from which the final products **7** are obtained by reaction with ethyl chloroformate and triethylamine (Scheme 5, Table 1). To substantiate this hypothesis, compounds **4k,l** are synthesized starting from diethyl methyl-, **2k**, and allyl malonate **2l**. These precursors are expected to give isolable allene products owing the impossibility of isomerization. When the chloroderivatives **4k,l** are treated with ethyl chloroformate, followed by reaction with triethylamine, the allenes **10k,l** are formed.

Scheme 3



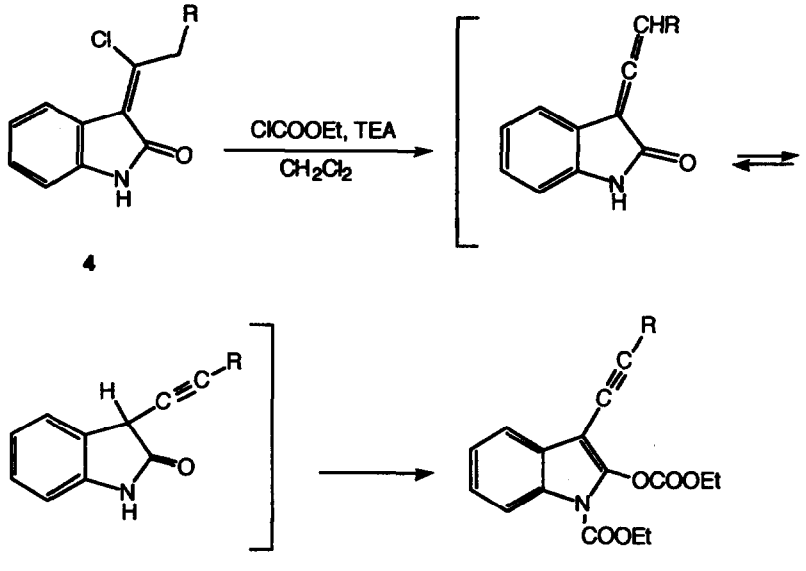
4a-f 7a-f

Scheme 4



4g 8

Scheme 5

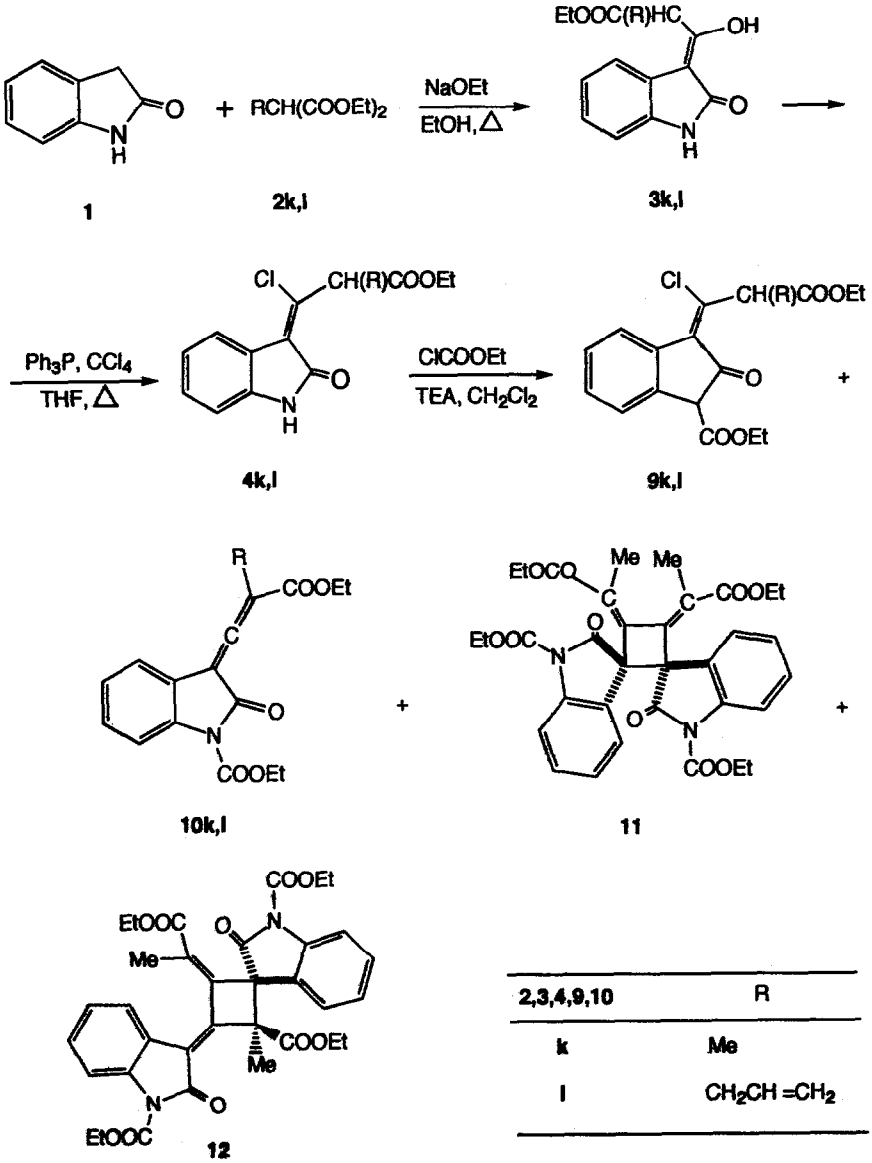


4 7

In both cases, besides the allene **10**, the N-acylated chloroderivatives **9k,l** are isolated. Whereas **10l** is obtained in good yield, the allene **10k** is formed in only 13% yield and other two compounds, **11** and **12**, are produced (Scheme 6, Table 1). Their structures are assigned on the basis of analytical and spectroscopic data as

well as diffraction analysis.[10] Figures 1 and 2 show an ORTEP view of the molecules with the atomic numbering scheme of heavy atoms. Compounds **11** and **12** arise from a [2+2] dimerization of the allene **10k** by "center-center" and "end-center" combination[11]. The allene **10k** contains 10% of the dimer **11** and is characterized as such. The order of addition of ethyl chloroformate and triethylamine is crucial. When the chloroderivatives **4a-f** are treated firstly with triethylamine and then with ethyl chloroformate, a very complex mixture of products is formed from which the ethynylindoles **7a-f** are obtained only in low yield.

Scheme 6



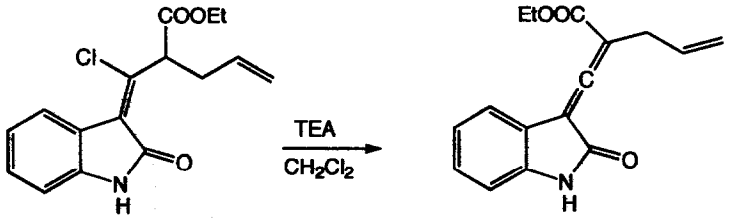
2,3,4,9,10	R
k	Me
l	$CH_2CH=CH_2$

When the chloro derivatives **4** are treated with triethylamine alone in methylene chloride, only from **41** the corresponding allene **13** is isolated. (Scheme 7, Table 1).

In all the other cases a mixture of compounds is formed from which no pure derivatives are obtained. The structure of compounds **11** and **12** suggest that the allenes firstly formed give dimeric derivatives.

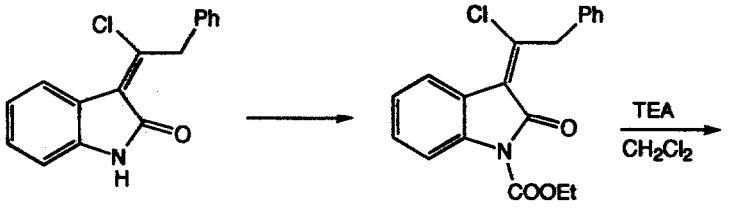
On the assumption that the acylation of the indolic nitrogen does not alter the reactivity of the chloro-compounds **4** with the triethylamine, and to have some suggestions on the nature of these dimers, compound **14** was prepared from **4a**. The treatment of a dichloromethane solution of **14** with triethylamine affords a reaction mixture from which a dimeric crystalline compound **15** is isolated (Scheme 8, Table 1).

Scheme 7

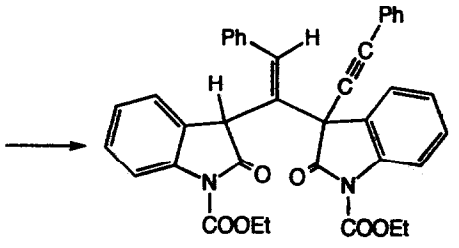


4c **13**

Scheme 8



4a **14**



15

Its structure is assigned on the basis of analytical and spectroscopic data as well as diffraction analysis.[10] Figure 3 shows an ORTEP view of the molecule with the atomic numbering scheme of heavy atoms. A reasonable path for the formation of **15** from **14**, *via* the intermediate allene in equilibrium with the corresponding alkyne, is reported in Scheme 9.

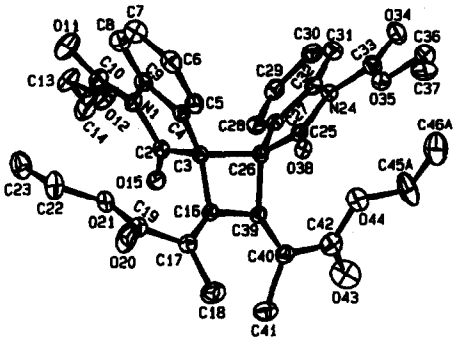


Figure 1. ORTEP of 11. The ethyl group bonded to O44 is disordered: only a conformation is reported. Hydrogen atoms are omitted

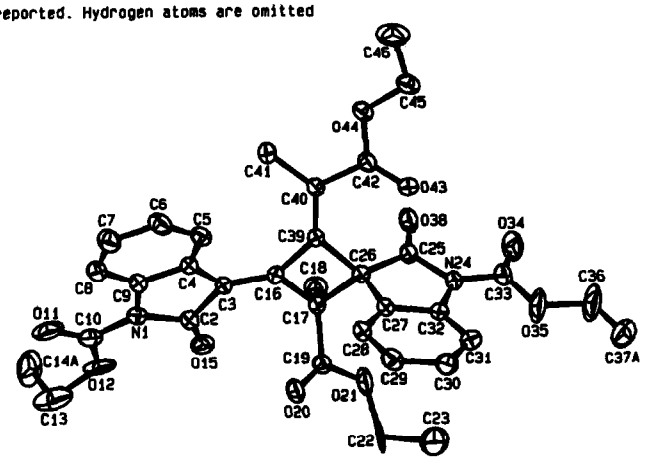


Figure 2. ORTEP of 12. The methyl groups bonded to C13 and C36 are disordered: only a conformation is reported. Hydrogen atoms are omitted.

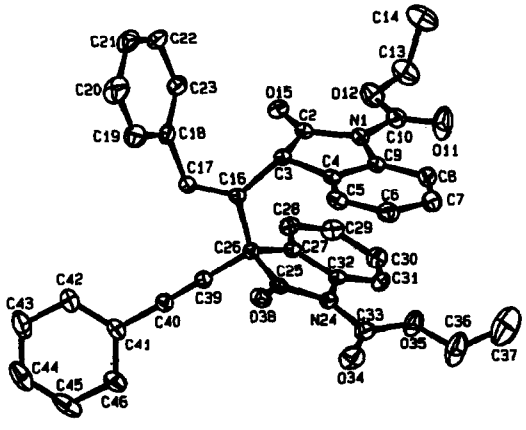
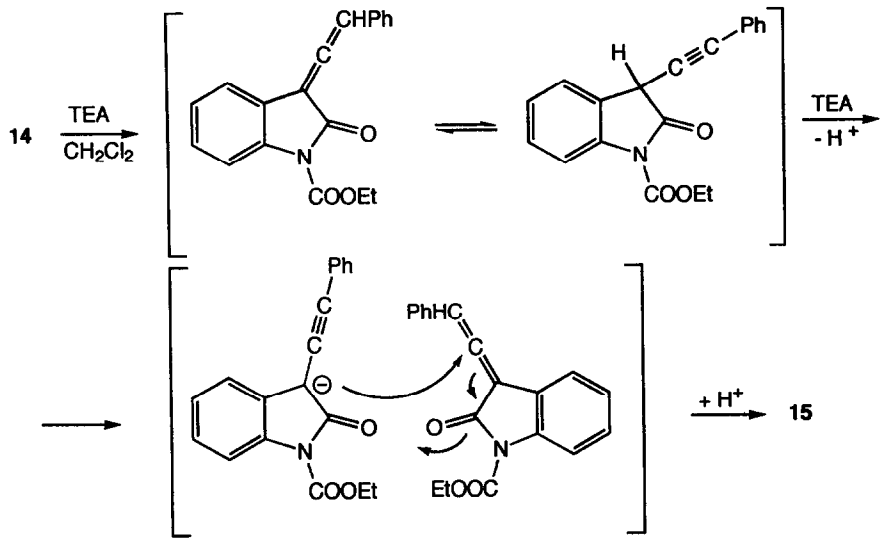


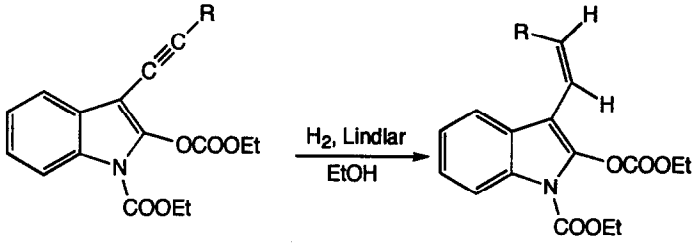
Figure 3. ORTEP of 15. The methyl group bonded to C36 is disordered: only a conformation is reported. Hydrogen atoms are omitted.

Scheme 9



Reduction of an ethanolic solution of the ethynylindoles **7** with hydrogen in the presence of the Lindlar catalyst, gives the corresponding 3-vinylindoles **16.** ^{1}H-NMR data suggest E stereochemistry for **16d.** From **7c**, an unseparable mixture of 3-vinyl- and 3-ethynylindole is obtained (Scheme 10, Table 1). Reduction of compound **7e** is achieved with Pd/C 10% in AcOEt.

Scheme 10



7a, b, d-f **16a, b, d-f**

In conclusion, reasonable yields of ethynylindoles **7** are obtained only if the intermediate allene is generated in the presence of the acylating agent. If no ethyl chloroformate is present, the allene dimerizes *via* a formal [2+2] cycloaddition[11] or *via* a Michael addition with the corresponding alkyne.

From **4h** we are unable to obtain the corresponding ethynylindole.

EXPERIMENTAL

Melting points were determined on a Buchi 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. ^{1}H-NMR were recorded on a Bruker AC 300 spectrometer in $CDCl_3$ solution unless otherwise stated. Column chromatography was performed on Merk Kieselgel 60, 0.063-0.2 mm. Evaporation was carried out under vacuum in a rotary evaporator.

Compounds **3a**[12], **3b**[7], **3c**[6], **3d**[7], **3e**[7], **3f**[8], **3h**[7] and **3i**[9] were prepared according to the literature procedure.

Ethyl 4-[2(1H)-oxoindol-3-ylidene]-4-hydroxy butanoate 3g.

Indol-2(3H)-one **1** (5.32 g, 40 mmol) was added, under stirring, to a warm NaOEt solution, prepared from Na (1.84 g, 80 mmol) and absolute EtOH (60 mL).

To this solution, diethyl succinate (20 mL, 120 mmol) was then added. The mixture was refluxed under stirring for 3h and the formed sodium salt filtered after cooling at 0° C for 30 min. A water (70 mL) suspension of the sodium salt was acidified with 16% HCl and the mixture extracted with CH_2Cl_2 (2 x 60 mL). The organic layer was dried (Na_2SO_4), filtered, evaporated and the residue crystallized (Table 1).

Ethyl 3[2(1H)-oxoindol-3-ylidene]-3-hydroxy-2-methyl propanoate 3k.

The reaction was carried out as reported for compound **3g** but diethyl methyl malonate (8 mL, 46 mmol) was added and the mixture was heated to reflux for 6h.

Ethyl 3-[2(1H)-oxoindol-3-ylidene]-2-allyl-3-hydroxy propanoate 3l.

The reaction was carried out as reported for compound **3g**, but diethyl allyl malonate (10 mL, 50 mmol) was added and the mixture was heated to reflux for 3h. After this time, the mixture was evaporated, the residue diluted with H_2O (70 mL) and extracted with Et_2O (50 mL). The aqueous layer was acidified with HCl 16% and extracted with CH_2Cl_2 (2 x 40 mL). The organic layer was dried (Na_2SO_4), filtered, evaporated and the residue crystallized (Table 1).

Compounds 4 from compounds 3.

Compound **3** (10 mmol) was dissolved in anydrous THF (60 mL) and Ph_3P (5.25 g, 20 mmol) and CCl_4 (5 mL) were added. The solution was heated to reflux for the reported time (Table 1). The residue obtained from the solvent evaporation, was purified by silica gel column chromatography and crystallized (Table 1). From this reaction, only compound **5** was isolated in the case of compound **3i**.

Compound 6 from compound 5.

Compound **5** (g, 10 mmol) was dissolved in CH_2Cl_2 (60 mL) and then Et_3N (5.57 mL, 40 mmol) was added. The reaction mixture was cooled at 0-5 °C and ethyl chloroformate (2.88 mL, 30 mmol) in CH_2Cl_2 (10 mL) was added under stirring. After being warmed to room temperature for the reported time (Table 1), the reaction mixture was washed with H_2O (2 x 40 mL), the organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was purified by silica gel column chromatography and crystallized (Table 1).

2-Ethoxycarbonyloxy-3-ehynylindoles 7 from compounds 4a-g.

Compound **4** (10 mmol) was dissolved in CH_2Cl_2 (70 mL) and then ethyl chloroformate (2.88 mL, 30 mmol) was added. The stirred reaction mixture was cooled at 0°C and a solution of Et_3N (5.57 mL, 40 mmol) in CH_2Cl_2 (15 mL) was added. After being warmed to room temperature for the reported time (Table 1), the reaction mixture was washed with H_2O (2 x 40 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated. The residue was purified by silica gel column chromatography and crystallized (Table 1). For the compound **4g** this reaction gives only compound **8**.

Compounds 9k,l, 10k,l, 11 and 12 from compounds 4k,l.

The reaction was carried out as reported above for compounds **4a-g**, but ethyl chloroformate (1.92 mL, 20 mmol) and Et_3N (4.18 mL, 30 mmol) were added. In the case of compound **4k**, besides compounds **9k** and **10k**, compounds **11** and **12** were also isolated after silica gel column chromatography (Table 1).

Compound 13 from compound 4l.

Compound **4l** (305 mg, 1 mmol) was dissolved in CH_2Cl_2 (40 mL) and treated with Et_3N (0.56 mL, 4 mmol) at room temperature. After 24h the mixture was evaporated and the residue purified by silica gel column chromatography and crystallized (Table 1).

Compound 14 from compound 4a.

Compound **4a** (2.70 g, 10 mmol) was dissolved in CH_2Cl_2 (80 mL) mg) and diethyl pyrocarbonate (2.2 mL, 20 mmol) and p-dimethylaminopyridine (50 mg) were added. After 10 min. at room temperature, the mixture was evaporated and the residue purified by silica gel column chromatography and crystallized (Table 1).

Compound 15 from compound 14.

Compound **14** (683 mg, 2 mmol) was dissolved in CH_2Cl_2 (30 mL) and Et_3N (0.56 mL, 4 mmol) was added. After 5 min. at room temperature, the residue was evaporated and purified by silica gel column chromatography and crystallized (Table 1).

Compounds 16 from compounds 7.

The compound **7** (1 mmol) was dissolved in EtOH (30 mL). Lindlar catalyst (50 mg) was added and the mixture was hydrogenated under atmospheric pressure at room temperature. After the reported time (Table 1) the catalyst was filtered off, the solvent evaporated and the residue distilled or crystallized from the reported solvent (Table 1). Compound **7e** was reduced in AcOEt solution and in the presence of Pd/C 10%.

X-ray structure determination of compounds 11, 12 and 15.

Single crystal X-ray measurements of **11** and **12** were performed on a SIEMENS P4 diffractometer, while data of **15** were collected on a Enraf-Nonius CAD-4.

In all cases, the radiation used was graphite-monochromatized Mo-kα (λ=0.71073 Å). The structures of **11** and **12** were solved and refined by SHELXTL/PC[13] and SHELXL93[14], that of **15** by SIR88[15] and

SDP[16]. All structures present disordered ethyl groups: they are indicated in the captions of Fig. 1, 2 and 3. The ethyl group, if ordered, has large thermal parameters in all the compounds. For this reason the quality of data is poor and the ratio data/parameters low, particularly for **11** and **12**. Only H atoms bonded to C_{sp2} of **15** were refined, while all the other were kept in fixed position. The refinement of disordered ethyl group in **11** and **12** was undertaken with some "soft" restraints on geometrical and thermal parameters, as allowed by cited SHELXL93 program.

Compounds **11** and **12** are particularly strained; in fact the bond C3-C26 of **11** and C17-C26 in **12** are 1.620(3) and 1.642(4) Å long, respectively. On the contrary, no particularly relevant strain is found in **15**.

Table 1. New Compounds Prepared.

Starting Material	Product[a]	Reaction Time (h)	Yield (%)	Eluent[b]	mp (°C) (solvent) or bp (°C/mmHg)
2g	**3g**	3	61	—	109-110 (Hx-CH_2Cl_2)
2k	**3k**	3	65	—	135-137 (Hx-Et_2O)
2l	**3l**	6	52	—	115-116 (Et_2O)
3a	**4a**	3	83	Hx-CH_2Cl_2 (1:1)	176-178 (CH_2Cl_2-Et_2O)
3b	**4b**	3.5	70	Hx-CH_2Cl_2 (1:1)	163-164 (CH_2Cl_2-Et_2O)
3c	**4c**	4	89	Hx-CH_2Cl_2 (1:1)	197-198 (CH_2Cl_2-Et_2O)
3d	**4d**	5	62	Hx-Et_2O (2:1)	132-133 (Et_2O)
3e	**4e**	5	73	Hx-Et_2O (2:1)	156-158 (Et_2O)
3f	**4f**	5	65	CH_2Cl_2-Et_2O (20:1)	165-167 (CH_2Cl_2)
3g	**4g**	3.5	75	Hx-Et_2O (1:1)	123-124 (Hx-Et_2O)
3h	**4h**	2	75	Hx-Et_2O (2:1)	159-160 (Et_2O)
3i	**5**	4	51	CH_2Cl_2-MeOH (30:1)	150-151 (Et_2O)
5	**6**	1	93	CH_2Cl_2-Et_2O (30:1)	88-89 (Hx-Et_2O)
3k	**4k**	3	75	Hx-Et_2O (2:1)	105-107 (Hx-Et_2O)
3l	**4l**	6	65	Hx-Et_2O (2:1)	110-111 (Hx-Et_2O)
4a	**7a**	1	55	Hx-CH_2Cl_2 (1:1)	106-107 (Hx-Et_2O)
4b	**7b**	10	57	Hx-CH_2Cl_2 (1:1)	73-74 (Hx-Et_2O)
4c	**7c**	1	45	Hx-CH_2Cl_2 (1:1)	63-64 (Hx-Et_2O)
4d	**7d**	1	77	Hx-CH_2Cl_2 (1:1)	85-86 (Hx-CH_2Cl_2)
4e	**7e**	2	45	Hx-CH_2Cl_2 (2:1)	80-81 (Hx-Et_2O)
4e	**7e**	0.5	15[c]	Hx-CH_2Cl_2 (2:1)	
4f	**7f**	1	75	CH_2Cl_2	62-63 (Hx-Et_2O)
4f	**7f**	1	36[c]	CH_2Cl_2	
4g	**8**	1	78	Hx-Et_2O (2:1)	65-66 (Hx-Et_2O)

4k	**9k**	2	24	Hx-isoPr$_2$O (2:1)	71-72 (pentane)
	10k		13		78-79 (pentane)
	11		24		169-170 (EtOH)
	12		4		184-186 (Hx-CH_2Cl_2)
4l	**9l**	4.5	5	Hx-Et$_2$O (30:1)	76-78 (Hx-Et$_2$O)
	10l		75		80-81 (Hx-Et$_2$O)
4l	**13**	24	34	CH_2Cl_2-Et$_2$O (30:1)	105-107 (Et$_2$O)
4a	**14**	0.1	89	—	112-113 (Hx-Et$_2$O)
14	**15**	0.5	40	CH_2Cl_2-Et$_2$O (50:1)	196 (CH_2Cl_2-isoPr$_2$O)
7a	**16a**	2.5	95	—	oil
7b	**16b**	4	90	—	170-175/ 0.28
7d	**16d**	4	92	—	71-72 (Hx-Et$_2$O)
7e[d]	**16e**	72	66	CH_2Cl_2	oil
7f	**16f**	8	91	—	oil

[a] Satisfactory microanalyses obtained: C ± 0.19, H ± 0.11, N ± 0.13. [b] Hx: hexane. [c] The reaction was carried out adding Et_3N firstly and then ethyl chloroformate. [d] The reaction was carried out with Pd/C 10%.

Table 2. Allylic Hydrogens Chemical Shift of **E**- and **Z**-**4** Derivatives.

(E)-4	H	(Z)-4	H
4a	4.74	**4a**	4.36
4b	3.40	**4b**	3.03
4c	2.94	**4c**	2.76
4d	4.50	**4d**	4.02
4e	4.42	**4e**	3.98
4f	4.88	**4f**	4.47
4g	3.67	**4g**	3.33
4h	5.04	**4h**	4.64
4l	6.05	**4l**	4.48
4k	5.93	**4k**	4.48

Table 3. Spectral Data of New Compounds.

Product	IR (Nujol or film) ν cm^{-1}	^{1}H-NMR δ, J (Hz)
3g	3150, 1723, 1661	1.27 (3H, t, 7.1), 2.81 (2H, t, 7.6), 3.14 (2H, t, 7.6), 4.18 (2H, q, 7.1), 6.98-7.22 (3H, m), 7.42 (1H, d, 8.0), 8.42 (1H, bs)[a], 13.80 (1H, bs)[a]
3k	3170, 1728, 1658	1.24 (3H, t, 7.1), 1.60 (3H, d, 7.2), 4.08 (1H, q, 7.2), 4.22 (2H, q, 7.1), 7.02 (1H, dd, 1.3, 8.3), 7.06-7.24 (2H, m), 7.41 (1H, d, 7.3), 8.03 (1H, bs)[a], 13.80 (1H, bs)[a]
3l	3200, 1755, 1670	1.23 (3H, t, 7.1), 2.72-2.94 (2H, m), 4.06 (1H, t, 7.5), 4.21 (2H, q, 7.1), 5.07 (1H, d, 10.2), 5.18 (1H, d, 17.1), 5.77-5.91 (1H, m), 7.00 (1H, d, 7.7), 7.08 (1H, t, 7.6), 7.19 (1H, t, 7.6), 7.45 (1H, d, 7.7), 8.85 (1H, bs)[a] 13.5 (1H, bs)[a]
4a	3080-3180, 1708, 1610	4.74 (2H, s), 6.84 (1H, d, 7.8), 7.02 (1H, t, 7.8), 7.22-7.40 (6H, m), 7.82 (1H, bs)[a], 8.09 (1H, d, 7.8)
4b	3080-3180, 1707, 1614	1.29 (3H, t, 7.4), 3.39 (2H, q, 7.4), 6.83 (1H, d, 7.8), 7.03 (1H, t, 7.7), 7.23 (1H, t, 7.6), 7.90 (1H, bs)[a], 8.11 (1H, d, 7.8)
4c	3000-3200, 1703, 1618	2.94 (3H, s), 6.84 (1H, d, 7.7), 6.93 (1H, t, 7.6), 7.24 (1H, m), 8.08 (1H, d, 7.8), 8.22 (1H, bs)[a]
4d	3080-3200, 1742, 1723, 1710, 1700, 1670	1.28 (3H, t, 7.1), 4.21 (2H, q, 7.1), 4.48 (2H, s), 6.83 (1H, d, 7.8), 7.04 (1H, t, 7.7), 7.26 (1H, t, 7.7), 7.96 (1H, bs)[a], 8.08 (1H, d, 7.8)
4e	3180, 1690, 1610	2.16 (3H, s), 4.42 (2H, s), 6.84 (1H, d, 7.8), 7.05 (1H, t, 7.7), 7.27 (1H, t, 7.6), 8.05 (1H, bs)[a], 8.13 (1H, d, 7.8)
4f	3080-3180, 1705, 1618	4.88 (2H, s), 6.84 (1H, d, 7.7), 6.94 (1H, m), 7.02 (1H, t, 7.3), 7.06 (1H, m), 7.18 (1H, dd, 0.9, 5.1), 7.26 (1H, t, 7.0), 7.92 (1H, bs)[a], 8.07 (1H, d, 7.8)
4g	3080-3180, 1739, 1710, 1617	1.25 (3H, t, 7.1), 2.71 (2H, t, 7.5), 3.69 (2H, t, 7.5), 4.15 (2H, q, 7.1), 6.82 (1H, d, 7.8), 7.03 (1H, t, 7.7), 7.24 (1H, t, 7.7), 7.73 (1H, bs)[a], 8.08 (1H, d, 7.8)
4h	3200, 1705, 1712sh, 1610	3.47 (3H, s), 5.05 (2H, s), 6.87 (1H, d, 7.8), 7.09 (1H, dt, 1.1, 7.7), 7.31 (1H, dd, 1.2, 7.7), 8.12 (1H, bs)[a], 8.20 (1H, d, 7.8)
4k	3150, 1724, 1695	1.23 (3H, t, 7.1), 1.49 (3H, d, 6.9), 4.10-4.28 (2H, m), 5.93 (1H, q, 6.9), 6.96 (1H, d, 7.8), 7.05 (1H, t, 7.7), 7.27 (1H, t, 7.7), 8.11 (1H, d, 7.8), 8.30 (1H, bs)[a]
4l	3080-3180, 1743, 1695	1.23 (3H, t, 7.1), 2.65 (1H, m), 2.91 (1H, m), 4.10-4.28 (2H, m), 4.99 (1H, d, 10.2), 5.13 (1H, dq, 1.5, 17.1), 5.68-5.82 (1H, m), 6.03 (1H, dd, 5.3, 9.7), 6.85 (1H, d, 7.7), 7.05 (1H, dt, 1.0, 7.8), 7.27 (1H, dt, 1.2, 7.8), 8.02 (1H, bs)[a], 8.12 (1H, d, 7.7)

5	3200-3400, 1730, 1621	2.42 (3H, s), 4.76 (1H, s), 6.86 (1H, s), 6.93 (1H, d, 7.7), 7.05 (1H, t, 7.5), 7.24 (2H, m), 8.56 (1H, bs)[a]
6	1778, 1745	1.45 (6H, m), 2.56 (3H, s), 4.41 (2H, q, 7.1), 4.50 (2H, q, 7.1), 7.20 (1H, s), 7.37 (2H, m), 7.88 (1H, m), 8.15 (1H, m)
7a	2224, 1773, 1745, 1632	1.43 (3H, t, 7.2), 1.46 (3H, t, 7.2), 4.40 (2H, q, 7.2), 4.49 (2H, q, 7.2), 7.34 (5H, m), 7.56 (2H, m), 7.69 (1H, dd, 2.0, 6.5), 8.08 (1H, dd, 1.6, 7.4)
7b	2240, 1780, 1750, 1624	2.12 (3H, s), 1.42 (3H, t, 7.1), 1.44 (3H, t, 7.1), 4.38 (2H, q, 7.1), 4.46 (2H, q, 7.1), 7.30 (2H, m), 7.60 (1H, dd, 1.9, 7.1), 8.04 (1H, dd, 1.5, 7.5)
7c	2120, 1782, 1736	1.42 (6H, q, 7.1), 3.33 (1H, s), 4.38 (2H, q, 7.1), 4.47 (2H, q, 7.1), 7.32 (2H, m), 7.61 (1H, d, 7.7), 8.05 (1H, d, 8.0)
7d	2220, 1780, 1755, 1707	1.36 (3H, t, 7.1), 1.44 (3H, t, 7.1), 1.46 (3H, t, 7.1), 4.31 (2H, q, 7.1), 4.41 (2H, q, 7.1), 4.50 (2H, q, 7.1), 7.36 (2H, m), 7.65 (1H, dd, 1.9, 7.0), 8.06 (1H, dd, 1.4, 7.5)
7e	2170, 1779, 1739, 1618	1.43 (6H, m), 2.49 (3H, s), 4.39 (2H, q, 7.1), 4.47 (2H, q, 7.1), 7.31 (2H, m), 7.62 (1H, m), 8.04 (1H, m)
7f	1785, 1743, 1628	1.43 (3H, t, 7.1), 1.46 (3H, t, 7.1), 4.40 (2H, q, 7.1), 4.49 (2H, q, 7.1), 7.01 (1H, dd, 3.7, 5.1), 7.28-7.40 (4H, m), 7.67 (1H, dd, 1.9, 7.0), 8.08 (1H, bd, 7.5)
8	1952, 1770, 1743, 1720	1.29 (3H, t, 7.1), 1.41 (3H, t, 7.1), 1.45 (3H, t, 7.1), 4.24 (2H, q, 7.1), 4.37 (2H, q, 7.1), 4.47 (2H, q, 7.1), 6.06 (1H, d, 6.5), 6.73 (1H, d, 6.5), 7.26-7.37 (2H, m), 7.69 (1H, d, 7.8), 8.08 (1H, d, 8.2)
9k	1740, 1737, 1612	1.23 (3H, t, 7.1), 1.47 (3H, t, 7.1), 1.50 (3H, d, 6.8), 4.18 (4H, m), 4.50 (2H, q, 7.1), 5.87 (1H, q, 6.8), 7.22 (1H, dt, 1.1, 7.8), 7.41 (1H, dt, 1.3, 8.0), 7.97 (1H, bd, 8.2), 8.30 (1H, dd, 1.3, 8.0)
9l	1750, 1735, 1613	1.23 (3H, t, 7.1), 1.47 (3H, t, 7.1), 2.65 (1H, m), 2.91 (1H, m), 4.08-4.24 (2H, m), 4.51 (2H, q, 7.1), 4.95 (1H, d, 10.2), 5.13 (1H, dq, 1.5, 17.0), 5.75 (1H, m), 5.98 (1H, dd, 5.4, 9.5), 7.22 (1H, bt, 7.8), 7.41 (1H, dt, 1.3, 7.8), 7.30 (1H, d, 8.0), 8.30 (1H, d, 7.8)
10k	1948, 1752, 1724, 1706	1.24 (3H, t, 7.1), 1.46 (3H, t, 7.1), 2.13 (3H, s), 4.22 (2H, q, 7.1), 4.48 (2H, q, 7.1), 7.23 (1H, t, 7.9), 7.41 (2H, m), 7.95 (1H, d, 7.9)
11	1759, 1730,1701	0.82 (6H, t, 7.2), 1.32 (6H, t, 7.1), 2.23 (6H, s), 3.12 (2H, m), 3.76 (2H, m), 4.32 (4H, q, 7.1), 7.07 (2H, dt, 1.1, 7.6), 7.25 (2H, dt, 1.5, 8.0), 7.32 (2H, dd, 1.3, 7.6), 7.73 (2H, d, 7.7)
12	1785, 1750, 1738, 1724	0.80 (3H, t, 7.0), 1.00 (3H, t, 7.2), 1.45 (3H, t, 7.0), 1.96 (3H, s), 2.02 (3H, s), 3.70 (2H, m), 3.98 (2H, m), 4.49 (4H, m),

		6.93-7.12 (3H, m), 7.20-7.33 (2H, m), 7.41 (1H, dt, 1.3, 8.4), 7.91 (1H, d, 8.4), 7.99 (1H, d, 8.4)
13	3080-3160, 1961, 1720, 1703	1.24 (3H, t, 7.1), 3.26 (2H, d, 6.6), 4.22 (2H, q, 7.1), 5.08 (1H, dd, 1.0, 10.0), 5.21 (1H, dd, 1.4, 17.0), 5.86 (1H, m), 6.88 (1H, d, 7.8), 7.02 (1H, t, 7.5), 7.26 (2H, m), 8.03 (1H, bs)[a]
14	1747, 1731	1.48 (3H, t, 7.1), 4.51 (2H, q, 7.1), 4.73 (2H, s), 7.18 (1H, m), 7.26-7.40 (6H, m), 7.94 (1H, d, 8.2), 8.25 (1H, d, 7.2)
15	1792, 1758, 1730, 1708	1.45 (6H, m), 4.38 (4H, m), 4.93 (1H, s), 6.90-7.50 (16H, m), 7.72 (2H, d, 6.9), 8.23 (1H, s)
16a	1779, 1744, 1642	1.36 (3H, t, 7.2), 1.44 (3H, t, 7.2), 4.29 (2H, q, 7.2), 4.47 (2H, q, 7.2), 6.43 (1H, d, 12.0), 6.82 (1H, d, 12.0), 6.90 (1H, d, 7.8), 7.00 (1H, t, 7.8), 7.10-7.30 (6H, m), 8.06 (1H, d, 8.4)
16b	1780, 1745, 1622	1.39 (3H, t, 7.1), 1.44 (3H, t, 7.1), 1.73 (3H, dd, 1.7, 6.9), 4.34 (2H, q, 7.1), 4.47 (2H, q, 7.1), 5.97 (1H, dq, 6.9, 11.2), 6.20 (1H, dq, 1.7, 11.2), 7.28 (2H, m), 7.31 (1H, dd, 1.5, 7.5), 8.08 (1H, d, 7.9)
16d	1770, 1742, 1727, 1644	1.08 (3H, t, 7.1), 1.39 (3H, t, 7.1), 1.44 (3H, t, 7.1), 4.10 (2H, q, 7.1), 4.34 (2H, q, 7.1), 4.47 (2H, q, 7.1), 6.13 (1H, d, 12.1), 6.85 (1H, d, 12.1), 7.32 (3H, m), 8.07 (1H, d, 8.2)
16e	1780, 1745, 1634	1.40 (3H, t, 7.1), 1.44 (3H, t, 7.1), 2.33 (3H, s), 6.35 (1H, d, 10.5), 6.37 (1H, d, 10.5), 7.28 (2H, m), 7.53 (1H, d, 7.9), 8.08 (1H, d, 7.9)
16f	1779, 1744, 1645	1.35 (3H, t, 7.1), 1.45 (3H, t, 7.1), 4.30 (2H, q, 7.1), 4.48 (2H, q, 7.1), 6.28 (1H, d, 11.6), 6.82 (1H, m), 6.92 (1H, m), 6.96 (1H, d, 11.6), 7.09-7.32 (4H, m), 8.10 (1H, d, 8.3)

[a] Exchange with D_2O.

Table 4. Details of crystallographic data, data collection and structure determination and refinement

Compound	**11**	**12**	**15**
System	Monoclinic	Monoclinic	Triclinic
space group	$P2_1/n$	$P2_1/n$	$P\bar{1}$
a (Å)	13.266 (2)	10.069 (1)	10.753 (1)
b (Å)	18.797 (2)	23.448 (2)	11.962 (1)
c (Å)	13.362 (2)	13.862 (2)	13.885 (2)
α, deg			79.96 (1)
β, deg	104.93 (1)	100.71 (1)	88.96 (1)
γ, deg			63.66 (1)
V ($Å^3$)	3219.5 (8)	3215.8 (6)	1572.3 (2)
Z	4	4	2
D_c ($g\,cm^{-3}$)	1.301	1.303	1.341
μ (mm^{-1})	0.096	0.097	0.085
ϑ limits, deg	1.5,23	2,23	2,25
No. independent reflections	4417	4445	5760
No. observed reflections [I>2σ(I)]	2900	2875	4016
Full matrix refinement on	I	I	F
R obs	0.045	0.057	0.048
wR obs	0.103	0.135	0.048
maximum residue in Δ map, $eÅ^{-3}$	0.222	0.371	0.231

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