Regiospecific Synthesis of Dihydropyrroles

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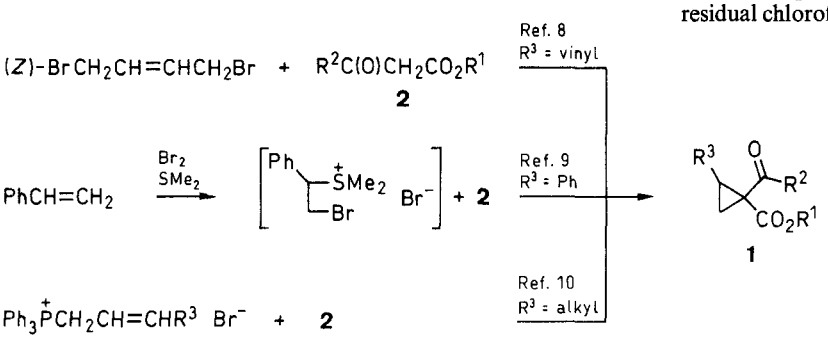
Received 1 August 1991; revised 30 December 1991

A regiospecific synthesis of substituted dihydropyrroles is reported via nucleophilic homoallylic addition of activated cyclopropanes, followed by intramolecular β-enamino ester formation.

We have recently shown that the venom of the ant *Monomorium minutum* is composed of 2,5-dialkylpyrrolines and 2,5-dialkylpyrrolidines: alkaloids which present some insecticidal properties.[1,2] In our continuing study towards the synthesis of such five membered ring heterocycles, we demonstrated that the reaction of 2-acylcyclopropanecarboxylic esters **1** (R^1, R^2 = alkyl, R^3 = H) with primary amines followed by ring closure afforded 4,5-dihydropyrrole-3-carboxylates **4** (R^3 = H) which constitutes a valuable dihydropyrrole synthesis in comparison with those described in the literature.[4-11] For a more detailed investigation of ring-cleavage reactions of activated cyclopropanes (with R^1 = H) and subsequent transformations, we have prepared vinyl, phenyl, and alkyl cyclopropyl oxo esters **1**.



Vinyl cyclopropanes **1** (R^3 = vinyl) were prepared by a α,α'-bisalkylation of methyl acetoacetate or ethyl benzoylacetate with 1,4-dibromo-2-butene.[12] Phenyl derivatives **1** (R^3 = Ph) were prepared by condensation of methyl acetoacetate or ethyl benzoylacetate with 1-phenylvinylsulfonium salts.[13] We have previously reported the formation of alkyl cyclopropanes **1** (R^3 = alkyl) by reaction of β-oxo esters **2** with 2-alkenylphosphonium salts.[14]

Here we present a convenient regiospecific reaction of primary alkyl or aryl amines with highly activated cyclopropanes **1** to give only 1,2,5-trisubstituted 4,5-dihydro-3-pyrrolecarboxylates **4**. We did not observe the formation of either isomeric dihydropyrroles **3** or lactams.[5]

Cyclopropanes **1** and primary amines having a boiling point above 140 °C were directly heated at 140 °C (Method A) without solvent, or were heated in a sealed tube containing a methanolic solution of compounds **1** and amines (Method B). The average reaction time was dependent on the nucleophilic character of the amines. All amines attacked so as to give ring opening at the less hindered carbon of the cyclopropanes **1**. This was followed by intramolecular condensation of the intermediate secondary amine with the ketone function. In cyclopropanes **1a–j** no reaction occurred on the double bond (Table 1).

All dihydropyrroles reported here (and twenty others prepared by the same methods) have been tested against termites *Reticulitermes (lucifugus) grassei*. The most active molecules are the dihydropyrroles **4d, 4e,** and **4j**; especially the last which shows an LD_{50} = 0.51 μg/mg of termite, which is nevertheless less active than natural 2-(5-hexenyl)-5-(8-nonenyl)pyrrolidine.[2]

In conclusion, the reaction of 2-acylcyclopropanecarboxylic esters with primary amines is a versatile new access to dihydropyrrole compounds.

Melting points were determined in open capillaries with a Büchi apparatus and are uncorrected. IR spectra were recorded with a Philips Model PU 9700 spectrometer. ^{1}H NMR spectra were measured with a Bruker WP 80 (80 MHz) spectrometer. ^{1}H chemical shifts are reported in ppm from an internal standard Me_4Si, or of residual chloroform (7.27 ppm). Analytical TLC was performed on Merck precoated silica gel 60 F plates. Merck silica gel 60 (230–400 mesh) was used for column chromatography. Cyclopropanes **1** were used as *E*/*Z* mixtures formed by the syntheses described below.

1-Acyl-2-vinylcyclopropanecarboxylates 1a,b; General Procedure:
To a stirred mixture of K_2CO_3 (72 g, 0.52 mol) and 3-oxoalkanoate (0.2 mol) in methanol (300 mL) was added 1,4-dibromo-2-butene (49 g, 0.23 mol). The mixture was stirred for 96 h, filtered, concentrated to eliminate the methanol and poured in H_2O (200 mL). The aqueous solution was extracted with Et_2O (4 × 50 mL), and the ether layer was dried (Na_2SO_4), evaporated and distilled.

Methyl 1-Acetyl-2-vinylcyclopropanecarboxylate **(1a)** *(E,Z Mixture):*

Yield 75%; bp 63 °C (1 Torr) [Lit[12] bp 40 °C (0.1 Torr)].

IR (neat): ν = 1640, 1710, 1740 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ = 1.40–2.00 (m, 2H), 2.26 (s, 2.1H), 2.33 (s, 0.9H), 2.20–2.80 (m, 1H), 3.70 (s, 3H), 4.90–5.50 (m, 3H).

Ethyl 1-Benzoyl-2-vinylcyclopropanecarboxylate **(19)** *E/Z Mixture):*

Yield 60%; bp 125–130 °C (0.1 Torr).

$C_{15}H_{16}O_3$	calc.	C 73.75	H 6.60
(244.3)	found	74.04	H 6.89

IR (neat): ν = 1580, 1600, 1680, 1730 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ = 0.82 (t, 2.01H, *J* = 8 Hz), 0.85 (t, 0.99H, *J* = 8 Hz), 1.30–2.00 (m, 2H), 2.40–3.00 (m, 1H), 3.93 (q, 1.34H, *J* = 7.5 Hz), 3.96 (q, 0.66H, *J* = 7.5 Hz), 4.80–6.10 (m, 3H), 7.15–8.10 (m, 5H).

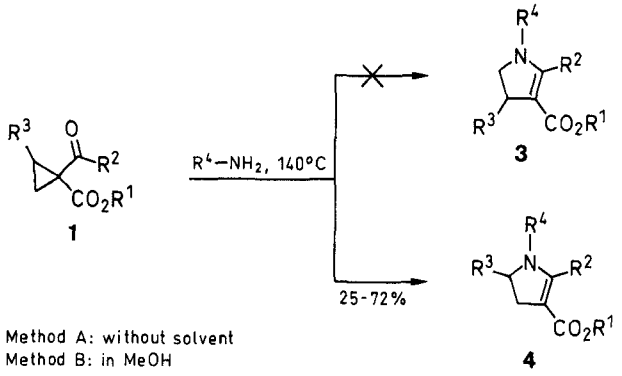
Table 1. 1,2,5-Trisubstituted 4,5-Dihydro-3-pyrrolecarboxylates **4** Prepared

Product	Method	Reaction Time (h)	Yield (%)	bp (°C)/Torr and/ or mp (°C)/Solvent or R_f/Et_2O : pentane	Molecular Formula[a] or Lit. mp (°C)	IR (neat) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, (ppm), J (Hz)
4a	A	8	60	145/0.01 51/isooctane	$C_{16}H_{19}NO_2$ (257.3)	1530, 1570, 1640[b]	2.32 (s, 3H, 2-CH_3), 2.30–3.30 (m, 2H, 4-H), 3.70 (s, 3H, $COOCH_3$), 3.70–4.10 (m, 1H, 5-H), 4.32 (dd, 2H, J = 10.5 and 3.5, Ph–CH_2), 5.00–6.10 (m, 3H, $CH=CH_2$), 7.00–7.40 (m, 5H, Ph)
4b	B	8	50	95/0.01	$C_{10}H_{15}NO_2$ (181.2)	1580, 1650[b]	2.25 (s, 3H, 2-CH_3), 2.30–3.30 (m, 2H, 4-H), 2.70 (s, 3H, N–CH_3), 3.70 (s, 3H, $COOCH_3$), 3.70–4.10 (m, 1H, 5-H), 5.00–6.10 (m, 3H, $CH=CH_2$)
4c	B	8	45	98/0.01	$C_{12}H_{17}NO_2$ (207.3)	1530, 1580, 1650[b]	0.55–0.80 (m, 4H, c-propyl), 2.10–3.20 (m, 3H, 1-CH + 4-H), 2.95 (s, 3H, 2-CH_3), 3.60 (s, 3H, CO_2CH_3), 3.60–4.10 (m, 1H, 5-H), 4.90–6.10 (m, 3H, $CH=CH_2$)
4d	A	20	58	135/0.01 51–55/isooctane	$C_{15}H_{17}NO_2$ (243.3)	1480, 1530, 1570, 1650[b]	2.15 (s, 3H, 2-CH_3), 2.30–3.40 (m, 2H, 4-H), 3.70 (s, 3H, CO_2CH_3), 4.25–4.70 (m, 1H, 5-H), 4.80–6.20 (m, 3H, $CH=CH_2$), 6.90–7.60 (m, 5H, Ph)
4e	A	20	41	150/0.01	$C_{15}H_{16}NO_2F$ (261.3)	1490, 1530, 1580, 1650[b]	2.10 (s, 3H, 2-CH_3), 2.30–3.30 (m, 2H, 4-H), 3.70 (s, 3H, CO_2CH_3), 4.10–4.60 (m, 1H, 5-H), 4.80–6.10 (m, 3H, $CH=CH_2$), 7.00 (d, 4H, J = 7, pF–Ar)
4f	A	8	72	68 (hexane)	$C_{22}H_{23}NO_2$ (333.4)	1480, 1570, 1600, 1650[b]	1.00 (t, 3H, J = 7, CH_2CH_3), 2.30–3.30 (m, 2H, 4-H), CH_2CH_3, 3.60–4.30 (m, 3H, $ArCH_2$ + 5-H), 3.90 (q, 2H, J = 7, CH_2CH_3), 4.80–6.10 (m, 3H, $CH=CH_2$), 6.90–7.30 (m, 5H, CH_2–Ar), 6.90–7.30 (m, 5H, CH_2–Ar), 7.00–7.20 (m, 5H, Ar)
4g	B	8	70	140/0.01	$C_{16}H_{19}NO_2$ (257.3)	1480, 1570, 1600, 1650[b]	0.90 (t, 3H, J = 7, CH_2CH_3), 2.35 (s, 3H, NCH_3), 2.50–3.30 (m, 2H, 4-H), 3.90 (q, 2H, J = 7, CH_2CH_3), 3.80–4.10 (m, 1H, 5-H), 5.00–6.10 (m, 3H, $CH=CH_2$), 7.15–7.30 (m, 5H, Ar)
4h	B	8	57	155/0.01	$C_{18}H_{21}NO_2$ (283.4)	1490, 1570, 1600, 1650[b]	0.16–0.35 (m, 4H, c-propyl), 0.90 (t, 3H, J = 7, CH_2CH_3), 2.10 (m, 1H, N–CH), 2.30–3.30 (m, 2H, 4-H), 3.80 (q, 2H, J = 7, CH_2CH_3), 3.80–4.30 (m, 1H, 5-H), 5.00–6.30 (m, 3H, $CH=CH_2$), 7.17–7.35 (m, 5H, Ar)
4i	A	20	60	160/0.01	$C_{21}H_{21}NO_2$ (199.3)	1500, 1580, 1600, 1620, 1670[b]	1.10 (t, 3H, J = 7, CH_2CH_3), 2.50–3.60 (m, 2H, 4-H), 3.90 (q, 2H, J = 7, CH_2CH_3), 4.30–4.70 (m, 1H, 5-H), 6.00–6.30 (m, 3H, $CH=CH_2$), 6.50–7.30 (m, 10H, Ar)
4j	A	20	44	175/0.01	$C_{21}H_{20}NO_2F$ (338.4)	1490, 1500, 1565, 1575, 1600, 1650[b]	1.10 (t, 3H, J = 7, CH_2CH_3), 2.50–3.50 (m, 2H, 4-H), 3.90 (q, 2H, J = 7, CH_2CH_3), 4.20–4.70 (m, 1H, 5-H), 4.90–6.30 (m, 3H, $CH=CH_2$), 6.70 (d, 4H, J = 6, pF–Ar), 7.20 (bs, 5H, Ar)
4k	B	8	69	145/0.09	$C_{14}H_{17}NO_2$ (231.3)	1490, 1580, 1650[b]	2.25 (s, 3H, 2-CH_3), 2.60 (s, 3H, NCH_3), 2.50–3.30 (m, 2H, 4-H), 3.60 (s, 3H, CO_2CH_3), 4.30 (t, 1H, J = 11, 5-H), 7.25 (bs, 5H, Ar)
4l	B	8	72	230/0.01	$C_{20}H_{21}NO_2$ (307.4)	1480, 1570, 1650[b]	0.90 (t, 3H, J = 7, CH_2CH_3), 2.35 (s, 3H, NCH_3), 2.70–3.60 (m, 2H, 4-H), 3.90 (q, 2H, J = 7, CH_2CH_3), 4.20–4.50 (m, 1H, 5-H), 7.10–7.50 (m, 10H, Ar)
4m	B	24	58	95/0.05	$C_{10}H_{17}NO_2$ (183.2)	1580, 1660	0.90 (t, 3H, J = 6, CH_2CH_3), 1.10–1.90 (m, 2H, CH_2CH_3), 2.15 (s, 3H, 2-CH_3), 2.00–2.60 (m, 2H, 4-H), 2.70 (s, 3H, NCH_3), 2.90–3.40 (m, 1H, 5-H), 3.55 (s, 3H, CO_2CH_3)
4n	B	16	35	140/0.01	$C_{15}H_{27}NO_2$ (253.4)	1570, 1650	0.90 (t, 3H, J = 7.5, $(CH_2)_6CH_3$), 1.00–1.90 (m, 12H, $(CH_2)_6$), 2.10 (s, 3H, 2-CH_3), 2.15–3.30 (m, 3H, 4-H + 5-H), 2.70 (s, 3H, NCH_3), 3.55 (s, 3H, CO_2CH_3)
4o	B	20	45	115/0.05	$C_{15}H_{27}NO_2$ (253.4)	1570, 1650	1.10–1.80 (m, 4H, $CH(CH_2)_2$), 1.80–2.20 (m, 2H, 4-H), 2.15 (s, 3H, 2-CH_3), 2.20–3.00 (m, 2H, $CH_2CH=CH_2$), 2.70 (s, 3H, NCH_3), 3.00–3.50 (m, 1H, 5-H), 3.50 (s, 3H, CO_2CH_3), 4.70–5.20 (m, 2H, $CH=CH_2$), 5.30–6.10 (m, 1H, $CH=CH_2$)
4p	B	24	50	220/0.05[a]	$C_{19}H_{33}NO_2$ (307.5)	1570, 1650	1.10–1.70 (m, 16H, $CH(CH_2)_8$), 1.70–2.20 (m, 2H, $CH_2CH=CH_2$), 2.10 (s, 3H, 2-CH_3), 2.20–3.50 (m, 3H, 4-H + 5-H), 2.70 (s, 3H, NCH_3), 3.55 (s, 3H, CO_2CH_3), 4.70–5.20 (m, 2H, $CH=CH_2$), 5.30–6.10 (m, 1H, $CH=CH_2$)

Table 1 (continued)

Product	Method	Reaction Time (h)	Yield (%)	bp (°C)/Torr and/ or mp (°C)/Solvent or R_f/Et_2O : pentane	Molecular Formula[a] or Lit. mp (°C)	IR (neat) ν (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, (ppm), J (Hz)
4q	B	15	25	0.30 (50 : 50)	$C_{14}H_{23}NO_2$ (237.3)	1570, 1650	1.50–2.20 (m, 4H, $(CH_2)_2$), 1.55 (s, 3H, $=CCH_3$), 1.65 (s, 3H, $=CCH_3$), 2.5 (s, 3H, 2-CH_3), 2.15–2.70 (m, 2H, 4-H), 2.70 (s, 3H, NCH_3), 2.70–3.50 (m, 1H, 5-H), 3.55 (s, 3H, CO_2CH_3), 4.80–5.10 (m, 1H, $=CH$)
4r	B	20	45	0.30 (40 : 60)	$C_{18}H_{31}NO_2$ (293.4)	1570, 1660	0.90 (d, 3H, $J = 6$, CH_3CH), 1.00–2.00 (m, 9H, $=(CH_2)_2CH(CH_2)_2$), 1.55 (s, 3H, $=CH_3$), 1.70 (s, 3H, $=CH_3$), 2.10 (s, 3H, 2-CH_3), 2.10–3.30 (m, 3H, 4-H + 5-H), 2.70 (s, 3H, NCH_3), 3.50 (s, 3H, CO_2CH_3), 4.80–5.20 (m, 1H, $=CH$)
4s	B	15	40	0.25 (50 : 50)	$C_{18}H_{25}NO_2$ (287.4)	1570, 1640	1.00–1.80 (m, 8H, $(CH_2)_4$), 2.10 (s, 3H, 2-CH_3), 2.20–2.85 (m, 3H, 4-H + 5-H), 3.55 (s, 3H, CO_1CH_3), 7.00–7.25 (m, 5H, Ar)

[a] Satisfactory microanalyses obtained: C ±0.32, N ±0.29, H ±0.34.
[b] Solution in $CHBr_3$.



Method A: without solvent
Method B: in MeOH

26.9 g of bromostyryldimethylsulfonium bromide (yield 80%); mp 151 °C [Lit.[9] mp 145–158 °C]. To a stirred solution of bromostyryldimethylsulfonium bromide (7 g, 0.021 mol) and 3-oxoalkanoate (0.021 mol), at 60 °C, was added a K_2CO_3 (10%) solution (100 mL). After 30 min, the mixture was decanted. The organic layer was dried (Na_2SO_4), evaporated and distilled.

Methyl 1-Acetyl-2-phenylcyclopropanecarboxylate (**1c**):

Yield: 80%; bp 98 °C (0.01 Torr).

$C_{13}H_{14}O_3$	calc.	C 71.54	H 6.47
(212.8)	found	71.36	6.53

IR (neat): ν = 1690, 1730 cm^{-1}.

^1H NMR ($CDCl_3$/TMS): δ = 1.50–1.90 (m, 1H), 1.90 (s, 2.1H), 2.00–2.30 (m, 1H), 2.40 (s, 0.9H), 3.25 (t, 1H, J = 8H), 3.30 (s, 2.1H), 3.75 (s, 0.9H), 7.00–7.35 (m, 5H).

1	R^1	R^2	R^3
a	Me	Me	$CH=CH_2$
b	Et	Ph	$CH=CH_2$
c	Me	Me	Ph
d	Et	Et	Ph
e	Me	Me	Et
f	Me	Me	n-C_7H_{15}
g	Me	Me	$(CH_2)_3CH=CH_2$
h	Me	Me	$(CH_2)_9CH=CH_2$
i	Me	Me	$(CH_2)_2CH=CMe_2$
j	Me	Me	$(CH_2)_2CH(Me)(CH_2)_2CH=CMe_2$
k	Me	Me	$(CH_2)_4Ph$

4	R^1	R^2	R^3	R^4
a	Me	Me	$CH=CH_2$	Bn
b	Me	Me	$CH=CH_2$	Me
c	Me	Me	$CH=CH_2$	c-C_3H_5
d	Me	Me	$CH=CH_2$	Ph
e	Me	Me	$CH=CH_2$	p-C_6H_4F
f	Et	Ph	$CH=CH_2$	Bn
g	Et	Ph	$CH=CH_2$	Me
h	Et	Ph	$CH=CH_2$	c-C_3H_5
i	Et	Ph	$CH=CH_2$	Ph
j	Et	Ph	$CH=CH_2$	p-C_6H_4F
k	Me	Me	Ph	Me
l	Et	Ph	Ph	Me
m	Me	Me	Et	Me
n	Me	Me	n-C_7H_{15}	Me
o	Me	Me	$(CH_2)_3CH=CH_2$	Me
p	Me	Me	$(CH_2)_9CH=CH_2$	Me
q	Me	Me	$(CH_2)CH=CMe_2$	Me
r	Me	Me	$(CH_2)CH(Me)(CH_2)_2CH=CMe_2$	Me
s	Me	Me	$(CH_2)_4Ph$	Me

1-Acyl-2-phenylcyclopropanecarboxylates 1c,d; General Procedure: To a stirred solution of styrene (10.4, 0.1 mol) and dimethyl sulfide (31 g, 0.5 mol) in CH_2Cl_2 (100 mL) was added bromine (16 g, 0.1 mol) in CH_2Cl_2 (20 mL). The reaction mixture became discoloured and a white solid was formed. The crystals were filtered off, washed with CH_2Cl_2 (20 mL) then dried under vacuum to obtain

Ethyl 1-benzoyl-2-phenylcyclopropanecarboxylate (**1d**):

Yield 45%, bp 160 °C (0.05 Torr).

$C_{19}H_{18}O_3$	calc.	C 77.53	H 6.16
(294.3)	found	77.76	6.22

IR (neat): ν = 1580, 1600, 1680, 1730 cm^{-1}.

^{1}H NMR (CCl_4/TMS): δ = 0.55 (t, 1.3 H, J = 7 Hz), 0.90 (t, 1.7 H, J = 7 H), 1.20–1.35 (m, 1 H), 1.90–2.40 (m, 1 H), 3.40 (q, 1.3 H, J = 7 H), 3.50 (q, 0.7 H, J = 7 H), 3.80–4.20 (m, 1 H), 6.90–8.00 (m, 10 H).

Methyl 1-Acyl-2-alkylcyclopropanecarboxylates **1e–k**: These were prepared according to the literature.[13]

1,2,5-Trisubstituted 4,5-Dihydro-3-pyrrolecarboxylates 4; General Procedure:

Method A: (With high boiling point primary amines (bp ≥ 140 °C). The primary amine (0.03 mol) and cyclopropyl oxo ester (0.03 mol) were heated, under nitrogen, for 8–20 h. After cooling, ether (60 mL) was added, the mixture was dried (Na_2SO_4), and the solvent was evaporated. The crude product was distilled or recrystallized.

Method B: The primary amine (0.03 mol) and cyclopropyl oxo ester (0.03 mol) in methanol (60 mL) were heated in a sealed tube for 8–24 h. The solvent was removed and the crude product was distilled or purified by flash chromatography with Et_2O/pentane 50:50 as the eluent.

The authors wish to thank E. I. Dupont de Nemours Company for their financial support.

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