Synthesis of 1-Acyl-2-alkylcyclopropanecarboxylic Esters from 2-Alkenylphosphonium Salts

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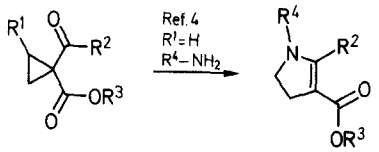
The one-pot reaction of allyltriphenylphosphonium bromide with the sodium salts of β-keto esters leads to the formation of alkyl 1-acyl-2-alkylcyclopropanecarboxylates.

Nucleophilic ring cleavage of electron-deficient cyclopropanes has found various practical applications in organic synthesis.[1,2,3] We have earlier shown that the reaction of 2-acylcyclopropanecarboxylic esters (R^1 = H, R^2 = alkyl, R^3 = Et) with primary amines followed by ring closure affords 2,3-dihydropyrrole-3-carboxylic esters[4] **2**.

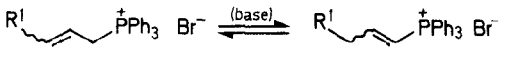


1 **2**

For the detailed investigation of such ring-cleavage reactions of activated cyclopropanes with $R^1 \neq H$ and subsequent transformations we needed substituted cyclopropanecarboxylic esters of the type **1**. Whereas the preparation of cyclopropyl ketones has been reviewed,[5] only few syntheses of highly activated cyclopropanes of the type **1** (R^1 = alkyl; R^2 = alkyl, aryl, or vinyl; R^3 = alkyl) have been reported. The α,α-bis-alkylation of β-keto esters with 1,4-dibromo-2-butene affords mixtures of 1-acyl-3-cyclopentene-1-carboxylic esters and 1-acyl-2-vinylcyclopropanecarboxylic esters;[6] on the other hand, the analogous reaction with 1,2-dibromoalkanes gives only low yields (10%) of 1-acylcyclopropanecarboxylic esters. The carbanions of β-keto esters also react with butadienyl- and 1-phenylvinylsulfonium salts[7,8] to give 2-phenyl- and 2-vinylcyclopropanecarboxylic esters, respectively; however, this type of reaction cannot be extended to alkylsulfonium salts to afford 1-acyl-2-alkylcyclopropanecarboxylic esters **1**.

We now describe the preparation of 2-alkenyltriphenylphosphonium salts **4** which are isomerized *in situ* to 1-alkenylphosphonium salts (vinylphosphonium salts) **3**. Reaction of these salts **3** with β-keto esters **9** leads to *P*-ylide (phosphorane) intermediates, which are better stabilized than the *S*-ylides (sulfuranes) formed from 1-alkenylsulfonium salts, and which cyclize with elimination of triphenylphosphine to give the desired 1-acyl-2-alkylcyclopropanecarboxylic esters **1**. The monoalkylation of β-keto esters[9] with vinylphosphonium salts has been reported.

Two methods for the preparations of vinylphosphonium salts **3** have been reported: thermal elimination of phenol from 2-phenoxyethyl(triphenyl)phosphonium bromide,[10] and the base-catalyzed isomerization of 2-alkenylphosphonium salts (allylphosphonium salts) **4**.[11–14]



4 **3**

Table 1. 2-Alkenols **5** and 1-Alken-3-ols **8** Prepared

Product	Yield (%)	bp (°C)/Torr	Molecular Formula[a] or Lit. bp (°C)/Torr	IR (neat) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
8c	65	74/0.05	90/20[17]	3350	0.90 (d, 3H, J = 4), 1.00–1.80 (m, 10H), 3.60 (s, 1H), 4.00 (m, 1H), 4.80–6.10 (m, 3H)
8d	58	50/30	125/76[18]	3380	0.90 (d, 6H, J = 7), 1.30–2.00 (m, 1H), 2.60 (s, 1H), 3.80 (m, 1H), 4.90–6.10 (m, 3H)
5e	80	75/13	72/10[16]	1630, 3320	2.10 (m, 4H), 3.90 (s, 1H), 4.10 (d, 2H, J = 4), 4.80–6.10 (m, 5H)
5f	72	80/13	$C_7H_{12}O$ (112.2)	1610, 3350	1.60 (m, 3H), 2.80 (m, 2H), 3.90 (s, 1H), 4.10 (d, 2H, J = 5), 5.50 (m, 4H)
8h	77	84/0.01	104/4[19]	1610, 3360	0.90 (d, 3H, J = 6), 1.00–2.20 (m, 13H), 2.80 (s, 1H), 4.06 (s, 1H), 4.70–6.10 (m, 4H)
5i	80	105/0.05	$C_{12}H_{16}O$ (176.2)	1580, 1600, 1640, 3350	1.40–2.30 (m, 4H), 2.30–2.90 (m, 2H), 3.20 (s, 1H), 4.10 (d, 2H, J = 5), 5.50 (m, 2H), 7.10 (m, 5H)

[a] Satisfactory microanalyses obtained: C ±0.16, H ±0.24.

Table 2. 1-Bromo-2-alkenes **6** Prepared

Product	Yield (%)	bp (°C)/Torr	Molecular Formula[a]	IR (neat) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
6e	75	65/15	$C_7H_{11}Br$ (175.1)	1640, 1655	2.10 (m, 4H), 3.90 (d, 2H, J = 7), 4.80–6.00 (m, 5H)
6f	75	75/15	$C_7H_{11}Br$ (175.1)	1640, 1650	1.70 (m, 3H), 2.80 (m, 2H), 3.90 (m, 2H), 5.00–6.00 (m, 4H)
6i	76	105/0.5	$C_{12}H_{15}Br$ (239.1)	1580, 1600, 1645	1.40–2.30 (m, 4H), 2.60 (t, 2H, J = 7), 3.80 (d, 2H, J = 8), 5.60 (m, 2H), 7.10 (m, 5H)

[a] Satisfactory microanalyses obtained: C ±0.34, H ±0.18, Br ±0.39.

Table 3. 2-Alkenyltriphenylphosphonium Bromides **4** Prepared

Product	Yield (%)	mp (°C) (solvent)	Molecular Formula[a] or Lit. mp (°C)	IR (neat) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
4a	85	225 (Et_2O)	225–227[10–14]	1580, 1430, 1120	3.70–4.20 (m, 2H), 5.30–5.60 (m, 3H), 7.40–8.00 (m, 15H)
4b	95	235 (Et_2O)	235–237[22]	1600, 1420, 1130	1.30–1.80 (m, 3H), 3.70–4.20 (m, 2H), 5.35–5.60 (m, 2H), 7.40–8.00 (m, 15H)
4c	75	165 (Et_2O)	174[23]	1580, 1430, 1105	0.50–0.95 (m, 3H), 1.00–1.60 (m, 8H), 1.80–2.15 (m, 2H), 3.70–4.20 (m, 2H), 5.20–5.90 (m, 2H), 7.30–8.10 (m, 15H)
4d	65	195 (Et_2O)	$C_{24}H_{26}PBr$ (425.3)	1570, 1425, 1120	0.80 (d, 6H, J = 7), 2.10–2.45 (m, 1H), 3.70–4.15 (m, 2H), 5.30–5.70 (m, 2H), 7.25–7.95 (m, 15H)
4e	90	140 (Et_2O)	$C_{25}H_{26}PBr$ (437.3)	1585, 1475, 1440, 1120	1.80–2.10 (m, 4H), 3.80–4.30 (m, 2H), 4.70–6.05 (m, 5H), 7.20–7.80 (m, 15H)
4f	80	135 (Et_2O)	$C_{25}H_{26}PBr$ (437.3)	1580, 1480, 1430, 1130	1.30–1.60 (m, 3H), 2.35–2.60 (m, 2H), 3.70–4.20 (m, 2H), 5.20–5.95 (m, 4H), 7.40–8.00 (m, 15H)
4g	75	180 (Et_2O)	$C_{26}H_{28}PBr$ (451.4)	1570, 1420, 1120	1.20–1.50 (m, 6H), 2.25–2.50 (m, 2H), 3.75–4.30 (m, 2H), 5.00–5.90 (m, 3H), 7.40–8.00 (m, 15H)
4h	90	80–95 (pentane)	$C_{30}H_{36}PBr$ (507.5)	1580, 1480, 1430, 1130	0.60–0.95 (m, 3H), 1.00–2.10 (m, 13H), 3.75–4.25 (m, 2H), 5.20–6.00 (m, 3H), 7.40–8.00 (m, 15H)
4i	60	168 (Et_2O)	$C_{30}H_{30}PBr$ (501.4)	1580, 1470, 1425, 1130	1.30–2.00 (m, 4H), 2.30–2.70 (m, 2H), 3.80–4.35 (m, 2H), 5.20–6.10 (m, 2H), 6.80–7.20 (m, 5H), 7.35–7.95 (m, 15H)

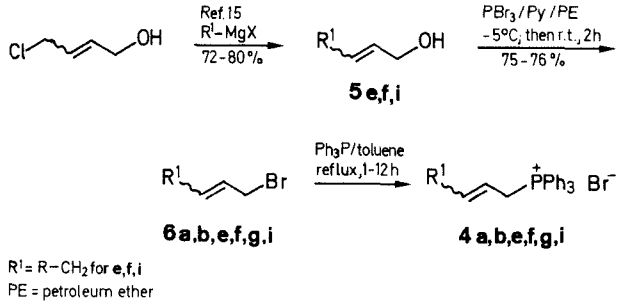
[a] Satisfactory microanalyses obtained: C ±0.32, H ±0.24, Br ±0.35.

The allyl-vinyl equilibrium is shifted completely to the side of derivatives **3** only for R = CH_3;[10-14] in the cases of R = C_2H_5 and higher alkyl, the isomers **3** are at least the major isomers.

We prepared the 2-alkenylphosphonium salts **4** by the nucleophilic substitution of 1-bromo-2-alkenes by triphenylphosphine (Table 3).

The primary allyl alcohols **5** were obtained from 4-chloro-2-butenol[15,16] and excess Grignard reagents (Method A, Table 1); we also developed a shorter sequence for the preparation of phosphonium salts **4** (Method B) via the 1-alkene-3-ols **8c**,[17] **8d**,[18] and **8h**[19] (Table 1).

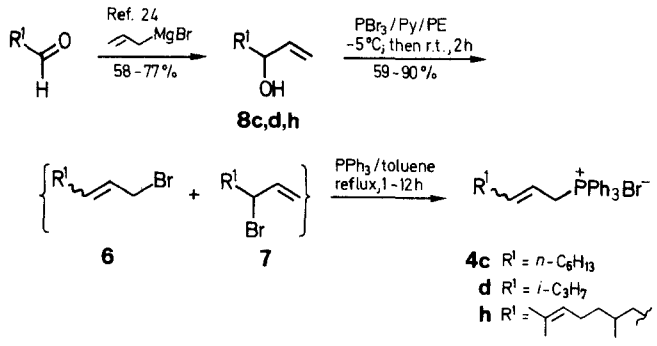
Method A:



4	5	6	R^1
a	–	–[a]	H
b	–	–[a]	CH_3
e	e	e	$CH_2CH_2CH=CH$
f	f	f	$CH_2CH=CHCH_3$
g	–	–[a]	$CH_2CH_2C(CH_3)=CH_2$
i	i	i	$(CH_2)_3Ph$

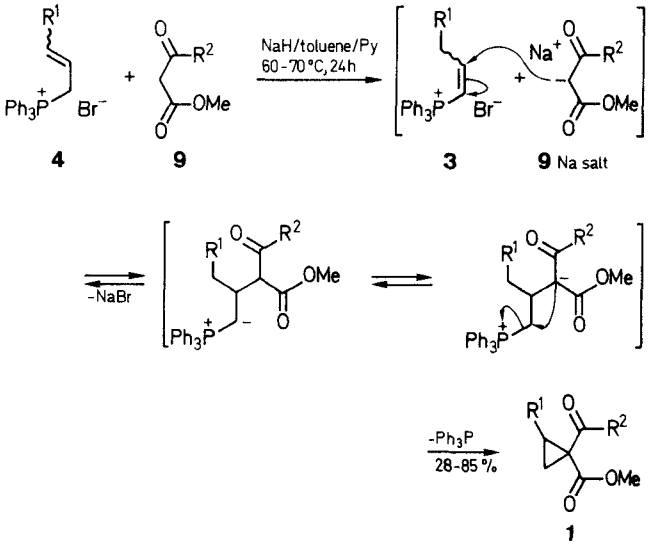
[a] Commercially available allyl halides.

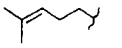
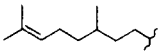
Method B:



Whereas the reaction of the phosphorus tribromide with the primary alcohols **5** affords 1-bromo-2-alkenes **6** with the secondary alcohols **8** gives mixtures of isomers **6** and **7** (Table 2). However, these mixture permits to react regiospecifically with triphenylphosphine by a S_N2^{20} mechanism (**6**) or by a S_N2' mechanism (**7**), respectively, to afford the same salts **4**, due to a steric hindrance as described for the case of 2-bromomethylenecyclohexane (Table 3).

The 2-alkenylphosphonium salts **4** were directly used to prepare the alkyl 1-acyl-2-alkylcyclopropanecarboxylates **1** by condensation with the β-keto ester sodium salts in toluene. (Table 4).



1	R^1	R^2
a	CH_3	CH_3
b	C_2H_5	CH_3
c	n-C_7H_5	CH_3
d	i-C_4H_9	CH_3
e	$(CH_2)_3CH=CH_2$	CH_3
f	$CH_2CH=CHCH_2$	CH_3
g		CH_3
h		CH_3
i	$(CH_2)_4Ph$	CH_3
j	C_2H_5	$CH_2CH_2CO_2Me$
k	$(CH_2)_3CH=CH_2$	n-C_9H_{19}

Under the reaction conditions of the last step of the sequence leading to products **1**, the allyl-vinyl equilibrium **4** ⇄ **3** is shifted to the side of **3** which then reacts with the β-keto ester **9**.

Melting points were determined in open capillaries with a Büchi apparatus and are uncorrected. IR were recorded with a Philips Model PU 9700 spectrophotometer. ^{1}H-NMR spectra were recorded on Varian A60-A, Bruker 80, and Bruker 500 MHz spectrometers.

2-Alkenols 5e,f,i:
These compounds are prepared according to the procedure of Lit.[15]; see Table 1.

1-Alken-3-ols 8c,d,h:
These compounds are prepared from aldehydes and vinylmagnesium bromides according to the procedure of Lit.[24]; see Table 1.

1-Bromo-2-alkenes 6 or Mixtures of 1-Bromo-2-alkenes 6 and 3-Bromo-1-alkenes 7; General Procedure:
To a stirred mixture of the 2-alkenol **5e,f,i** or the 1-alken-3-ol **8c,d,h** (0.85 mol) and pyridine (6 mL) in petroleum ether (250 mL) at − 5 °C is added a solution of PBr_3 (100 g, 0.36 mol) in petroleum ether (70 mL), and stirring is continued for 2 h at room temperature. Then, Et_2O (500 mL) and H_2O (500 mL) are added. The organic layer is separated and washed with sat. Na_2CO_3 solution (2 × 250 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product is distilled (Table 2). When a mixture of **6** and **7** is obtained, this mixture is quickly distilled then used directly in the reaction with triphenylphosphine.

Table 4. Methyl 1-Acyl-2-alkylcyclopropanecarboxylates **1** Prepared

Product	Yield (%)	bp (°C)/Torr	*E*/*Z* Ratio[a]	Molecular Formula[b]	IR (neat) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, *J*(Hz)
1a	65	45/0.5	30 : 70	$C_8H_{12}O_3$ (156.2)	1670, 1710	0.90–1.60 (m, 5H), 1.60–2.10 (m, 1H), 2.30 (s, 3H), 3.70 (*E*) and 3.75 (*Z*) (s, 3H)
1b	80	52/0.05	30 : 70	$C_9H_{14}O_3$ (170.2)	1680, 1710	0.80–1.60 (m, 7H), 1.60–2.00 (m, 1H), 2.28 (*Z*), 2.32 (*E*) (s, 3H), 3.70 (*E*), 3.75 (*Z*) (s, 3H)
1c	58	93/0.5	30 : 70	$C_{14}H_{24}O_3$ (240.3)	1690, 1710	0.90 (t, 3H, *J* = 4), 0.90–1.50 (m, 14H), 1.50–2.10 (m, 1H), 2.29 (*Z*) and 2.30 (*E*) (s, 3H), 3.76 (*E*), 3.75 (*Z*) (s, 3H)
1d	28	70/0.05	40 : 60	$C_{11}H_{18}O_3$ (198.2)	1680, 1710	0.70–2.10 (m, 12H), 2.30 (s, 3H), 3.75 (s, 3h)[c]
1e	85	90/0.05	30 : 70	$C_{12}H_{18}O_3$ (210.3)	1630, 1680, 1710	1.10–1.75 (m, 6H), 1.75–2.20 (m, 3H), 2.22 (*Z*) and 2.26 (*E*) (s, 3H), 3.65 (*E*), 3.70 (*Z*) (s, 3H), 4.80–6.00 (m, 3H)
1f	40	90/0.05	20 : 80	$C_{12}H_{18}O_3$ (210.3)	1630, 1680, 1710	1.10–1.70 (m, 7H), 1.70–2.30 (m, 3H), 2.33 (*Z*), 2.37 (*E*) (s, 3H), 3.75 (*E*), 3.80 (*Z*) (s, 3H), 5.45 (m, 2H)
1g	55	95/0.05	30 : 70	$C_{13}H_{20}O_3$ (224.3)	1640, 1680, 1710	1.10–1.70 (m, 4H), 1.60 (d, 6H, *J* = 5), 1.70–2.20 (m, 3H), 2.30 (*Z*), 2.33 (*E*) (s, 3H), 3.70 (*E*), 3.75 (*Z*) (s, 3H), 5.10 (m, 1H)
1h	52	145/0.05	25 : 75	$C_{17}H_{28}O_3$ (280.4)	1640, 1680, 1710	0.80 (d, 3H, *J* = 5), 1.00–1.70 (m, 9H), 1.60 (d, 6H, *J* = 4), 1.71–2.10 (m, 3H), 2.25 (s, 3H), 3.70 (s, 3H), 5.00 (m, 1H)[c]
1i	61	152/0.05	0 : 100	$C_{17}H_{22}O_3$ (274.3)	1430, 1690, 1720	1.27–1.48 (m, 6H), 1.60–1.67 (m, 2H), 1.95 (m, 1H), 2.35 (s, 3H), 2.59 (t, 2H, *J* = 7.5), 3.74 (s, 3H), 7.17 (m, 3H), 7.27 (m, 2H)
1j	45	125/0.5	30 : 70	$C_{12}H_{18}O_5$ (242.3)	1690, 1725, 1735	0.70–1.60 (m, 7H), 1.60–2.00 (m, 1H), 2.40 (m, 2H), 2.90 (m, 2H), 3.55 (s, 3H), 3.70 (*E*) and 3.75 (*Z*) (s, 3H)
1k	75	170/0.5	0 : 100	$C_{20}H_{34}O_3$ (322.4)	1630, 1690, 1725	0.80 (t, 3H, *J* = 5), 1.00–1.70 (m, 20H), 1.70–2.30 (m, 3H), 2.30–2.80 (m, 2H), 3.70 (s, 3H), 4.70–6.10 (m, 3H)[c]

[a] Determined by GC analysis (capillary column CP-SIL-5 Chrompack).

[b] Satisfactory microanalyses obtained: C ±0.28, H ±0.32.

[c] Data of the *Z* isomer.

2-Alkenyltriphenylphosphonium Bromides 4; General Procedure:
A mixture of the bromoalkene **6** or **6** + **7** (0.5 mol) and triphenylphosphine (131 g, 0.5 mol) in dry toluene (300 mL) is heated at reflux temperature until no more precipitate is formed (1–12 h). The precipitate is filtered off and washed with hot Et_2O (3 × 100 mL). If the product is still yellow it is suspended in Et_2O (200 mL) and MeCN is added until the solid is colorless. The product is then isolated by suction and recrystallized.

Methyl 1-Acyl-2-alkylcyclopropanecarboxylates 1; General Procedure:
The methyl 3-oxoalkanoate **9**[25] (0.1 mol) is added to a stirred suspension of NaH (2.4 g, 0.1 mol) in anhydrous toluene (25 mL). The Na salt of **9** is formed when the mixture becomes white. Then, a solution of the 2-alkenyltriphenylphosphonium bromide **4** (0.1 mol) in pyridine (150 mL) is rapidly added and the mixture is stirred and heated at 60–70 °C for 24 h. A white precipitate of sodium bromide appears. The organic solution is washed with H_2O (100 mL), with 10% aq HCl (3 × 100 mL), and with H_2O (100 mL), dried (Na_2SO_4), and evaporated. Pentane (100 mL) is added to the oily residue to precipitate PPh_3. The filtrate is evaporated and the residue is stirred in MeOH (100 mL) at 0 °C. The second crop of PPh_3 is filtered off, and the solvent removed. The crude residue is distilled to give a mixture of the geometric isomers of **1**. It is then possible to isolate the pure *Z* isomers of compounds **1i** and **1k** after by flash chromatography[26] on silica gel using Et_2O/pentane (10:90) as eluent (Table 4).

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