Stereoselective Synthesis of (*E*)-Alkylidenesuccinates by Palladium-catalyzed Carbonylation

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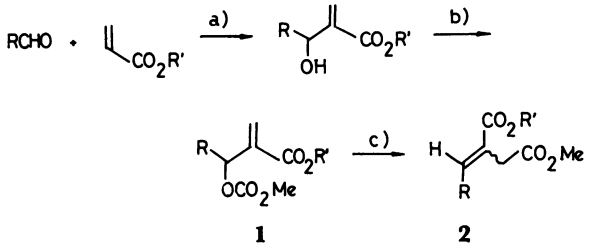
Synopsis. (*E*)-Alkylidenesuccinates have been prepared stereoselectively starting with acrylates by a three-step procedure involving a palladium-catalyzed carbonylation of allylic carbonates.

The well-known Stobbe condensation of aldehydes with an ester of succinic acid is rather limited to the use of aromatic aldehydes, because in the case of aliphatic ones possible isomerization of the produced alkylidenesuccinic acids often yields positional as well as geometrical isomers.[1]

We report here that (*E*)-alkylidenesuccinic acid esters can readily be prepared by a three-step procedure which consists of a base-catalyzed addition of acrylates to aliphatic aldehydes,[2] carbonate formation of the resulting allylic alcohols, and facile palladium-catalyzed carbonylation of the allylic carbonates reported recently by one of us.[3] Scheme 1 shows the procedure.

Although the addition of acrylates to common aldehydes was found to take place slowly but in moderate yields, the yield in carbonate formation was rather inconsistent with recovery of the starting allylic alcohols (40—85% yield).



a) 1,4-Diazabicyclo[2.2.2]octane (DABCO) (20 mol%). b) $ClCO_2Me$/pyridine/benzene. c) $Pd(OAc)_2+2PPh_3$ (2 mol%)/CO (20 kg/cm²).

Scheme 1.

The decarboxylation–carbonylation was carried out by using allyl methyl carbonates thus obtained in the presence of a catalytic amount (2 mol%) of a palladium(0)–phosphine complex generated *in situ* under carbon monoxide pressure at 50 °C.[3]

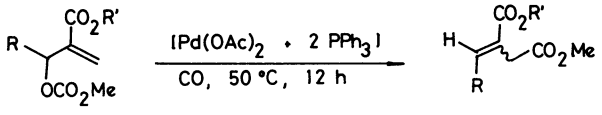
It should be mentioned that the palladium-catalyzed carbonylation is very characteristic of allylic carbonates, other allylic derivatives, such as halides or acetates, being hardly applicable to the catalytic process.

In Table 1 are summarized the results of the preparation of alkylidenesuccinates (**2**).

Three points may be worth commenting: 1) CO pressure affects significantly both the yield of **2** and the selectivity for *E*/*Z* isomers (Table 1, entries 1—3). 2) Satisfactorily high *E*-selectivity (entries 3—5) must be a direct consequence of the carbonylation from *anti*-η^3-allylpalladium intermediate which contains an alkoxycarbonyl group at 2-position. 3) While an isopropyl ester in **1b** has no effect in favor of forming (*E*)-**2b**, an isopropyl substituent of R in **1c** enhances *E*-selectivity of **2c**.

In addition to these results, it was found that the carbonylation of the corresponding cyano analogue of **1**, which was obtained similarly starting with acrylonitrile, afforded mainly (*Z*)-alkylidenesuccinic acid mononitrile (**3**) (*E*/*Z*=1/6), reflecting *syn*-η^3-allylpalladium intermediate to be carbonylated preferably. It follows, therefore, that effect of an alkoxycarbonyl group at 2-position of *anti*-1,2-disubstituted η^3-allylpalladium is steric rather than electronic.

TABLE 1. PREPARATION OF (*E*)-ALKYLIDENESUCCINATES (**2**)



1a—c **2a—c**

Entry	Substrate, **1** R	R′		CO kg/cm²	Yield %	**2**	*E* : *Z*[a]	By-product[b] %
1	*i*-Bu	Me		10	27		7 : 1[c]	60
2	*i*-Bu	Me	**1a**	15	79	**2a**	8 : 1	10
3	*i*-Bu	Me		25	82		11 : 1	5
4	*i*-Bu	*i*-Pr	**1b**	20	70	**2b**	10 : 1	—
5	*i*-Pr	Me	**1c**	20	67	**2c**	14 : 1	—

a) Determined by GLC analysis. b) Allylic methyl ether (*E*/*Z*=5/1). c) Isolated by preparative GLC.

Experimental

Preparation of 3-(Methoxycarbonyloxy)-2-methylenealkanoate (1). A typical procedure is as follows: A mixture of isovaleraldehyde (40 mmol), methyl acrylate (40 mmol), and DABCO (8 mmol) was stirred at room temperature for several days.[2] Remaining acrylate was removed *in vacuo*, the residue was taken up in dichloromethane, washed with 1M HCl(1 M=1 mol dm^{-3}), and dried ($MgSO_4$). The concentrated material was distilled under reduced pressure to give methyl 3-hydroxy-5-methyl-2-methylenehexanoate, bp 48—50 °C/2 Torr (52% yield) (1 Torr=133.322 Pa). The latter (10 mmol) was treated with methyl chloroformate (30 mmol) and pyridine (30 mmol) in dry benzene (50 mL) in a usual manner giving methyl 3-(methoxycarbonyloxy)-5-methyl-2-methylenehexanoate (**1a**), bp 62—64 °C/2 Torr (85%).

Similarly, from isopropyl 3-hydroxy-5-methyl-2-methylenehexanoate (bp 65—67 °C/3 Torr, 62%), isopropyl 3-(methyoxycarbonyloxy)-5-methyl-2-methylenehexanoate (**1b**) was obtained and purified by column chromatography (70% yield with 43% recovery of the starting alcohol). From methyl 3-hydroxy-4-methyl 2-methylenepentanoate (bp 78—80 °C/4 Torr, 51%), methyl 3-(methoxycarbonyloxy)-4-methyl-2-methylenepentanoate (**1c**) was prepared and purified similarly as above (40% yield with 26% recovery of the starting material).

Proton NMR data of **1a—c** are given below: ^{1}H NMR (90 MHz, $CDCl_3$, TMS) **1a**: δ=0.93 (d, *J*=5.9 Hz, 3H), 0.96 (d, *J*=5.7 Hz, 3H), 1.54—1.68 (m, 3H), 3.78 (s, 3H), 3.79 (s, 3H), 5.47—5.61 (m, 1H), 5.84 (br s, 1H), and 6.30 ppm (br s, 1H). **1b**: 0.94 (d, *J*=6.4 Hz, 3H), 0.95 (d, *J*=6.2 Hz, 3H), 1.29 (d, *J*=6.4 Hz, 6H), 1.35—1.58 (m, 2H), 1.60—2.04 (m, 1H), 3.77 (s, 3H), 5.10 (sept, *J*=6.3 Hz, 1H), 5.45 (br t, *J*=7.2 Hz, 1H), 5.77 (t, *J*=1.2 Hz, 1H), and 6.18 (d, *J*=0.7 Hz, 1H). **1c**: 0.92 (d, *J*=6.6 Hz, 3H), 0.96 (d, *J*=6.8 Hz, 3H), 1.82—2.26 (m, 1H), 3.78 (s, 3H), 3.79 (s, 3H), 5.34 (dd, *J*=0.9 and 5.5 Hz, 1H), 5.80 (t, *J*=1.0 Hz, 1H), and 6.37 (d, *J*=0.9 Hz, 1H).

General Procedure for the Palladium-catalyzed Carbonylation. In a 50 mL micro-autoclave with glass lining were placed under a nitrogen atmosphere an allylic carbonate (**1**) (5 mmol), $Pd(OAc)_2$ (2 mol%) and PPh_3 (4 mol%). Carbon monoxide was introduced (20 kg/cm^2) and the mixture was heated at 50 °C overnight with stirring. The red-brown solution was filtered through a short Florisil column to remove the catalyst, the latter being rinsed with little ether. The filtrate was condensed *in vacuo*, and the residue was purified by distillation under reduced pressure (Kugelrohr) to give the corresponding alkylidenesuccinate (**2**). (*Z*)-Isomer as a minor component was isolated by preparative GLC and identified by ^{1}H and/or ^{13}C NMR. Yields and the ratios of *E*- and *Z*-isomers of **2** are summarized in Table 1, and spectral and analytical data of **2a—c** and **3** are given below:

Dimethyl (E)-(3-Methylbutylidene)succinate (2a): ^{1}H NMR 0.94 (d, *J*=6.4 Hz, 6H), 1.32—1.92 (m, 1H), 2.09 (dd, *J*=6.4 and 7.5 Hz, 2H), 3.36 (s, 2H), 3.68 (s, 3H), 3.75 (s, 3H), and 7.00 (t, *J*=7.5 Hz, 1H). ^{13}C NMR (22.5 MHz) δ=22.4 (MeX2), 28.2, 32.2, 38.0, 51.9 (OMeX2), 125.9, 144.9, 167.4, and 171.2 ppm. IR (neat) 1263, 1715, and 1745 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.82; H, 8.47%. Found: C, 61.82; H, 8.37%. (*Z*)-**2a**: ^{1}H NMR 0.92 (d, *J*=6.2 Hz, 6H), 1.20—1.90 (m, 1H), 2.47 (dd, *J*=6.8 and 7.5 Hz, 2H), 3.28 (s, 2H), 3.68 (s, 3H), 3.74 (s, 3H), and 6.09 (t, *J*=7.5 Hz, 1H).

1-Isopropyl 4-Methyl (E)-2-(3-Methylbutylidene)succinate (2b): ^{1}H NMR 0.94 (d, *J*=6.4 Hz, 6H), 1.26 (d, *J*=6.4 Hz, 6H), 1.60—2.00 (m, 1H), 2.08 (t, *J*=7.3 Hz, 2H), 3.34 (s, 2H), 3.67 (s, 3H), 5.06 (sept, *J*=6.3 Hz, 1H), and 7.04 (t, *J*=7.6 Hz, 1H). ^{13}C NMR 21.8 (MeX2), 22.5 (MeX2), 28.3 32.4, 37.9, 51.9, 68.1, 126.6, 144.1, 166.4, and 171.4. IR (neat) 1260, 1710, snf 1740 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15%. Found: C, 64.18; H, 9.07%. (*Z*)-**2b**: ^{1}H NMR 0.93 (d, *J*=6.6 Hz, 6H), 1.25 (d, *J*=6.4 Hz, 6H), 1.44—1.85 (m, 1H), 2.47 (t, *J*=7.2 Hz, 2H), 3.26 (s, 2H), 3.67 (s, 3H), 5.07 (sept, *J*=6.3 Hz, 1H), and 6.05 (t, *J*=7.5 Hz 1H). ^{13}C NMR 21.8 (MeX2), 22.4 (MeX2), 28.8, 38.4, 40.4, 51.8, 67.8, 126.0, 145.9, 166.8, and 172.0.

Dimethyl (E)-(2-Methylpropylidene)succinate (2c): ^{1}H NMR 1.04 (d, *J*=6.6 Hz, 6H), 2.24—2.95 (m, 1H), 3.36 (s, 2H), 3.68 (s, 3H), 3.74 (s, 3H), and 6.77 (d, *J*=10.1 Hz, 1H). ^{13}C NMR 21.9 (MeX2), 28.5, 32.2, 52.0 (OMeX2), 123.2, 152.1, 167.6, and 171.3. IR (neat) 1265, 1710, and 1740 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05%. Found: C, 60.33; H, 8.07%. (*Z*)-**2c**: ^{1}H NMR 1.02 (d, *J*=6.6 Hz, 6H), 3.12—3.48 centered at 3.37 (decoupled) (m, 1H), 3.24 (s, 2H), 3.68 (s, 3H), 3.74 (s, 3H), and 5.84 (d, *J*=9.9 Hz, 1H).

Methyl (Z)-3-Cyano-6-methyl-3-heptenoate (3): ^{1}H NMR 0.96 (d, *J*=6.4 Hz, 6H), 1.56—2.12 (m, 1H), 2.32 (dd, *J*=7.0 and 7.3 Hz, 2H), 3.24 (s, 2H), 3.75 (s, 3H), and 6.33 (t, *J*=7.7 Hz, 1H). ^{13}C NMR 22.2 (MeX2), 28.2, 39.0, 40.6, 52.4, 108.0, 116.9, 151.1, and 169.5. IR (neat) 1260, 1740, and 2200 cm^{-1}. Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34;, N, 7.73%. Found: C, 66.16; H, 8.40; N, 7.58%. (*E*)-**3**: ^{1}H NMR 0.93 (d, *J*=6.4 Hz, 6H), 1.56—1.96 (m, 1H), 2.10 (dd, *J*=6.6 and 7.3 Hz, 2H), 3.26 (s, 2H), 3.75 (s, 3H), and 6.58 (t, *J*=7.6 Hz, 1H). ^{13}C NMR 22.2 (MeX2), 28.1, 34.1, 37.7, 52.4, 107.8, 116.7, 150.8, and 168.9.

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