A Simple and Efficient Route to 2-Alkyl-2-alkenoic Acids and 2-Phenyl-2-Alkenoic Acids by the Horner Synthesis. Application to the Stereoselective Synthesis of the Pheromone Manicone

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A general synthesis of α-branched α,β-unsaturated carboxylic acids is described. A Horner reaction of 2-diethoxyphosphorylalcanoic acid dianions (lithium α-lithiocarboxylates) with carbonyl compounds is used. The reaction is applied to the stereoselective synthesis of Manicone.

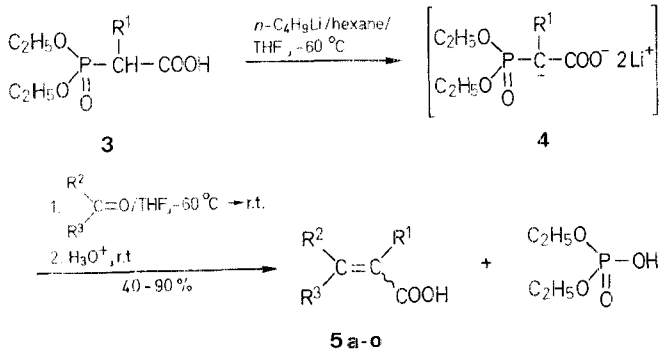
Some years ago[1,2] we developed a highly efficient synthesis of 2-alkenoic acids and 2-chloro-2-alkenoic acids by the two carbon homologation of aldehydes and ketones using the reagents diethoxyphosphorylacetic acid **1** and diethoxyphosphorylchloroacetic acid, **2**, respectively.

1 **2**

The synthesis of 2-alkenoic acids by the Horner reaction has also previously been achieved using dibenzyloxyphosphorylacetic acid[3] and trimethylsilyl diethoxyphosphorylacetate[4]. A recent publication mentions the preparation of chain-functionalized 2-alkenoic acids from ethyl diethoxyphosphorylacetate by a Horner reaction in heterogeneous media of low basicity[5].

The direct synthesis of 2-alkenoic acids substituted in the 2-position with an alkyl or a phenyl group **(5)** by a Horner synthesis has not yet been described to our knowledge.

We have now found that 2-diethoxyphosphorylalcanoic acids (**3**; $R^1 = CH_3$, n-C_3H_7, n-C_5H_{11}, C_6H_5), for which we have recently reported a general preparation[6], are very convenient reagents for the one step synthesis of **5** from carbonyl compounds.



3 **4**

5a-o

2-(Diethyloxyphosphorylalcanoic acids **3** are converted to their dianions (lithium α-lithiocarboxylates) **4** by treatment with n-butyllithium in a mixture of hexane-tetrahydrofuran at −60 °C. After addition of the carbonyl compound at this

Table. 2-Alkyl-2-alkenoic Acids and 2-Phenyl-2-alkenoic Acids **5** Prepared.

5	R^1	R^2	R^3	Yield [%]	E/Z ratio	Molecular Formula[b] or Lit. m.p. or b.p. [°C]	m.p. or b.p. [°C]	^{1}H-NMR (CCl_4/TMS)[c] or (CCl_4/DMSO-d_6/TMS) δ [ppm]
a	CH_3	3-Cl—C_6H_4[a]	H	73[a]	100/0	m.p. 106[10]	m.p. 106	2.02 (d, J = 1.3 Hz, 3H); 7.0–8.0 (m, 6H)
b	CH_3	3,4-methylene-dioxyphenyl	H	90[a]	100/0	m.p. 200–201[11]	m.p. 200	2.4 (s, 3H); 6.3 (s, 2H); 7.2 (s, 3H); 7.8 (s, 1H); 9.8 (s, 1H)
c	CH_3	4-$H_3COC_6H_4$—	H	53[a]	100/0	m.p. 158[12]	m.p. 159	2.06 (d, J = 1.3 Hz, 3H); 3.8 (s, 3H); 6.7–7.5 (2d, J = 8.7, 8.7 Hz, 4H); 7.6 (s, 1H); 9.3 (s, 1H)
d	CH_3	CH_3—CH=CH— (*E*)	H	73[a,d]	100/0	m.p. 100–101[13]	m.p. 100	1.9 (s, 6H); 5.9–6.7 (m, 2H); 7.0–7.4 (d, J = 9.3 Hz, 1H); 12.5 (s, 1H)
e	CH_3	*i*-C_3H_7	H	71	87/13	b.p. 115–117/15 torr[14]	b.p. 88–92/1.5 torr	(E) 1.04 (d, J = 6.7 Hz, 6H); 1.82 (d, J = 1.3 Hz, 3H); 2.3–3.0 (m, 1H); 6.7 (dd, J = 10, 1.3 Hz, 1H) (Z) 1.0 (d, J = 6.7 Hz, 6H); 2.17 (d, J = 1.3 Hz, 3H); 3.1–3.8 (m, 1H); 5.8 (dd, J = 10, 1.3 Hz, 1H)
f	CH_3	*s*-C_4H_9	H	81	86/14	b.p. 85–87/0.5 torr[8,9]	b.p. 73–75/0.2 torr	(E) 1.8 (d, J = 1.3 Hz, 3H); 2.0–2.7 (m, 1H); 6.7 (d, J = 10 Hz, 1H) (Z) 2.8–3.5 (m, 1H); 5.8 (d, J = 10 Hz, 1H)
g	CH_3	*t*-C_4H_9	H	86	100/0	b.p. 123/15 torr	b.p. 84–86/0.1 torr	1.2 (s, 9H); 1.9 (d, J = 1.3 Hz, 3H); 6.9 (m, 1H); 12.6 (s, 1H)
h	CH_3	—$(CH_2)_5$—		40[a]	—	m.p. 83[15]	m.p. 83	1.6 (s, 6H); 1.9 (s, 3H); 2.26 (s, 2H); 2.64 (s, 2H); 12.6 (s, 1H)
i	*n*-C_3H_7	C_6H_5	H	76	100/0	m.p. 93[16]	m.p. 82[e]	1.0 (t, J = 6.7 Hz, 3H); 1.2–2.0 (m, 2H); 2.2–2.8 (m, 2H); 7.35 (s, 5H); 7.82 (s, 1H); 12.5 (s, 1H)
j	*n*-C_3H_7	*i*-C_3H_7	H	65	65/35	$C_9H_{16}O_2$ (152.2)	b.p. 89–93/0.5 torr	(E) 1.04 (d, J = 6.7 Hz, 6H); 6.7 (d, J = 10 Hz, 1H) (Z) 1.0 (d, J = 6.7 Hz, 6H); 3.0–3.5 (m, 1H); 5.7 (d, J = 10 Hz, 1H)
k	*n*-C_5H_{11}	C_6H_5	H	62[a]	100/0	m.p. 80[16]	m.p. 80	0.6–2.0 (m, 9H); 2.2–2.8 (m, 2H); 7.3 (s, 5H); 7.7 (s, 1H); 12.6 (s, 1H)
l	*n*-C_5H_{11}	*i*-C_3H_7	H	77	50/50	$C_{11}H_{20}O_2$ (184.3)	b.p. 89–93/0.1 torr	(E) 6.7 (d, J = 10 Hz, 1H) (Z) 5.75 (d, J = 10 Hz, 1H); 3.0–3.7 (m, 1H)
m	C_6H_5	*i*-C_3H_7	H	61[a]	100/0	$C_{12}H_{14}O_2$ (190.2)	m.p. 132	1.0 (d, J = 6.7 Hz, 6H); 2.0–2.8 (m, 1H); 6.9 (d, J = 10 Hz, 1H); 7.0–7.5 (m, 5H); 12.4 (s, 1H)
n	C_6H_5	*n*-C_3H_7	H	58[a]	100/0	m.p. 71[17]	m.p. 72	0.9 (t, J = 6.7 Hz, 3H); 1.1–1.8 (m, 2H); 1.8–2.3 (m, 2H); 6.9–7.5 (m, 6H); 12.6 (s, 1H)
o	C_6H_5	C_6H_5	H	53[a]	100/0	m.p. 172–174[18]	m.p. 173	6.9–7.5 (m, 11H); 7.8 (s, 1H)

[a] Yield of recrystallized products.
[b] Microanalyses obtained: C ±0.33, H ±0.20.
[c] Only characteristic chemical shifts are given in the cases of mixture of *Z*- and *E*-isomers **(5e, 5f, 5j, 5l)**. The *E*-isomer gave a doublet (with further fine splitting) for the C-3 vinyl proton at δ 6.7 whereas the signal for the *Z*-isomer appeared at δ 5.7–5.8. The C-4 allylic proton appeared as multiplet at δ 3.0–3.8 for the *Z*-isomer and δ 2.0–2.8 for the *E* isomer. The overlap of the remaining signals precluded further assignments.
[d] *E,E*-isomer.
[e] There is a great difference between the literature data and the melting point reported here.
$C_{12}H_{14}O_2$: (190.2) calc. C 75.77 H 7.42; found 75.48 7.43

temperature and subsequent hydrolysis, 2-alkyl or 2-phenyl-2-alkenoic acids **5** and diethyl hydrogen phosphate are obtained.

The diethyl hydrogen phosphate is easily separated from the carboxylic acid **5**: if acids **5** are insoluble **(5a, 5b, 5c, 5i, 5k, 5m, 5n, 5o)** filtration is used; if they are soluble in the acid medium **(5d, 5e, 5f, 5g, 5h, 5j, 5l)**, the reaction mixture is adjusted to pH 4, and the carboxylic acid **5** is extracted selectively.

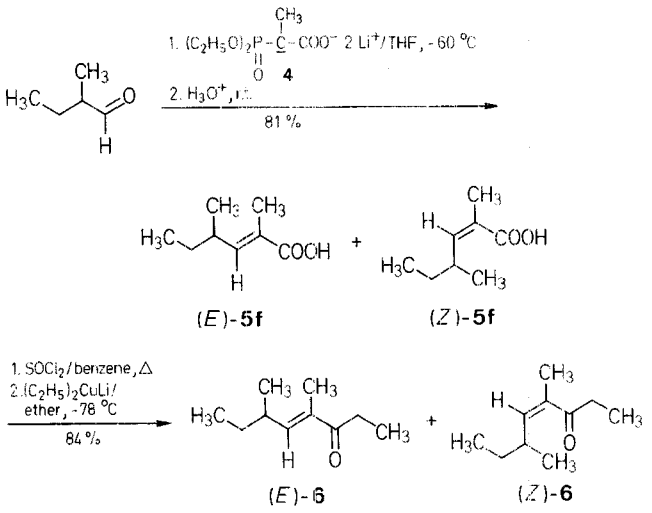
In all the cases studied, the dianions **4** only react with the more reactive carbonyl compounds. With aliphatic or aromatic aldehydes, the reaction gives good yields of alkenoic acids **5**, whereas with ketones the reaction has no synthetic value. Only cyclohexanone reacts to give **5** in the case where R^1 is methyl, but in poor yield. With the same dianion (**4**, $R^1 = CH_3$), attempts with butanone, benzophenone, 6-methyl-5-hepten-2-one and pseudoionone failed.

With aromatic aldehydes the reaction is totally stereoselective

and gives only the *E*-isomers, but the 2-alkenoic acids **5** obtained from aliphatic aldehydes are mixtures of the *Z*- and *E*-isomers in which the *E*-isomer predominates. We observe that the relative amount of the *Z*-isomer becomes greater when the alkyl group R^1 becomes sterically bulky (**5e**, **5j**, **5l**). Moreover, it is worth noting that with aliphatic aldehydes the *E*-isomers predominate. When the methyl 2-diethoxyphosphoryl propanoate is used as the Horner reagent instead of **3**, the reaction leads to corresponding methylesters of **5**, mostly with a *Z* stereochemistry[7].

To demonstrate the synthetic utility of our method, we have applied it to the synthesis of Manicone, the principal alarm pheromone of certain species of Manica ants. This pheromone was isolated from the mandibular glands of *M. Mutica* and *M. Bradleyi* and identified as (*E*)-4,6-dimethyl-4-octen-3-one[8,19], (*E*)-**6**.

Manicone, (*E*)-**6** was prepared from methyl-2-butanal and from the dilithium dianion **4** ($R^1 = CH_3$) as shown.



The mixture of carboxylic acids (*E*)-**5f** and (*Z*)-**5f**, in which the *E*-isomer again predominates [(*E*)-**5f**/(*Z*)-**5f**, 86:14 by NMR analysis], was converted to the corresponding acid chloride mixture with thionyl chloride. This was then treated with lithium diethylcuprate to give (*E*)-**6** and (*Z*)-**6** in 84% yield for the two steps sequence. The major isomer is the E-isomer [(*E*)-**6**/(*Z*)-**6**, 88:12 by NMR analysis] and shown to be identical with Manicone by comparison with published NMR and IR data[8].

This route to Manicone is very attractive because it is much simpler and faster than other methods previously described and gives the pheromone (*E*)-**6** with high stereoselectivity.

2-Alkyl- or 2-Phenylalkenoic Acids 5; General Procedure:

A 2.6 molar solution (16 ml, 42 mmol) of butyllithium in hexane is added to tetrahydrofuran (70 ml) at −60 °C followed by the dropwise addition at this temperature of diethoxyphosphoryl alcanoic acid **3** (20 mmol) in tetrahydrofuran (20 ml). After 30 min. stirring at −60 °C ($R^1 = CH_3$, C_6H_5) or 60 min. stirring at −60 °C ($R^1 = n\text{-}C_3H_7$, $n\text{-}C_5H_{11}$) the carbonyl compound (20 mmol) in tetrahydrofuran (10 ml) is added dropwise at −60 °C. Stirring is continued for 1 h at −60 °C; the reaction mixture is then allowed to warm to room temperature. After an additional 3 hours stirring to complete the reaction (for an aldehyde or 15 hours for the cyclohexanone) the mixture is hydrolyzed with water (50 ml), the organic layer is washed with 10% aqueous hydrogen sodium carbonate solution (2 × 25 ml), and the combined aqueous layers washed with ether (2 × 50 ml).

If the carbonyl compound is aromatic or if $R^1 = C_6H_5$, the aqueous phase is acidified to pH 1 with 6 normal hydrochloric acid; the alkenoic acids **5** precipitate under these conditions. After filtration, the precipitate is washed with water, further dessicated under vacuum, and recrystallized from ethanol/water.

If the starting carbonyl compound is aliphatic and R^1 = alkyl, the aqueous layer is acidified dropwise to pH 4 (controlled by a pH-meter), saturated with sodium chloride and extracted with ether (3 × 50 ml). After drying with magnesium sulfate, the solvent is evaporated under reduced pressure to leave the crude 2-alkenoic acid as an oil, which is purified by distillation *in vacuo* or by recrystallization.

Manicone (*E*)-6:

2,4-Dimethyl-2-hexenoic acid (**5f**) is obtained exactly as described above; yield: 81% after distillation [(*E*)-**5f**/(*Z*)-**5f**, 86:14].

A solution of this **5f** isomer mixture (2.5 g, 18 mmol) is added to freshly distilled thionyl chloride (4.3 g, 36 mmol) in benzene (10 ml). The mixture is refluxed for 2 h and then concentrated under reduced pressure to give the 2,4-dimethyl-2-hexenoyl chloride as an oil, which is used in the next step; yield: 2.8 g (~ 100%).

To a solution of lithium diethylcuprate (25 mmol) in ether (50 ml), the 2,4-dimethyl-2-hexenoyl chloride (2.8 g, 18 mmol) is added dropwise with stirring at −78 °C. The mixture acquires a brown color. After stirring for 15 min. at −78 °C, methanol (2.7 ml) is added and the solution is allowed to warm to room temperature. Then, a solution of aqueous saturated ammonium chloride (40 ml) is added. The product is extracted with ether (2 × 50 ml), the combined organic layers are dried with magnesium sulfate, and the solvent is removed under reduced pressure. The residue is purified by distillation *in vacuo*; yield (*E*)-**6** + (*Z*)-**6**: 2.4 g (84%) [(*E*)-**6**/(*Z*)-**6**, 88:12]; b.p. = 74–76 °C/12 torr.

^{1}H-NMR (CCl_4/TMS): (*E*): δ = 0.9 (t, J = 7.0 Hz, 3 H), 1.02 (d, J = 7.0 Hz, 3 H), 1.06 (t, J = 7.0 Hz, 3 H), 1.4 (m, 2 H), 1.73 (d, J = 1.3 Hz, 3 H), 2.4 (m, 1 H), 2.59 (q, J = 7.0 Hz, 2 H), 6.24 ppm (d, J = 10 Hz, 1 H).

(*Z*): δ = only a very weak signal at 5.22 (d, 1 H) reveals the presence of the (*Z*) isomer

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