The Michael Addition of Dimethyl Malonate to α,β-Unsaturated Aldehydes Catalysed by Proline Lithium Salt

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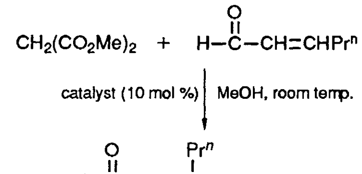
In the presence of 10 mol% of proline lithium salt, Michael adducts were obtained from dimethyl malonate and α,β-unsaturated aldehydes in high yield.

Although Michael addition of malonates to α,β-unsaturated aldehydes can occur, control is difficult and in fact only a few successful examples are described in the literature.[1,2] An improved method utilizing a phase-transfer catalyst (K_2CO_3 and $BnNEt_3^+$ Cl^-; Bn = $PhCH_2$) has been reported, although the yields of the adducts were moderate.[3] We have now found that the Michael addition proceeded smoothly with a catalytic amount of proline lithium salt.

An initial search for an efficient amine catalyst for the Michael addition reaction revealed that a modest yield of adducts could be obtained with secondary amines (Table 1, entries 1–5). In order to improve the yields, amine–lithium salt complex systems were examined, such systems having recently been shown to be effective for the activation of active methylene compounds.[4] After various trials,[‡] the lithium salt



Scheme 1

Table 1 The effect of catalysts on the Michael addition of dimethyl malonate to hex-2-enal (Scheme 1)

Entry	Catalyst	Yield (%)
1	Et_3N	No reaction
2	DBU[a]	Trace
3	Cs_2CO_3	No reaction
4	Pyrrolidine	33
5	L-Proline	44
6	Pyrrolidine–LiOAc	42
7	L-Proline Li salt	93
8	L-Valine Li salt	32

[a] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

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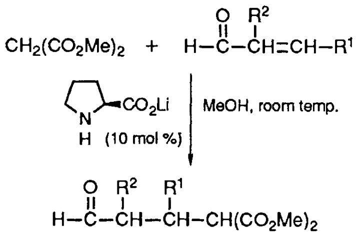
[‡] The Michael reaction was examined first with Et_3N–$LiClO_4$ as catalyst. Although the system worked efficiently for unsaturated ketones, yields with unsaturated aldehydes were modest.

Table 2 The Michael addition of dimethyl malonate to α,β-unsaturated aldehydes (Scheme 2)[a]

Aldehyde	t/h	Yield (%)[b]
MeCH=CHCHO	0.5	89
Pr^nCH=CHCHO	1	93, 86[c]
PhCH=CHCHO	1	77
cyclo-$C_6H_{11}CH$=CHCHO	3	60
$CH_2[CH_2]_2CH$=CCHO	3	61
CH_2=CHCHO	0.5	40
CH_2=CMeCHO	0.5	51

[a] The following procedure for the synthesis of dimethyl (3-oxo-1-propylpropyl)malonate is typical. Under a nitrogen atmosphere, a mixture of dimethyl malonate (117 mg, 0.89 mmol), hex-2-enal (59 mg, 0.60 mmol), and proline lithium salt (7 mg, 0.06 mmol) in methanol (3 ml) was stirred for 1 h. The reaction was quenched by adding 2 mol dm^{-3} HCl, and organic materials were extracted with ethyl acetate. The Michael adduct (129 mg, 93%) was obtained by a standard work-up: ^{1}HNMR ($CDCl_3$–CCl_4) δ 0.7–1.1 (3H, m), 1.1–1.6 (4H, m), 2.2–3.0 (3H, m), 3.42 (1H, d, J 7 Hz), 3.72 (6H, s) and 9.70 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 13.8, 19.9, 32.3, 34.5, 45.7, 52.2, 54.0, 168.7, 168.9 and 200.9; IR (neat) ν 1730 cm^{-1}. Satisfactory elemental analyses were obtained. [b] Isolated yields are shown. All new compounds gave satisfactory ^{1}HNMR, ^{13}CNMR and IR spectra and elemental analysis by combustion. [c] Reaction carried out on a 10 mmol scale.



Scheme 2

of proline§ in methanol turned out to be quite effective. The combination of pyrrolidine and LiOAc resulted in a modest yield (entry 5). With regard to the amino acid moiety, proline lithium salt gave a higher yield of the adduct than valine lithium salt (entry 8), a primary amine derivative.

The method has been applied to several α,β-unsaturated aldehydes, and the results are summarized in Table 2. The reaction generally is rapid, and 1,2-adducts were not obtained. The present catalyst is especially effective for unsaturated aldehydes with β-substituents. Cyclopentene-1-carbaldehyde also gave the adduct in good yield.

Although the role of proline lithium salt in the present reaction is not fully clear, the catalyst seems to activate the Michael acceptor as well as the Michael donor. When a catalytic amount of the lithium salt was added to a CD_3OD solution of dimethyl malonate, a very rapid proton exchange occurred at the active methylene moiety. A gradual ester exchange also proceeded from the CH_3 to the CD_3 ester. Cinamaldehyde was also activated with the catalyst in CD_3OD, and in the absence of the Michael donor it decomposed rapidly. Since the use of secondary amine derivatives is essential (Table 1), the formation of iminium salts from aldehydes is probable. Under the present reaction conditions, virtually no asymmetric induction was observed in spite of the use of optically active amino acids.

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§ The lithium salts of the amino acids were prepared by the reaction of 1 equiv. of the amino acid and LiOH in methanol at room temperature for 10 min and evaporation. The salts were dried at room temperature *in vacuo* for 3 h.

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