Kinetic 1,4-Addition of a Dithioacetate Enolate to α-Enones

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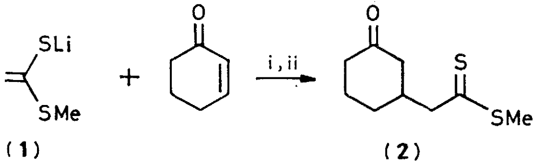
Lithium methyl dithioacetate reacts with enones at low temperature *via* a selective 1,4-*C*-addition to give 5-oxodithioesters; further elaboration by thiophilic addition and alkylation furnishes masked 1,5-dicarbonyl compounds.

Dithioesters have recently been introduced as synthetically useful reagents,[1–5] but studies of their metal enolates have been limited to reactions with alkyl halides,[6] giving sulphur alkylation, and with some aldehydes,[3,7] yielding aldols by carbon addition. No report deals with their behaviour towards Michael acceptors. Assuming that dithioester enolates are soft nucleophiles, as compared with carbonyl enolates, 1,4-addition to the conjugated system of α-enones should be favoured[8] relative to 1,2-addition. The expected reacting site of the ambident nucleophile, whether carbon or sulphur, was unknown.[9]

I report that selective carbon 1,4-addition is observed for the lithium thioenolate (**1**) (Scheme 1). Deprotonation of methyl dithioacetate with lithium di-isopropylamide in tetrahydrofuran (THF), followed by treatment with various enones at low temperature and quenching with aqueous ammonium chloride gave 5-oxodithiocarboxylates (Table 1).† Side reactions were not observed. Control experiments at low conversion rates indicated that this process was kinetically controlled. Its mode contrasts with the reported 1,2-addition of lithium carboxylic ester enolates with enones under comparable conditions.[10] Dithioesters are therefore one of the rare examples of carbonyl derivatives[11] whose enolates give Michael additions, without being doubly stabilized, as for malonates.



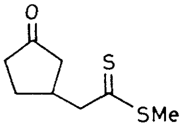
Scheme 1. *Reagents:* i, tetrahydrofuran (THF), −45 °C, 15 min; ii, NH_4Cl, H_2O.

Table 1. Addition of lithium methyl dithioacetate to α-unsaturated ketones.

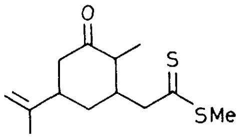
Enone	T/°C[a]	Time/ min	Product	% Yield[b]
Cyclopent-2-enone	−50	15	(**3**)	78
Cyclohex-2-enone	−45	15	(**2**)	86
(−)-Carvone	−30	10	(**4**)	70[c]
3-Methylcyclohex-2-en-1-one	−10	30	(**5**)	52
But-3-en-2-one	−98	15	(**6**)	30
3-Methylbut-3-en-2-one	−55	15	(**7**)	73
Pent-3-en-2-one	−60	15	(**8**)	74
Chalcone	−78	10	(**9**)	73

[a] Deprotonation of methyl dithioacetate has been carried out at the same temperature. [b] Yield of the isolated product. [c] Mixture of two stereoisomers in a 3 : 1 ratio.

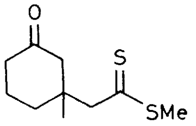
The readily prepared 5-oxodithiocarboxylates (**2**)—(**9**) are 1,5-dicarbonyl precursors with functional differentiation as shown by the following reactions (Scheme 2). Selective protection of the carbonyl moiety in (**2**) was carried out quantitatively by acetalization with ethylene glycol under acidic conditions [$Me(C_6H_4)SO_3H$ or $NC_5H_5{}^+Me(C_6H_4)$-$SO_3{}^-$,[12] benzene, reflux]. Thiophilic addition[13] of isopropylmagnesium bromide to the dithioester (**10**) gave a dithioacetal carbanion, which could be alkylated by various electrophiles (E) to afford protected 1,5-dicarbonyl compounds of potential synthetic use (Table 2).



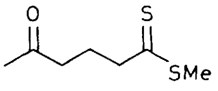
(**3**)



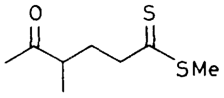
(**4**)



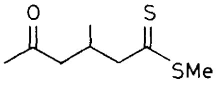
(**5**)



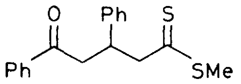
(**6**)



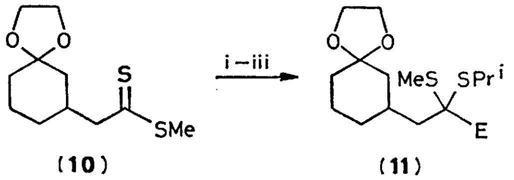
(**7**)



(**8**)



(**9**)



Scheme 2. *Reagents and conditions:* i, Pr^iMgBr, THF, −17 °C, 20 min; ii, E^+, −17 °C, 1—4 h; iii, NH_4Cl, H_2O.

Table 2. Thiophilic addition and alkylation (**10**) → (**11**).

Electrophile	% Yield[a]
H_2O	87
MeI	78
EtBr[b]	85
Allyl Br	77

[a] Isolated product. [b] 6 mol. equiv. of hexamethylphosphoramide were added.

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† All new compounds (**2**)—(**11**) had satisfactory elemental analyses and gave the expected spectroscopic data (i.r., u.v., and ^1H and ^{13}C n.m.r.).

Thus, the overall scheme (**1**) → (**11**) makes possible the 1,4-addition of a regiocontrolled ketone enolate equivalent, by use of the synthon $^{-}CH_2$–C(=O)$^{-}$.[7]

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