

A New Route to Unsymmetrical Ketones from Thioimidates *via* Ketenimines; a One-pot Synthesis of *ar*-Turmerone

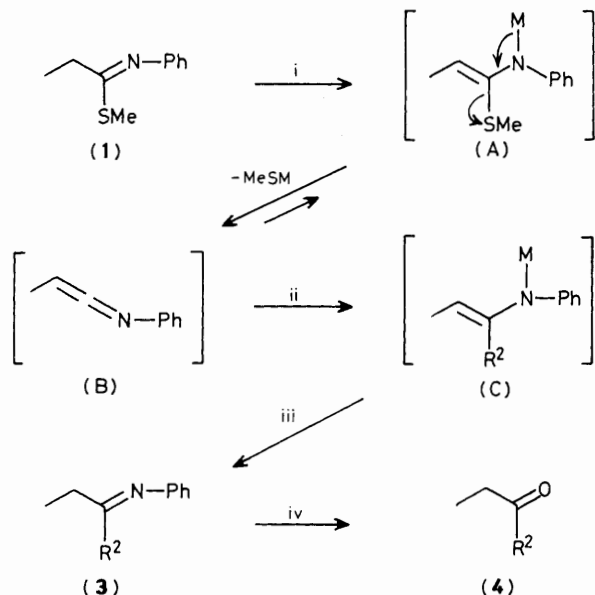
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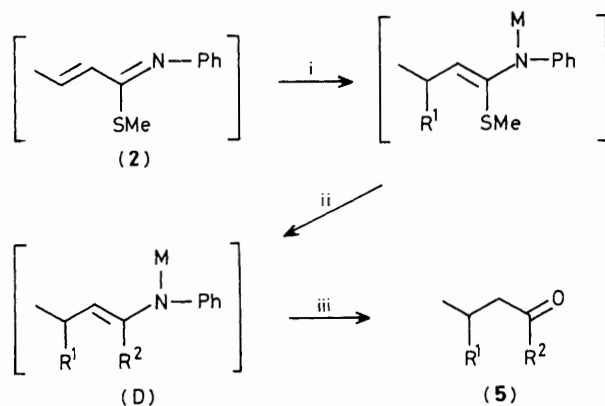
Ketones may be synthesised by the generation and thermal decomposition of thio-*N*-metallated-enamines followed by trapping of the resulting ketenimines with an organometallic reagent.

N-Phenylthioimidates, which can be used as precursors of dithioesters or *O*-thioesters are readily available from organometallic compounds and phenylisothiocyanate.¹⁻³ The metallation-alkylation of these thioimidates [such as (1)] and the 1,4-addition of organometallic reagents (RLi or RMgX) to the α,β -unsaturated analogue (2) described previously,^{2,4}

have shown the utility of these compounds for selective carbon-carbon bond formation. We observed that, when the reactions were performed at temperatures higher than -5 °C, significant amounts of tarry by-products attributed to the instability of the intermediate carbanions were obtained. However, in the presence of an excess of organometallic



Scheme 1. (R¹ = Bu). Reagents and conditions: i, R¹M, tetrahydrofuran (THF), -40 °C; ii, R²M, then 20 °C; iii, aq. NH₄Cl, room temp., Et₂O extraction; iv, aq. AcOH, 24 h, 20 °C.



Scheme 2. Reagents and conditions: i, R¹M, THF, M = Li -78 °C, M = MgBr -10 °C; ii, R²M, then 20 °C; iii, aq. AcOH, 24 h.

reagent (RM), secondary products resulting from replacement of the alkylthio group by R were detected. We now report results indicating the synthetic interest of this reaction.

The thioimide (1) (1 equiv.) was first added to a solution (tetrahydrofuran-hexane) of n-butyl-lithium (2.2 equiv.) at -40 °C. The temperature was then allowed to rise to room temperature. After rapid hydrolysis, followed by extraction with ether, the imine (3a) (Scheme 1) was mainly formed; the corresponding ketone (4a) was obtained in 60% yield after prolonged hydrolysis (24 h at 20 °C in aqueous acetic acid). Likewise, addition of (1) to only 1 equiv. of n-butyl-lithium (R¹M) at low temperature followed by phenyl-lithium (R²M) (1 equiv.) with subsequent elevation of temperature led, after hydrolysis, to the propiophenone (4b).

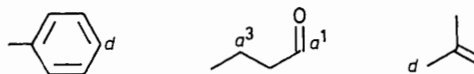
Via a Michael addition (Scheme 2) and of a greater synthetic interest are the successive and selective additions of two different organometallic reagents to the α,β-unsaturated thioimide (2) (on C-3 and C-1). The same type of one-pot procedure was employed and the various unsymmetrical ketones (5a-f) were thus readily synthesized and isolated with the yields (non-optimised) indicated in Table 1.

The behaviour of these thioimides can be related to the

Table 1. Preparation of (4) and (5).

Thioimide	R ¹ M	R ² M	Ketone % yield ^a
(1)	Bu ⁿ Li	Bu ⁿ Li	(4a), 60
(1)	Bu ⁿ Li	PhLi	(4b), 82
(2)	Bu ⁿ Li	YMgCl ^b	(5a), 57
(2)	Bu ⁿ Li	EtMgBr	(5b), 69
(2)	Bu ⁿ Li	Pr ⁿ MgBr	(5c), 61
(2)	Bu ⁿ Li	PhLi	(5d), 63
(2)	Bu ⁿ Li	MeLi	(5e), 65
(2)	<i>p</i> -Tolyl-MgBr	YMgCl ^b	(5f), 71

^a After column chromatography on silica gel (eluant, light petroleum-ethyl acetate, 95:5). ^b Y = MeC(=CH₂)CH₂-.



reactions of dihydro-1,3-oxazines with organometallic reagents which give α-substituted ketones via a metallated oxazine-ketenimine rearrangement.^{5,6} Thus, our results can be rationalized by a mechanism involving intermediate ketenimines such as (B) arising from thermal decomposition (loss of MeSM) of the N-metallated enamines such as (A)† initially generated by metallation or 1,4-addition. The reactive ketenimines are then trapped by the second equivalent of organometallic reagent affording the metallated enamines such as (C) or (D).

The ketone (5f) is iso-ar-turmerone, easily converted, by a trace of base, into its conjugated isomer, ar-turmerone, for which several preparations have been published.⁷ However our (7 C + 4 C + 4 C) one-pot synthesis using (2) as an a³a¹ synthon appears to provide easier access to this flavouring terpene.

We also attempted to create another carbon-carbon bond by subsequent addition of iodomethane to the N-phenyl enamine (C; R² = Ph) but alkylation occurred mainly on nitrogen and hydrolysis of the enamine so formed led again to the propiophenone (4b). It is known that metallated N-phenyl-imines, in contrast to their N-alkylated analogues, can often lead to N-alkylation.⁸ The behaviour of N-alkyl thioimides will be examined in further investigations.

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† The relative stability of these carbanions allows controlled thermal decomposition and the use of different organometallic reagents for each step (deprotonation or Michael addition to the ketenimine) of these reactions.