Carboxylate-substituted Nitrones as Aldehyde Synthons for the Addition of Ketone Enolates

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The addition of a ketone enolate to an ester-substituted nitrone gives an adduct, which upon Hofmann degradation can be elaborated to give a γ-keto-α,β-unsaturated ester, the formal product of a directed aldol condensation.

As part of a programme to develop new reactions of enolates and their derivatives, we have studied the additions of these intermediates to functionalised nitrones such as (**1**)[1] and (**2**).‡ The literature contains scattered reports of the addition of stabilised carbanions to nitrones,[2] and simple enol ethers are reported to undergo cycloaddition with nitrones.[3]

No reaction occurs between the nitrones (**1**) and (**2**) and the trimethylsilyl enol ether of cyclopentanone (**3**), or with other enol derivatives,[4] even on prolonged heating in solution or in a neat mixture with (**1**). We find, however, that ketone lithium enolates readily add to the nitrones (**1**) and (**2**). While the primary enolate–nitrone adducts are difficult to purify and characterise, silylation yields a more tractable product, the structure of which depends on the nature of the *N*-substituent of the nitrone. The *N*-methyl nitrone (**1**) gives the 5-(silyloxy)isoxazolidine-3-esters (**5**) and (**6**),§ which are the formal products of [2 + 3]cycloaddition to the enol ethers (**3**) and (**4**) (Scheme 1). The ester (**5**) was isolated as a separable mixture of diastereoisomers in a 4:1 ratio. The products of reaction with the *N*-cyclohexyl nitrone (**2**) are the γ-keto-α-silyloxyamino esters (**7**) and (**8**)§ (Scheme 2). Apparently, the initial enolate–nitrone adduct does not cyclise to the isoxazolidine in this case because of the bulkier substituent on nitrogen. This difference in structure is borne out most clearly

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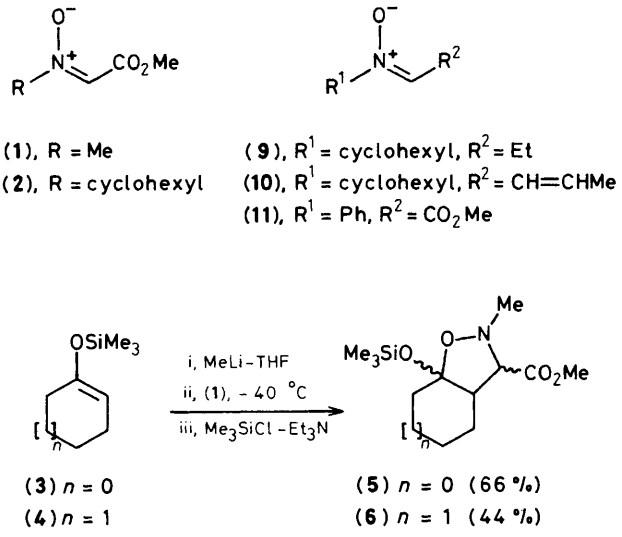
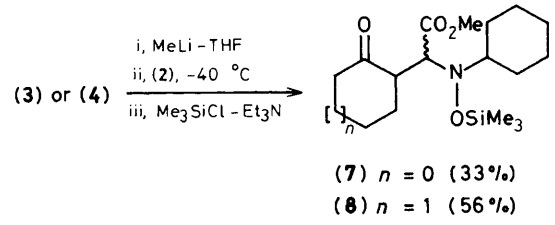
‡ The nitrone (**1**) was prepared by a modification of the literature procedure: concentrated aqueous MeNHOH · HCl was neutralized with concentrated aqueous NaOH, and a suspension of the product in chilled methylene chloride was treated first with methyl glyoxalate (prepared by the periodate cleavage of methyl tartrate: T. R. Kelly, T. E. Schmidt, and J. G. Haggerty, *Synthesis*, 1972, 544) and then with anhydrous magnesium sulphate. The solution was filtered and concentrated to give crystalline (**1**) in 59% yield. The nitrone (**2**) was prepared similarly using cyclohexylhydroxylamine hydrochloride, in 61% yield, m.p. 93—95 °C (from Et_2O): crude (**2**): $\nu_{max.}$ ($CHCl_3$) 3000, 2940, 2865, 1725, and 1540 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 1.1—2.2 (m, 10H), 3.79 (s, 3H), 5.6 (quintet, *J* 4.5 Hz, 1H), and 7.0 (s) and 7.12 (s) [ratio 3:1]; the δ 7.0 and 7.12 absorptions indicate a mixture of *E*- and *Z*-isomers, probably with the *Z*-isomer predominating. For a discussion of the stereochemistry of aldonitrones, see: L. W. Boyle, M. J. Peagram, and G. H. Whitham, *J. Chem. Soc. B*, 1971, 1728.

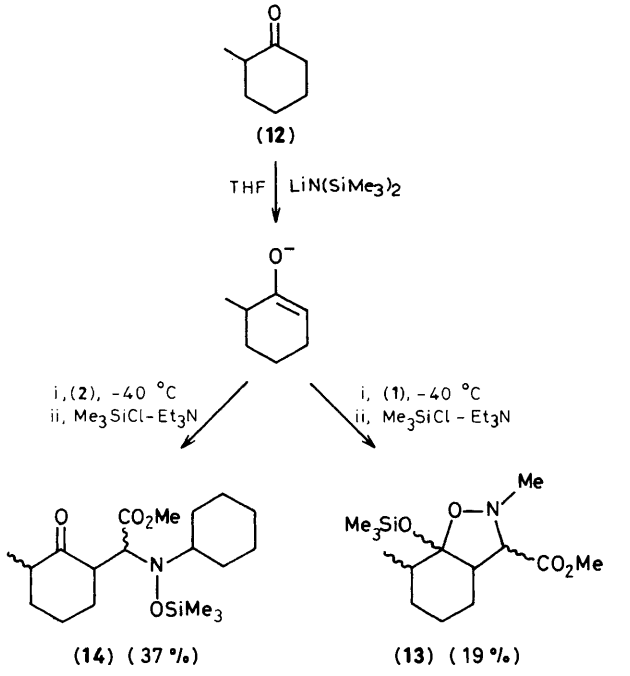
§ Selected spectroscopic data: (**5**), major isomer, $\nu_{max.}$ (thin film), 2970, 2880, and 1750 cm^{-1}; ^1H n.m.r. ($CDCl_3$), δ 0.17 (s, 9H), 1.5—2.1 (m, 6H), 2.69 (s, 3H), 2.85 (br. s, 1H), 3.00 (d, *J* 5 Hz, 1H), and 3.73 (s, 3H); *m/z* (chemical ionisation, c.i.), 274 (M^+ + 1); data for (**6**) comparable. (**7**), $\nu_{max.}$ (thin film), 2940, 2850, 1755, and 1730 cm^{-1}; ^1H n.m.r. ($CDCl_3$), δ 0.17 (s, 9H), 1.0—1.2 (m, 16H), 2.53 (m, 1H), 2.91 (m, 1H), 3.08 (d, *J* 8 Hz, 1H), and 3.73 (s, 3H); *m/z* (c.i.), 342 (M^+ +1); data for (**8**) comparable. (**13**), $\nu_{max.}$ (thin film), 2930, 2855, and 1750 cm^{-1}; ^1H n.m.r. ($CDCl_3$), δ 0.13 (s, 9H), 0.88 (d, *J* 5.5 Hz, 3H), 1.1—1.8 (m, 7H), 2.7 (m, 1H), 2.71 (s, 3H), 3.09 (d, *J* 9.5 Hz, 1H), and 3.71 (s, 3H); *m/z* (c.i.), 302 (M^+ + 1). (**14**), $\nu_{max.}$ (thin film), 2930, 2860, 1755, and 1735 cm^{-1}; ^1H n.m.r. ($CDCl_3$), δ 0.18 (s, 9H), 0.90 (d, *J* 6 Hz, 3H), 1.1—2.2 (m, 17H), 2.68 (m, 2H), 3.51 (d, *J* 9 Hz, 1H) and 3.72 (s, 3H); *m/z* (c.i.) 370 (M^+ + 1). (**15**), $\nu_{max.}$ (thin film), 2935, 2865, 1720, 1630, and 1435 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 1.15 (d, *J* 8 Hz, 3H), 1.3—2.8 (m, 7H), 3.76 and 3.87 (each s, ratio 9:1), and 5.2 (br. s) and 6.3a (dd, *J* 1.5 and 3 Hz) (ratio 1:9); data are comparable with literature data for similar compounds (see reference 8).



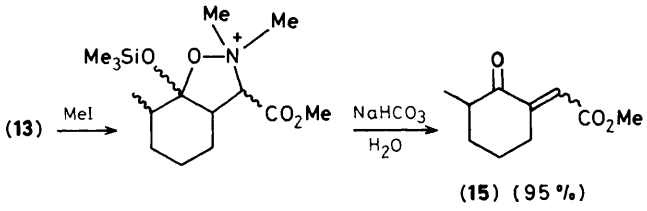
Scheme 1. Yields throughout are for isolated products after purification by flash chromatography.[5] Conditions have not been optimised.



Scheme 2



Scheme 3



Scheme 4

by the two carbonyl absorptions (ester + ketone) in the i.r. spectra of (**7**) and (**8**) [and (**14**)], in contrast to the single such absorption for (**5**) and (**6**) [and (**13**)].

Attempted reaction of the enolates of (**3**) and (**4**) with the nitrones (**9**) and (**10**) [prepared from freshly distilled propionaldehyde and crotonaldehyde, respectively, as for (**1**); i.r. and ^{1}H n.m.r. characterization] under the same conditions resulted in the reisolation of starting materials, presumably owing to the absence of the activating ester group on the nitrone.[6] The reaction with (**11**) [prepared rapidly from phenylhydroxylamine[7] and methyl glyoxalate, as for (**1**); ^{1}H n.m.r. and i.r. characterisation] failed, even with a freshly prepared sample of the nitrone, probably owing to the more rapid dimerisation of this unstable dipolar compound.

The regiospecificity of this reaction was probed by using the kinetic enolate of the unsymmetrical ketone (**12**). Reaction with the nitrones (**1**) and (**2**) followed by silylation gives the corresponding adducts (**13**) and (**14**)§ (Scheme 3), with no evidence (^{1}H n.m.r.) for the regioisomeric adducts. Reaction at −78 °C in tetrahydrofuran (THF), or at −50 °C in Et_2O (in which the nitrones are poorly soluble), followed by silylation, leads only to the trimethylsilyl enol ether of the kinetic enolates of (**12**) and unchanged nitrone. Although (**13**) and (**14**) appear to be single compounds, the stereochemistry cannot confidently be assigned yet.

In a typical procedure, a solution of 2-methylcyclohexanone (**12**) (0.919 mmol) in dry THF (2 ml) was added to a solution of the base prepared from bis(trimethylsilyl)amine (1.07 mmol) and 2.2 M n-butyl-lithium (1.01 mmol) in THF (3 ml) at −78 °C. After 10 min, the solution was warmed to −40 °C, and transferred by cannula to a stirred solution of the nitrone (**1**) (0.962 mmol) in THF (1.5 ml) at −40 °C. The mixture was stirred for 10 min, and then chlorotrimethylsilane (0.5 ml) and triethylamine (0.5 ml) were added. Standard aqueous work-up gave a yellow oil (214.3 mg), which was purified by flash chromatography (silica; methylene chloride–pentane, 1 : 1) to yield (**13**) as a pale yellow oil (52.4 mg, 19%).

The production of these adducts is best viewed as occurring *via* a nucleophilic addition of the ketone enolate to the electrophilic C=N group of the nitrone, followed in the case of the *N*-methyl nitrone by formation of the internal hemiacetal between the ketone carbonyl and the hydroxylamine.

The synthetic utility of these adducts was explored in one case by employing the Hofmann degradation. The isoxazolidine (**13**) was quaternised by heating with an excess of methyl iodide, and was cleaved by vigorous stirring in a two-phase system of methylene chloride and saturated aqueous sodium hydrogen carbonate, to give (**15**)¶ in 95% yield (Scheme 4). The enone ester (**15**) is formally the result of a directed aldol condensation between the ketone (**13**) and methyl glyoxalate,

¶ The enone ester (**15**) was prepared previously from the trimethylsilyl enol ether of (**12**) by reaction with methyl 2-chloro-2-phenylthioacetate with $ZnBr_2$ catalysis, followed by periodate oxidation and elimination, in 56% overall yield (no spectral data were reported): I. Fleming and J. Iqbal, *Tetrahedron Lett.*, 1983, **24**, 327.

which itself is an unsatisfactory reaction for which there are few synthetic alternatives.[8] Our sequence compares not unfavourably with that reported by Fleming.¶ The ability of suitably activated nitrones to act as aldehyde equivalents should find ready application in synthesis.

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