Tandem Intramolecular Michael Addition and 1,3-Dipolar Cycloaddition Reactions of Oximes; Versatile New Carbon–Carbon Bond Forming Methodology

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Oximes undergo intramolecular Michael addition to proximate electronegative alkenes, generating cyclic nitrones which can be trapped inter- and intra-molecularly in 1,3-dipolar cycloaddition reactions taking place either separately or in tandem.

Oximes react with Michael acceptors and dipolarophiles in a two-step process [**(1)** → **(2)** → **(3)**] to give isoxazolidines in good yields.[1] There are four broad variants of the consecutive Michael addition–cycloaddition sequence (Table 1), and examples of classes 1 and 2 have been described.[1]

Classes 3 and 4 provide an easy new route to cyclic nitrones; this can be achieved conceptually *via* either an *exo-trig* (or *exo-dig*) cyclisation **(4)** → **(5)**, or an *endo-trig* (or *endo-dig*) cyclisation **(6)** → **(7)**. The *exo-trig* cyclisation **(4)** → **(5)** is related to, and complements, Gallagher's metal-catalysed allenic oxime cyclisations **(8)** → **(9)**.[2]

Class 3 processes can be carried out stepwise with isolation of the intermediate nitrone, or the tandem sequence can be carried out in a one-pot process. Thus **(10)** reacts with hydroxylamine in water at room temperature over 3.5 h to give the nitrone **(11)** (72%).† When **(11)** is treated in chloroform at room temperature with *N*-methylmaleimide it gives, *via* a diastereofacially specific cycloaddition, a 3 : 1 mixture (100%) of **(12)** and **(13)**. In boiling toluene however, the product is predominantly (> 90%) **(12)**. Proton H_A in **(11)** gives rise to an n.m.r. multiplet at δ 4.27 due to coupling to the two adjacent methylene groups and long-range coupling to the C(Me) group. The coupling of H_A to the ring methylene protons H_B and H_C ($J_{AB} + J_{AC}$) is 14 Hz, showing that H_A is pseudoaxial.

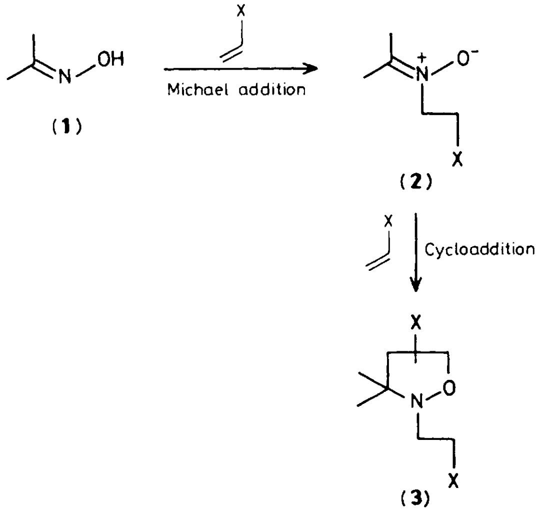
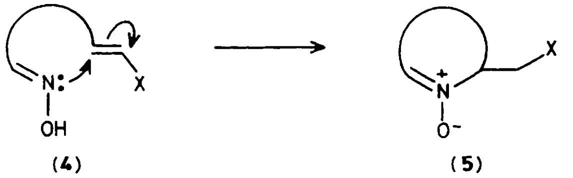
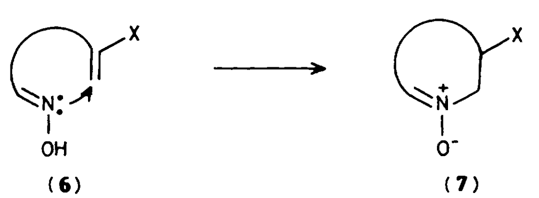


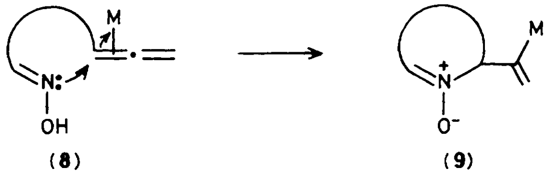
Table 1. Synthetic variants of the two-step tandem oxime cycloaddition process.

Class	Michael addition	Cycloaddition
1	Intermolecular	Intermolecular
2	Intermolecular	Intramolecular
3	Intramolecular	Intermolecular
4	Intramolecular	Intramolecular

The ketone **(14)** similarly reacts with hydroxylamine to give a 3.3 : 1 mixture (58%) of nitrones **(15)** and **(16)**. This mixture on treatment with *N*-methylmaleimide in boiling chloroform







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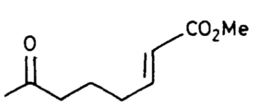
† All new compounds gave satisfactory analytical and spectroscopic data.



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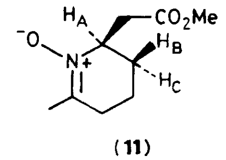

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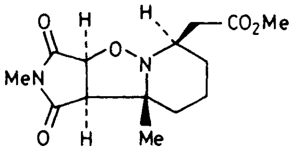

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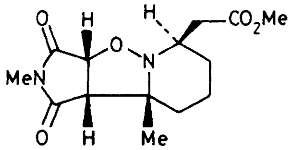

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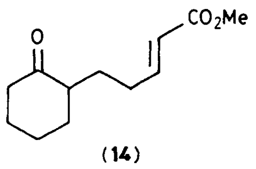

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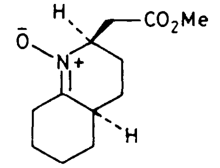

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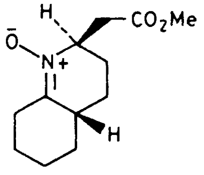

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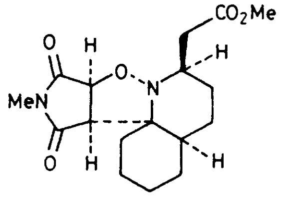

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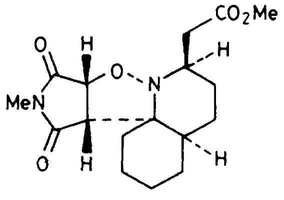

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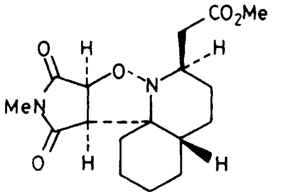

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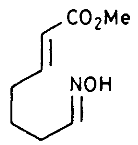

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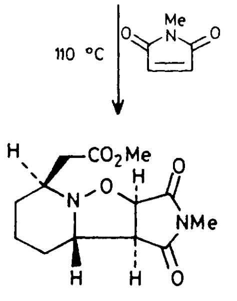

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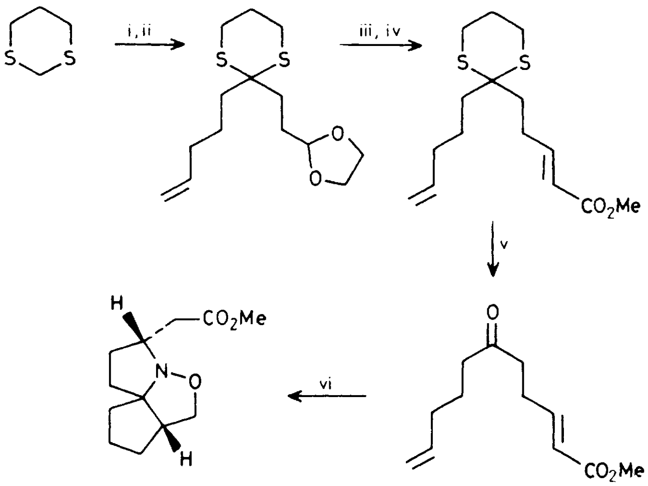
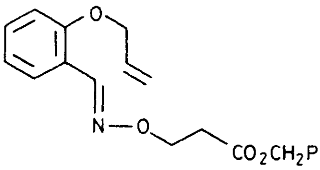


Scheme 1. *Reagents:* i, Bu^{n}Li, THF, −78 °C $H_2C{=}CH[CH_2]_3Br$; ii, Bu^{n}Li, $PO(NMe_2)_3$, −78 °C, 1,3-dioxolan-2-ylethyl bromide; iii, 1M HCl/tetrahydrofuran, 60 °C, 3 h; iv, $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, 25 °C; v, *N*-chlorosuccinimide, $AgNO_3$, aq. MeCN, 15 min; vi, $NH_2OH{\cdot}HCl$, NaOAc, wet xylene, 140 °C, 16 h.



(22)

gives a 4 : 3 : 2 mixture (100%) of (**17**)—(**19**) *via* a diastereofacially specific cycloaddition. The one-pot reaction is exemplified by the reaction of (**20**) with *N*-methylmaleimide in toluene (110 °C; 3 h) to give (**21**) in 90% yield.

The examples involving (**10**), (**14**), and (**20**) generate nitrones *via exo-trig* processes. Examples of nitrone formation by the *endo-trig* Michael addition process (**6**) → (**7**) are under study.

Class 4 reactions are exemplified by the sequence shown in Scheme 1. All steps occur in > 80% yield and in the final cyclisation step (82% yield) it is convenient to generate the oxime *in situ*.

We have briefly explored one further aspect of the mechanism of these tandem Michael addition–1,3-dipolar cycloaddition processes. The possible intervention of an initial *O*-Michael adduct, *e.g.* (**22**), was studied. Heating (**22**) at 140 °C for 24 h in xylene failed to give any cycloadduct. In cases where the oxime is not isolated, the possibility of initial Michael addition of hydroxylamine to the α,β-unsaturated ester/sulphone exists.

The cycloadditions reported herein are illustrative of a large number of such reactions we have carried out. The ready reductive cleavage of the N–O bond of isoxazolidines and the potential for further synthetic manipulations involving the NCH_2CH_2X moiety augur well for application of this methodology to natural product synthesis.

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References

1 P. Armstrong, R. Grigg, and W. Warnock, preceding communication.

2 T. Gallagher, D. Lathburg, and P. Vernon, *Tetrahedron Lett.*, 1986, **27**, 6009.

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