

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 nitron, 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 nitron (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.

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

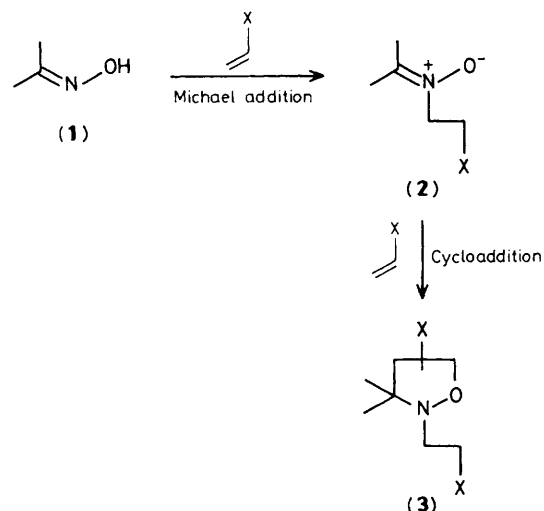
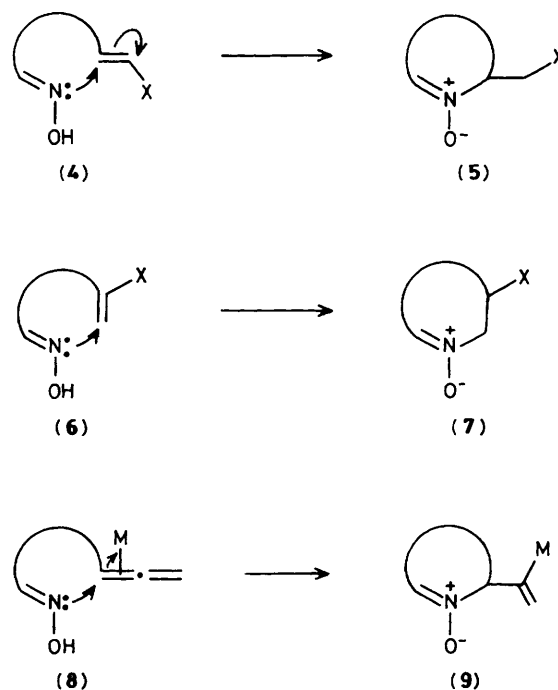
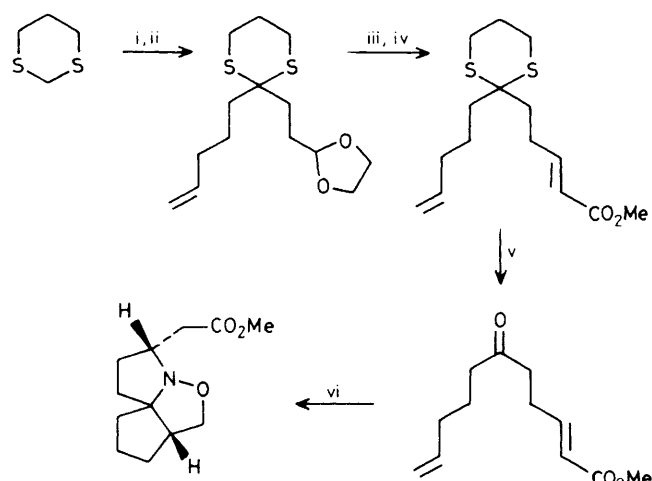
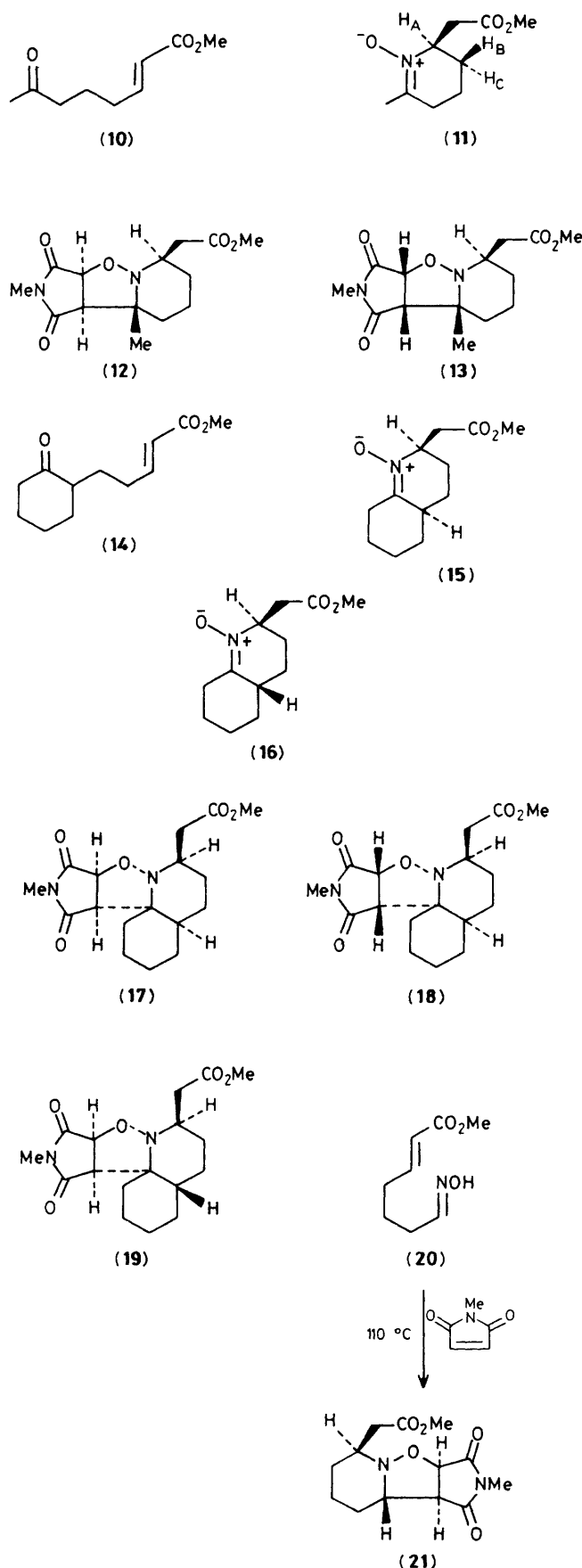


Table 1. Synthetic variants of the two-step tandem oxime cycloaddition process.

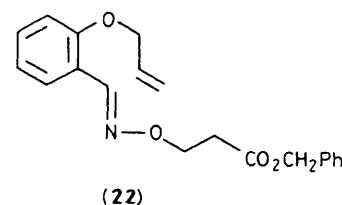
Class	Michael addition	Cycloaddition
1	Intermolecular	Intermolecular
2	Intermolecular	Intramolecular
3	Intramolecular	Intermolecular
4	Intramolecular	Intramolecular



[†] All new compounds gave satisfactory analytical and spectroscopic data.



Scheme 1. Reagents: i, Bu^nLi , THF, -78°C $\text{H}_2\text{C}=\text{CH}(\text{CH}_2)_3\text{Br}$; ii, Bu^nLi , $\text{PO}(\text{NMe}_2)_3$, -78°C , 1,3-dioxolan-2-ylethyl bromide; iii, 1M HCl /tetrahydrofuran, 60°C , 3 h; iv, $\text{Ph}_3\text{P}=\text{CHCO}_2\text{Me}$, CH_2Cl_2 , 25°C ; v, N -chlorosuccinimide, AgNO_3 , aq. MeCN, 15 min; vi, $\text{NH}_2\text{OH}\cdot\text{HCl}$, NaOAc , wet xylene, 140°C , 16 h.



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) \rightarrow (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 $\text{N}-\text{O}$ bond of isoxazolidines and the potential for further synthetic manipulations involving the $\text{NCH}_2\text{CH}_2\text{X}$ moiety augur well for application of this methodology to natural product synthesis.

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References

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