Cycloaddition Reactions of Oximes; Powerful New Carbon–Carbon Bond Forming Methodology

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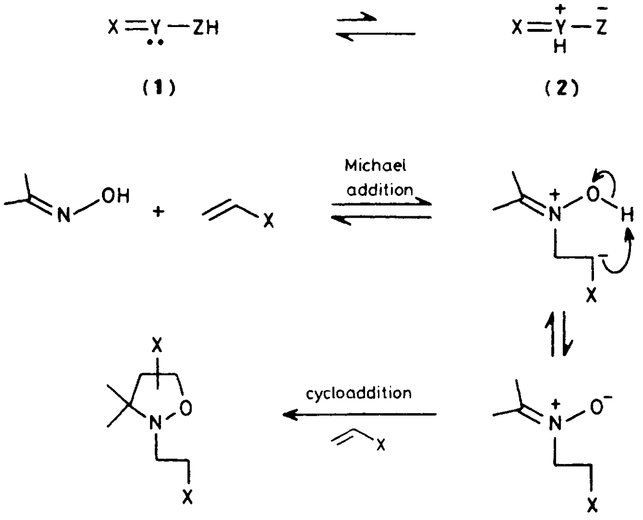
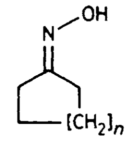
Oximes react with Michael acceptors and dipolarophiles, usually regio- and stereo-specifically, *via* a tandem Michael addition–1,3-dipolar cycloaddition process, to give isoxazolidines in good yield; analysis of the tandem process identifies four broad synthetic variants, and examples of those involving initial intermolecular Michael addition are given.

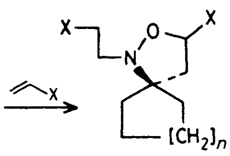
Our discovery of the new general prototropic route to 1,3-dipoles [(**1**) $\rightleftharpoons$ (**2**)] provides a simple approach to the synthesis of a wide variety of heterocyclic compounds by trapping the 1,3-dipole (**2**) in cycloaddition reactions.[1] We have previously established that the process (**1**) $\rightleftharpoons$ (**2**) occurs in imines, hydrazones,[2] and oximes,[3] although oximes require special structural features to encourage prototropy and generally prefer to react as shown in Scheme 1.[4]



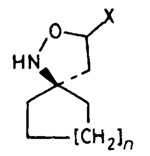
Scheme 1. X = electron-withdrawing group.



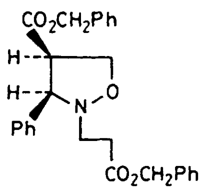
(**3**) **a**; *n* = 1
b; *n* = 2



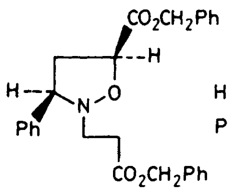
(**4**)



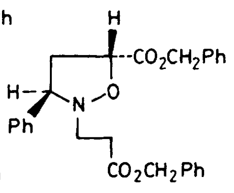
(**5**)



(**6**)



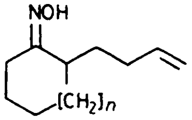
(**7**)



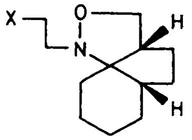
(**8**)

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

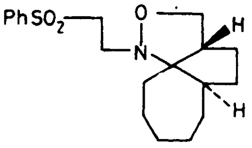
Class	Michael addition	Cycloaddition
1	Intermolecular	Intermolecular
2	Intermolecular	Intramolecular
3	Intramolecular	Intermolecular
4	Intramolecular	Intramolecular



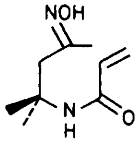
(9) a; *n* = 1
b; *n* = 2



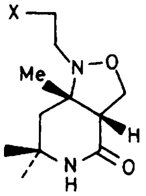
(10) a; X = SO_2Ph
b; X = CO_2CH_2Ph



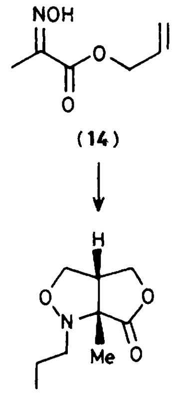
(11)



(12)

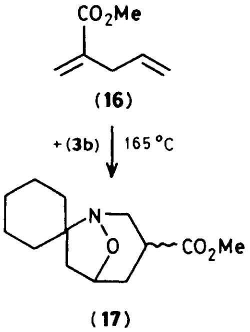


(13)
X = SO_2Ph or CO_2CH_2Ph

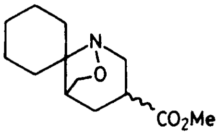


(15)

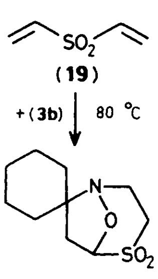
Thus our earlier studies showed that the lowest-energy path in simple oximes involves consecutive Michael addition and cycloaddition. The reaction produces isoxazolidines in high yield but as a mixture of regio- and stereo-isomers,[4] and this made the reaction unattractive for most synthetic applications. However, more recent work has resulted in a better understanding of the reaction and we have now identified conditions, solvents, Michael acceptors, and dipolarophiles that result in excellent yields of single products in most cases, *i.e.* regio- and stereo-specific processes. Examination of Scheme 1 indicates that four broad synthetic variants should be achievable; these are listed in Table 1. The variants will depend for their existence on the ability of oximes to discriminate chemospecifically between Michael acceptor and dipolarophile.



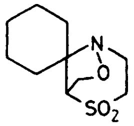
(17)



(18)



(20)



(21)

The problem of chemospecific discrimination between Michael acceptor and dipolarophile is readily solved and the oxime cycloaddition reaction now provides powerful and versatile new carbon–carbon bond forming methodology. Class 1 and 2 reactions are considered in this communication and class 3 and 4 reactions in the accompanying communication.[5]

Class 1 reactions were discussed in our previous paper,[4] but at that time we were unable to achieve regio- and stereospecific processes. However, we now report that oximes of cyclic ketones react with 2 mol. equiv. of an electronegative alkene (benzyl acrylate or phenyl vinyl sulphone) in xylene at 140 °C to give single adducts in excellent yield (>75%), *e.g.* (**3a,b**) → (**4a,b**; X = CO_2CH_2Ph or SO_2Ph).† By-products include small amounts of *O*-Michael adduct and retro-Michael cycloadduct (**5**). The regiospecificity observed in these cases contrasts sharply with the lack of regiospecificity in the case of acyclic oximes; *e.g.* benzaldehyde oxime gives a 7:5:4 mixture of (**6**), (**7**), and (**8**) under the same conditions,‡ presumably owing to the steric influence of the carbocyclic ring in (**3**).

Class 2 reactions (Table 1) can be achieved in two distinct ways, making this class particularly valuable in synthesis. Thus the dipolarophile can be incorporated into the oxime component; *e.g.* (**9a,b**) → (**10**) and (**11**), respectively, in quantitative yield on heating in xylene (140 °C) with the appropriate Michael acceptor. Similarly (**12**) gives (**13**) in quantitative yield even though the oxime (**12**) is a 65:35 mixture of stereoisomers, and (**14**) gives (**15**) in 71% isolated yield. The adduct (**15**) is a masked α,α-disubstituted α-amino acid; this general approach should provide a range of such compounds.

An alternative approach to class 2 reactions is to incorporate the Michael acceptor and dipolarophile into the same molecule. Thus 1,ω-dienes of various types provide a wide spectrum of possibilities. Two typical cases are the reactions of (**3b**) with (**16**) (mesitylene, 165 °C, 4 d) to give (56%) a 2:1

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† All new compounds gave satisfactory analytical and spectroscopic data.

‡ Stereochemistry of the compounds reported herein is assigned on the basis of nuclear Overhauser effects.

mixture of (**17**) and (**18**), and with (**19**) on heating in acetonitrile at 80 °C to give a 1.3 : 1 mixture of (**20**) and (**21**).

These reactions are representative of a large number of such cycloadditions we have carried out. Further aspects and applications of these reactions are under investigation.

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References

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5 P. Armstrong, R. Grigg, S. Surendrakumar, and W. Warnock, following communication.