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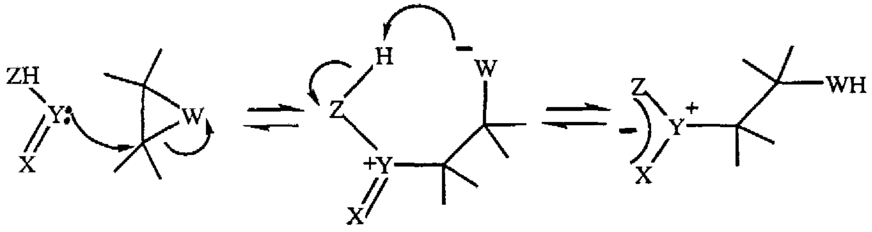
TANDEM NUCLEOPHILIC SUBSTITUTION - 1,3 DIPOLAR CYCLOADDITION REACTIONS OF OXIMES WITH EPOXIDES AND DIPOLAROPHILES.[1]

Ronald Grigg* and Jasothara Markandu

School of Chemistry, University of Leeds, Leeds LS2 9JT.

Abstract Regiospecific nucleophilic substitution reactions involving attack of the nitrogen atom of oximes on epoxides are used to generate nitrones which are then trapped in 1,3-dipolar cycloaddition reactions. These tandem processes are shown to be flexible and to have wide synthetic scope for the construction of complex molecular frameworks.

Recently we described a new tandem Michael addition - 1,3-dipolar cycloaddition process in oximes.[2] This tandem process is a powerful and flexible method for the construction of complex molecular frameworks[3] and prompted efforts to develop other related processes involving X = Y-ZH systems. Tandem processes involving 1,3-dipoles generated from X=Y-ZH systems can be envisgaged that involve an initial Michael addition *via* the Y lone pair,[2] the ZH group,[4,5] or the X atom[5]. An analogous series of reactions involving nucleophilic substitution *via* the Y lone pair, the ZH group, or the X atom offers an alternative approach to 1,3-dipoles. A general process that attracted our attention as a source of 1,3-dipoles involves nucleophilic attack on 3-membered heterocycles via the Y lone pair of an X=Y-ZH system and is shown in the scheme.



Scheme

Our initial studies have involved oximes as prototypical X=Y-ZH systems and epoxides (W=O) have proved useful substrates in such reactions. The resultant tandem process has four broad synthetic variants (Table) analogous to those discussed earlier for the tandem Michael addition - 1,3-dipolar cycloaddition process,[2] and we have demonstrated examples of all four classes. Class 1 processes are illustrated by the reaction (THF, LiCl, 25°C, 18h) of anti-benzoaldoxime with epoxide (1) to give the trans-oxazolidine (2) (70%). Reaction of (2) with N-methylmaleimide (NMM) (xylene, 140°C, 45 min) affords a 1 : 1.8 mixture of (3) and (4) each of which comprises a 1 : 1 mixture of two diastereomers in 90% yield.

Table Synthetic Variants of the Epoxide Opening - 1,3-Dipolar Cycloaddition Process

Class	***Epoxide Opening***	***Cycloaddition***
1	intermolecular	intermolecular
2	intermolecular	intramolecular
3	intramolecular	intermolecular
4	intramolecular	intramolecular

An example of a Class 2 process is provided by the lithium chloride promoted reaction (THF, 60°C, 16 h) of the δ-alkenyl oxime (5) with the epoxide (1) to give (6) as a 1 : 1 mixture of diasteromers in 60% yield. Thus ring opening of the epoxide is regiospecific. Appropriate blank experiments[6] have established that the process does not proceed *via* 1,2-prototropy,[7] intramolecular cycloaddition, and subsequent nucleophilic attack of the resulting oxazolidine on the epoxide.

Typical examples of Class 3 processes are provided by the reaction (xylene, 140°C, 1 h) of the oxime (7)[8] with NMM to give a 6 : 1 mixture of exo (9)- and endo (10)-cycloadducts in 80% yield. The oxime (7) generates the nitrone (8) *via* a 6-exo tet opening of the epoxide moiety. An analogous reaction (xylene, 140°C, 8 h) of (7) with styrene affords a 3 : 1 mixture of (11a) and (11b) in 50% yield. Class 4 processes are illustrated by the conversion of (12) into (13) in 90% yield on heating in xylene at 140°C for 6 h. The same reaction occurs in chloroform at 60°C over 22 h.

Generation of the intermediate nitrone (8) in the Class 3 and 4 examples discussed above recalls the formation of bicyclic ketals and aminals by acid catalysed ring opening of δ, ε-epoxy ketones [9] and imines.[10] Kliegel observed that the base catalysed reaction of oximes with epoxides gave 3-6% of the corresponding N-hydroxyethyl nitrones. He further sought evidence for ring-chain isomerism of such nitrones with N-hydroxyoxazolidines.[12]

Further exemplification and extension of these processes are under investigation.

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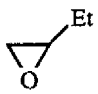
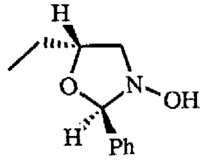
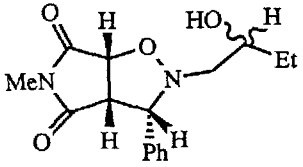


(1)



(2)



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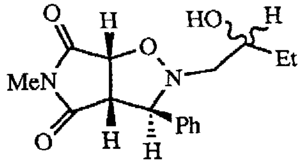

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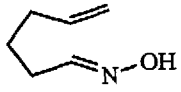
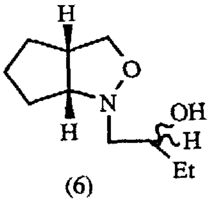


(5)



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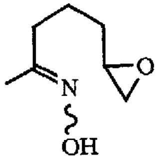

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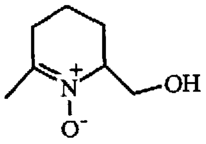

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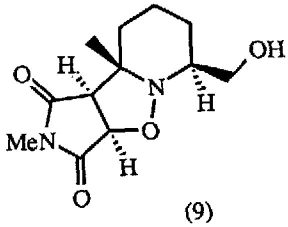

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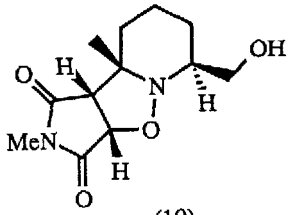

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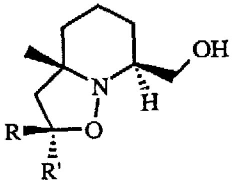
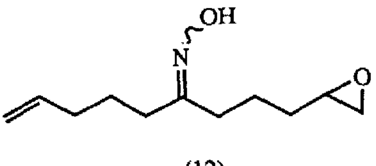


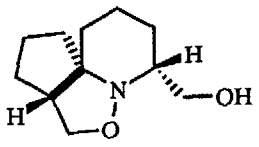
(11)

a. R=Ph, R'=H

b. R=H, R'=Ph



(12)



(13)

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5. Michael addition or nucleophilic substitution *via* the Z or X atoms of an X=Y-ZH system could involve a lone pair of electrons on Z or X, if present, or proceed *via* the ambident anion $X = Y\text{-}\bar{Z} \longleftrightarrow \bar{X}\text{-}Y{=}Z$. In cases where reaction is initiated by the Z or X atoms formation of the 1,3-dipole requires a subsequent 1,2-prototropic shift e.g. see ref. 4.
6. e.g. (5) is recovered unchanged on heating in xylene for 24 h.
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