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Chemoselective Formation of Symmetrically linked Bisisoxazole Units: Steps toward Isoxazoline/Isoxazolidine Based Macrocycles

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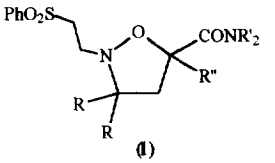
Abstract: Symmetrically linked bisisoxazole derivatives can be formed from a chemoselective one-pot three component reaction between oximes, dipole generating and dipole trapping components. The use of bifunctional dipole generating moieties affords bisisoxazolines (**11**), linked through their *N*-atoms. The employment of bifunctional dipolarophilic agents leads to bisisoxazolidines (**3** and **4**) linked *via* their *C*-5 carbon atoms. Copyright © 1996 Elsevier Science Ltd

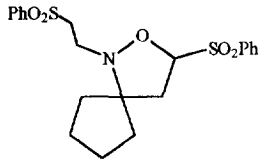
The first example of the generation of macrocycles using quadruple cycloadditions as cornerstones was recently reported. Multiple cycloadditions between bifunctional dipoles (nitrile oxides) and bifunctional dipolarophiles (diacrylates or divinyl ethers) gave [1+1] or [2+2] crown ether type macrocycles.[1] Whilst the potential of multiple cycloadditions for the construction of large molecular frameworks has not been widely illustrated [2] there are numerous simple examples of double 1,3-dipolar cycloaddition reactions employing both bisdipoles and bisdipolarophiles. Dinitrile oxides, dinitrones and dinitrile imines [3] react with various dipolarophiles furnishing the corresponding bisheterocycles in a manner closely related to that which affords the monocyclic unit (chemical yields vary greatly). The range of bifunctional dipolarophiles used in double cycloaddition reactions include many dienes [4] (1,2-, 1,3 -, 1,4-dienes *etc.*), 1,3-diynes [5] and 1,3-enynes.[6]

In this paper we report that by employing bifunctional starting materials (bifunctional dipole generating components or bisdipolarophiles) in the tandem oxime-nitrone-cycloaddition sequence [7] symmetrically linked bisisoxazole derivatives can be attained. The synthetic strategy designed to lead to these twin heterocyclic units is outlined in Scheme 1; two routes are feasible, the key step in path A involves an *in situ* formation of a bisnitrone from reaction between two moles of oxime and a bifunctional dipole generating component whilst path B entails a bifunctional dipolarophile in a cycloaddition reaction with two moles of an *in situ* generated nitrone. Clearly the success of the proposal depends on the chemoselectivity of the one-pot reaction; the oxime must be able to discriminate between the dipole generating component and the dipolarophile.

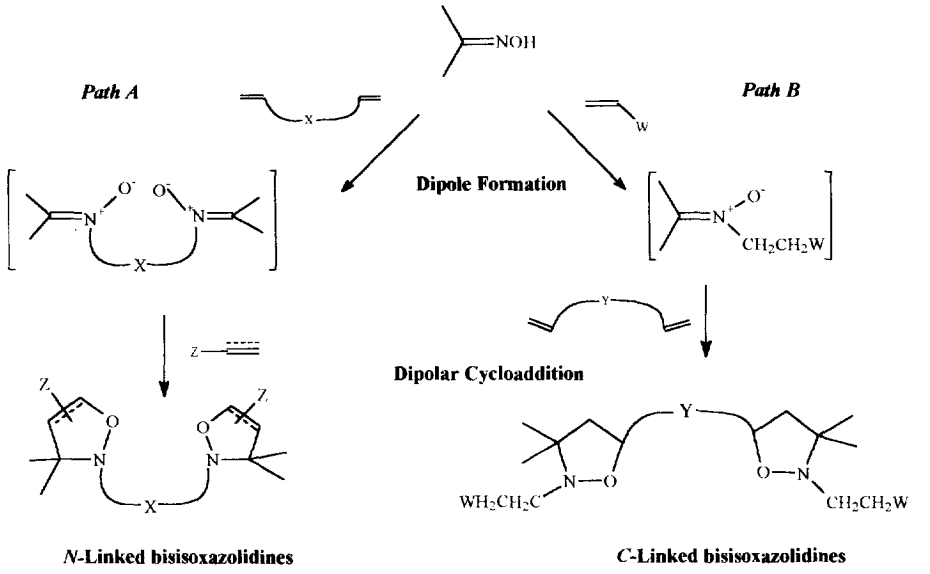
When oximes were allowed to react in one-pot with equimolar quantities of phenyl vinyl sulphone and acrylamides (toluene, 110 °C) the dominant reaction product was the unsymmetrically substituted adduct (**1**)



(**1**)
R = Me, R,R = cC_5H_{10}, cC_4H_8
R', R" = H, Me

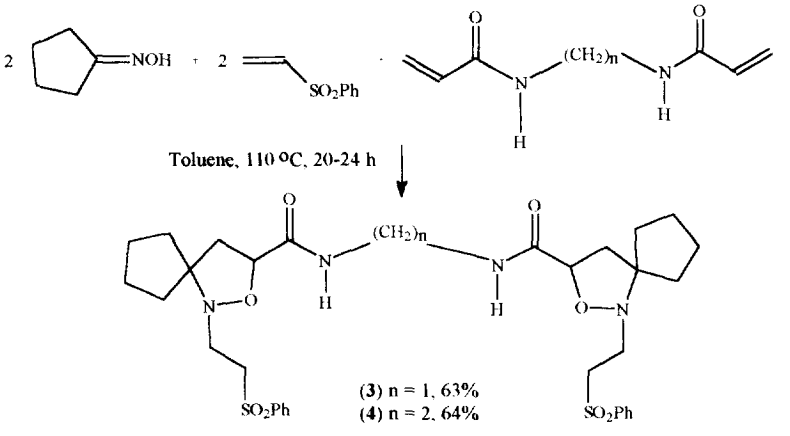


(**2**)



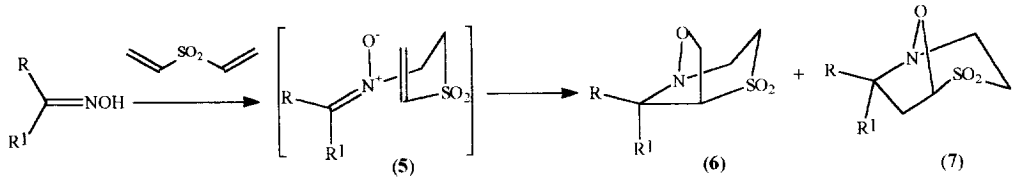
Scheme 1

(57-73%). For this reason we explored the dipolarophilic activity of *N,N'*-methylenebisacrylamide and it was allowed to react in one-pot with cyclopentanone oxime and phenyl vinyl sulphone in a 1:2:2 molar ratio. Analysis of the crude reaction mixture indicated the desired bisheterocycle (**3**) was the main product of reaction, also present was the 2:1 olefin/oxime adduct (**2**,18%). The obtaintion of (**3**) in 63% yield indicated the reaction proceeded with a high degree of chemoselectivity and that *N,N'*-methylenebisacrylamide functioned well as a bisdipolarophile, the yield for each cycloaddition step was ~80%; further (**3**) is formed in a regio- and stereospecific manner with each cycloaddition reaction taking place to give the 5-substituted isomer. Examination of the ^{1}H- and ^{13}C-NMR spectral data for (**3**) reveals only half the expected number of signals, this observation is consistent with the highly symmetrical nature of the adduct.



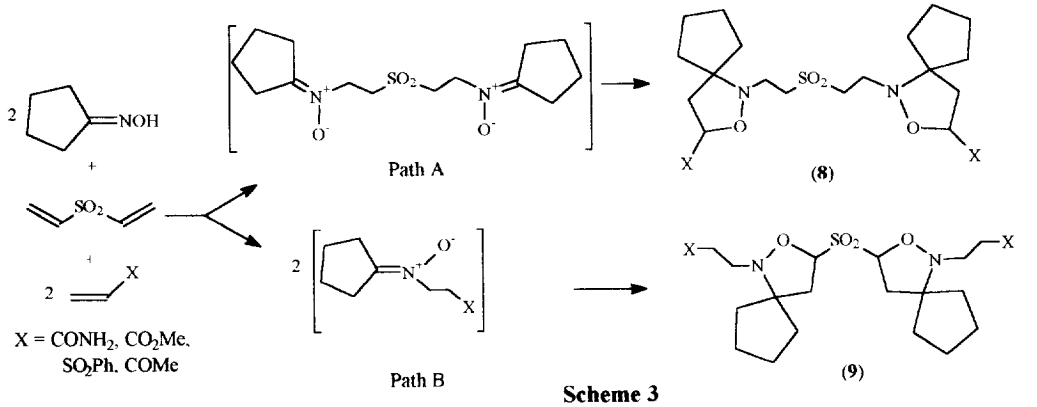
The next highest homologue *N,N'*-ethylenebisacrylamide participated similarly in this reaction scheme and the bisisoxazolidine (**4**) was formed in 64% yield together with the 2:1 phenyl vinyl sulphone-oxime adduct (**2**,15%).

Divinyl sulphone reacts readily with oximes to give the adducts (**6**) and (**7**).[8] The formation of the regioisomeric adducts is by way of a tandem intermolecular 1,3-azaprotio cyclotransfer-intramolecular cycloaddition sequence (Scheme 2). Divinyl sulphone thus has the potential to behave either as a bifunctional dipole generating component or as a bisdipolarophile in the current reaction scheme.



Scheme 2

We envisaged that upon reaction with an oxime in the presence of a carefully chosen dipolarophile that divinyl sulphone may behave as a bisdipole generating agent resulting in the formation of *N*-linked bisisoxazolidines (Scheme 3, path A). On the other hand if the third reaction component were a more potent dipole generator than divinyl sulphone then the latter may be encouraged to behave as a bisdipolarophile, in such cases *C*-linked isoxazolidines would result (Scheme 3, path B).

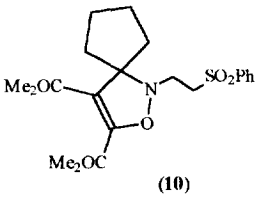


Scheme 3

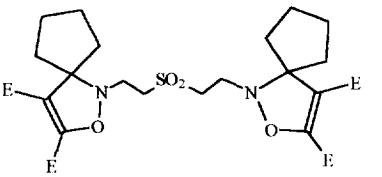
When one mole equivalent of divinyl sulphone was allowed to react with two moles of each of cyclopentanone oxime and one of a range of olefinic components (ranging from moderately to highly electron deficient) the only products of reaction were the 1:1 adducts (**6**) and (**7**) together with the corresponding 2:1 olefin/oxime adducts. There was no trace of any bisheterocyclic product, *i.e.* neither path A nor path B (Scheme 3) could be exemplified.

We have observed that in an oxime-olefin-acetylene one-pot reaction the activated acetylenes (methyl propiolate or dimethyl acetylenedicarboxylate) behaved only as dipolarophiles and the olefins (phenyl vinyl sulphone, methyl acrylate or methyl vinyl ketone) only as dipole generating moieties. In this way unsymmmetrically substituted spirocyclic isoxazolines such as (**10**) could be generated, yields were essentially quantitative Consequently an oxime-divinyl sulphone-dimethyl acetylenedicarboxylate combination was allowed to react in boiling toluene (110 °C, 20 h). The dominant product arising from this reaction was the desired 1:2:2 bisisoxazole (**11**, 51%), also present were minor amounts of the 1:1 oxime/divinyl sulphone adducts (**6**, 8%) and (**7**, 16%). These results clearly indicate that dimethyl acetylenedicarboxylate is the only

dipolarophile able to compete with the intramolecular cycloaddition of (**5**) and that divinyl sulphone is too reactive to be generally useful in this reaction which requires such delicate balance of chemoreactivity.



(10)



(11)
E = CO_2Me

In conclusion these results illustrate for the first time the preparation of symmetrically linked bisisoxazole derivatives formed in a one-pot reaction from oxime precursors. Bisisoxazolines linked *via* their *N*-atoms may be formed by employing a bifunctional dipole generating component (divinyl sulphone) whilst the use of a bisdipolarophile (*N,N'*-(m)ethylenebisacrylamide) allows the formation of bisisoxazolidines linked through their *C-5* carbon atoms. The chemoselectivity and the regio- and stereochemical integrity of this one-pot reaction makes construction of the highly functionalised bisheterocyclic units akin to molecular meccano. Work continues in this area.

Note 1% w/w Hydroquinone was added to all thermal reactions to prevent olefin polymerisation

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