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Stereoselective Cycloaddition of Nitrile Oxides to 4-Vinyl-Oxazolines and -Oxazolidines

Ewan C. Boyd and R. Michael Paton*

Department of Chemistry, The University of Edinburgh, West Mains Road, Edinburgh, EH9 3JJ, UK

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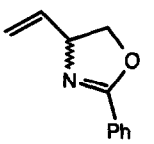
Abstract: Cycloaddition of nitrile oxides to 4-vinyl-2-oxazoline **1** and to 4-vinyloxazolidine **2** afford diastereomeric mixtures of 2-isoxazolines in which the *erythro* product predominates (32-64% d.e.). In contrast, the corresponding reactions with acyclic analogue **3** favoured the *threo*-adducts and were less selective (8-20% d.e.).

1,3-Dipolar cycloaddition of nitrile oxides to alkenes is an important step in the nitrile oxide/isoxazoline route[1] to natural products and the factors influencing the stereoselectivity of this process have therefore been examined in some detail. Particular attention has been paid to the effect of allylic substituents, and high levels of diastereoselectivity have been observed for cycloadditions to various chiral allyl ethers.[2,3] π–Facial selectivities range from 56% to 93% d.e. and in each case adducts with *erythro* stereochemistry predominate. In contrast, the directing effect of allylic nitrogen substituents is less well understood. Some examples of nitrile oxide cycloadditions to vinyl-glycines, 2-aminobut-3-en-1-ol derivatives and related dipolarophiles have been reported,[4-7] but in general selectivities were low and less predictable (d.e. -32% to +42%). With a view to exploiting vinyl-glycine derivatives as chiral source materials for the synthesis of natural products and analogues including amino-sugars we have examined the reactions of several nitrile oxides with *RS*-2-phenyl-4-vinyl-2-oxazoline **1** and *R*-3-(*t*-butoxycarbonyl)-2,2-dimethyl-4-vinyloxazolidine **2**. We now report that, using benzonitrile oxide **4a**, ethoxycarbonylformonitrile oxide **4b** and bromoformonitrile oxide **4c** as representative examples, higher levels of selectivity are obtained for these cyclic compounds than for the acyclic analogue *R*-2-(*t*-butoxycarbonylamino)but-3-en-1-ol **3**.



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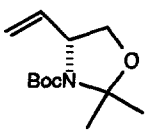

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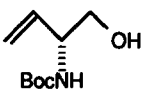

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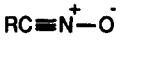
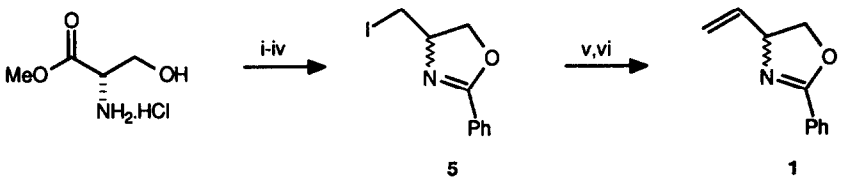


4a R = Ph
b R = EtO_2C
c R = Br

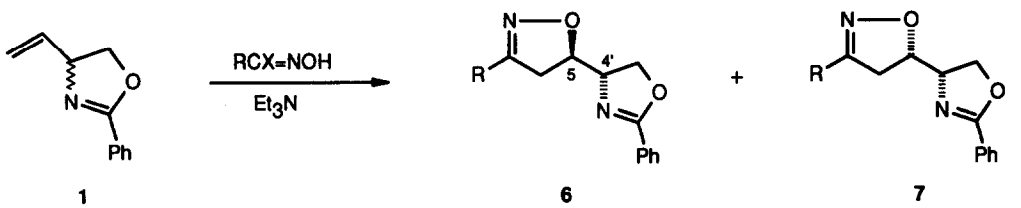
Racemic vinyloxazoline **1** was prepared from *S*-serine methyl ester hydrochloride by conversion of the β–aminoalcohol to the 2-oxazoline, reduction of the ester and halogenation of the resulting alcohol to afford iodomethyl compound **5**, followed by Wittig olefination of its phosphonium derivative with formaldehyde as illustrated in Scheme 1. In order to minimise the formation of furazan *N*-oxide (furoxan) dimers the nitrile oxides were generated *in situ* from the corresponding hydroximoyl halides by dehydrohalogenation with triethylamine.[8]



Scheme 1 *Reagents:* (i) PhC(OEt)=NH; (ii) $LiAlH_4$; (iii) $SOBr_2$; (iv) NaI, acetone; (v) Ph_3P; (vi) BuLi, H_2C=O

Reaction of benzonitrile oxide **4a**, generated at room temperature by slow addition of triethylamine to a solution of benzohydroximoyl chloride[9] and alkene **1** (1.1:1) in diethyl ether, afforded a diastereomeric mixture of 2-isoxazolines **6a** and **7a** in 88% combined yield. The products were separated by chromatography and the structure of the major adduct established by X-ray crystallography[10,11] as **6a** for which there is an *erthyro* relationship between the new asymmetric centre at C(5) of the isoxazoline ring and the adjacent C(4') of the oxazoline. The isomer ratio **6a**:**7a** = 76:24 was determined by HPLC analysis of the reaction mixture.

Cycloaddition to alkene **1** of ethoxycarbonylformonitrile oxide **4b**, generated similarly from ethyl chloro-oximinoacetate,[12] yielded an 82:18 mixture isoxazolines **6b** and **7b** in 65% yield. The structures of the individual isomers were assigned by correlation of their physical properties and NMR spectra with those of the benzonitrile oxide adducts. The diastereoselectivity observed in this case (64% d.e.) is the largest recorded for cycloaddition to a vinyl group bearing an allylic nitrogen substituent. The corresponding reaction with bromoformonitrile oxide **4c**,[6] formed by treatment of dibromoformaldoxime with triethylamine, proved to be the least selective yielding isoxazolines **6c** and **7c** in the ratio 69:31.

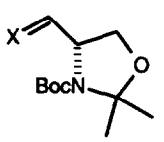


Scheme 2[11] (**a**, R = Ph; **b**, R = EtO_2C; **c**, R = Br)

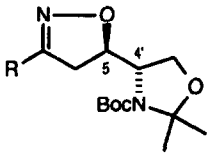
S-Serine methyl ester also provided the source of chiral vinyloxazolidine **2** and its partially deprotected derivative **3**. Conversion to known aldehyde **8**,[13] followed by treatment with methyltriphenylphosphonium iodide and potassium *t*-butoxide (1:1) yielded alkene **2** with no loss of optical purity.[14] Subsequent deacetonisation using *p*-toluenesulphonic acid in methanol afforded **3**.

The procedure used for the cycloadditions to these dipolarophiles was similar to that described above for vinyloxazoline **1**. Benzonitrile oxide reacted readily with vinyloxazolidine **2** to give an inseparable mixture (66:34 by ^{1}H-NMR) of isoxazoline cycloadducts **9a** and **10a** in 85% yield. Treatment of the reaction mixture with trifluoroacetic acid and water yielded β–amino-alcohols **11a** and **12a** which also proved to be inseparable.

However, partial deprotection (TsOH/MeOH) afforded a mixture from which were isolated *N-t*-butoxycarbonyl derivatives **13a** (51%) and **14a** (29%). The configurations of the asymmetric centres in the products were established by reacting amino-alcohol **12a**, formed by hydrolysis of **13a**, with ethyl benzimidate and comparison of the resulting 2-oxazoline with compounds **6a** and **7a** for which the structures had previously been assigned unambiguously. This showed that the minor product derived from vinyloxazolidine **2** has *threo* structure **10a**; the major isomer therefore has *erythro* stereochemistry **9a**. Nitrile oxides **4b** and **4c** reacted similarly with alkene **2** to give, respectively, isoxazolines **9b** and **10b** (68:32, 89%), and **9c** and **10c** (65:35, 87%). *Erythro* products are therefore favoured for cycloadditions of nitrile oxides to both cyclic dipolarophiles **1** and **2**.



8 X = O
2 X = CH_2



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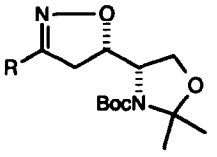

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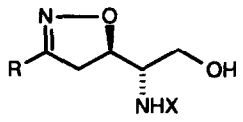
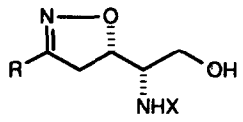
In contrast, the corresponding cycloadditions to acyclic dipolarophile **3** under similar conditions proceeded in lower yield and with reversed π–facial selectivity. Nitrile oxides **4a** and **4b** yielded, respectively, isoxazolines **13a** (28%) and **14a** (43%), and **13b** (31%) and **14b** (36%). In both cases *threo* adducts predominate. A similar preference for *threo* products has been reported[2,3] for cycloadditions to allylic alcohols and for the reactions of **4c** and benzenesulphonylformonitrile oxide ($PhSO_2CNO$) to *N*-protected 2-aminobut-3-en-1-ols.[5]

The π–facial selectivities observed for reaction of nitrile oxides with dipolarophiles **1** and **2** can be rationalised by adapting the "inside-alkoxy group" hypothesis proposed by Houk *et al*[2] for the corresponding cycloaddition to chiral allyl ethers. The preferred formation of *erythro* adduct **6** from alkene **1** (and **9** from **2**) is consistent with product formation *via* the transition state which locates the nitrogen substituent in the "inside" position, the hydrogen outside and the -CH_2- moiety *anti* (Figure 1). The reduced and reversed selectivity found for aminobutenol analogue **3** is attributed to hydrogen bonding interaction between the oxygen of the nitrile oxide and the free hydroxyl in the dipolarophile.[2]



11 X = H
13 X = Boc



12 X = H
14 X = Boc

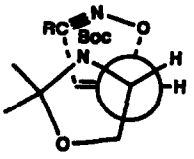
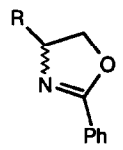
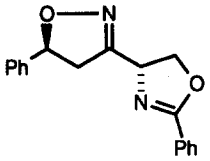


Figure 1

The effect of incorporating an asymmetric centre in the nitrile oxide component rather than the dipolarophile was also examined. Cycloaddition to styrene of oxazoline-nitrile oxide **15**, generated by dehydration of nitromethyl compound **16** using tolylene diisocyanate and triethylamine,[15] afforded a 55:45 mixture of 5-phenylisoxazolines **17** and **18** in 59% yield.[11] The much lower selectivity for this reaction is attributed to the greater distance between the asymmetric centre and the prochiral =CH of the dipolarophile.



15 R = CNO
16 R = CH_2NO_2



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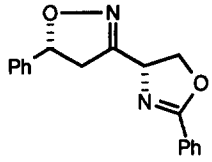

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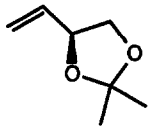

19

In summary, the degree of diastereoselectivity in favour of *erythro*-products observed for cycloaddition of nitrile oxides to alkenes **1** and **2** is comparable with those reported[16] for allyl ethers such as 1,3-dioxolane analogue **19**, whereas there is a slight preference for *threo*-adduct formation for the corresponding reactions with open-chain but-3-en-1-ol derivative **3**.

Acknowledgement We thank Castrol Limited for a research grant.

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