Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 2283–2291

Investigations of regio- and stereoselectivities in the synthesis of cytotoxic isoxazolidines through 1,3-dipolar cycloadditions of nitrones to dipolarophiles bearing an allylic oxygen

Rajinder Singh,[a] Surinderjit Singh Bhella,[a] A. K. Sexana,[b] M. Shanmugavel,[b] Abdul Faruk[a] and M. P. S. Ishar[a,*]

[a]*Bio-organic and Photochemistry Laboratory, Department of Pharmaceutical Sciences, Guru Nanak Dev University, Amritsar 143 005, Punjab, India*
[b]*Pharmacology Division, Regional Research Laboratory, Jammu 184 001, J & K, India*

Received 1 June 2006; revised 21 December 2006; accepted 21 December 2006
Available online 27 December 2006

Abstract—Regio- and stereoselectivities in cycloadditions of nitrones to dipolarophiles bearing an allylic oxygen, which furnishes substituted-isoxazolidine analogs of the furanose ring of nucleosides, have been investigated. Although the obtained regioselectivities are anticipated, a rationalization of the preferred formation of *endo*-cycloadducts necessitates the involvement of an allylic oxygen in secondary interaction. The obtained isoxazolidines display cytotoxic activities against a number of human cancer cell lines.

1. Introduction

There has been an ever-increasing quest for modified nucleosides due to their potential applications in antiviral and anticancer therapies.[1] In a recent approach to modified nucleosides, the furanose ring has been replaced by other heterocyclic analogs.[2] Among these N and O containing five-membered heterocycles, isoxazolidines, and isoxazoline derivatives have emerged as important candidates, and have been shown to display useful anticancer and antiviral properties.[3] It is pertinent to mention here that substituted isoxazolidines have been known to display cytotoxicity as in the case of alkaloids such as pyrinodemin-A and isoxazolidinium salts employed in the therapy of malignant tumors (Fig. 1).[4]

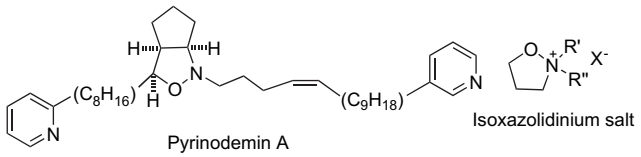
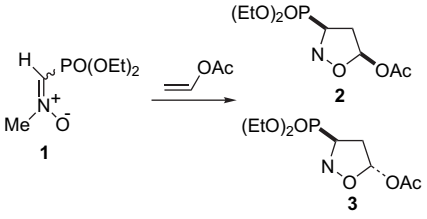


Figure 1.

Consequently, synthetic studies on isoxazolidines have drawn considerable attention and 1,3-dipolar cycloadditions of nitrones afford the most straightforward route to isoxazolidines. For instance, in one of the approaches, nitrophosphonate **1** has been reacted with vinyl acetate to obtain a mixture of epimeric isoxazolidines **2** and **3** (Scheme 1), which have been utilized as precursors to the synthesis of reverse-transcriptase inhibitors.[1e]



Scheme 1.

The formation of epimeric products is the outcome of two different approaches of the dipole to the dipolarophile. In the above example (Scheme 1), with the nitrone reacting in its most stable *Z*-form, the cis-product **2** arises from an *exo*-transition state and the trans-product **3** from an *endo*-transition state; the *exo*-adduct **2** was reported to be the major product.[1e] Similar predominance of an *exo*-adduct has also been reported in the addition of α-(2-pyridyl)-*N*-benzylnitrone to allyl alcohol.[2c] A variety of secondary factors have

Keywords: Cycloadditions; Nitrone; Stereoselectivities; Secondary interactions; Isoxazolidines; Anticancer activity.
* Corresponding author. Tel.: +91 183 2258802x3321; fax: +91 183 2258820; e-mail: mpsishar@yahoo.com

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.12.076

been invoked to explain stereoselectivities in 1,3-dipolar cycloadditions.[5] The predominant occurrence of *endo* selectivity in the cycloaddition reactions has generally been attributed to the role of secondary orbital interactions (SOI) or some secondary interactions (SI), however, contribution of such interactions is disputed and recently it has been contended that the existence of such SOI/SI is negated by closed-shell repulsions.[5a,c] However, more recent calculations favor the existence of such interactions in controlling stereoselectivity.[6] Consequently, the importance of secondary interactions in controlling stereoselectivities is far from settled. Recently, the involvement of oxygen atoms at allylic and homo-allylic positions in secondary interactions with LUMO-dipole has been reported to control the stereochemical outcome of nitrone addition to such dipolarophiles leading to the predominance of *endo*-adducts,[5d,e] which is in contradiction with the stereoselectivities reported in the nitrone cycloadditions discussed above.[1e,2c] We have investigated stereoselectivities in 1,3-dipolar cycloadditions of a variety of α-aryl-*N*-phenylnitrones with a number of dipolarophiles possessing oxygen at the allylic position so as to investigate the proposed involvement of allylic oxygen in secondary interactions with nitrogen of the nitrone and the obtained substituted isoxazolidines have also been evaluated for cytotoxic activity against a number of human cancer cells lines.

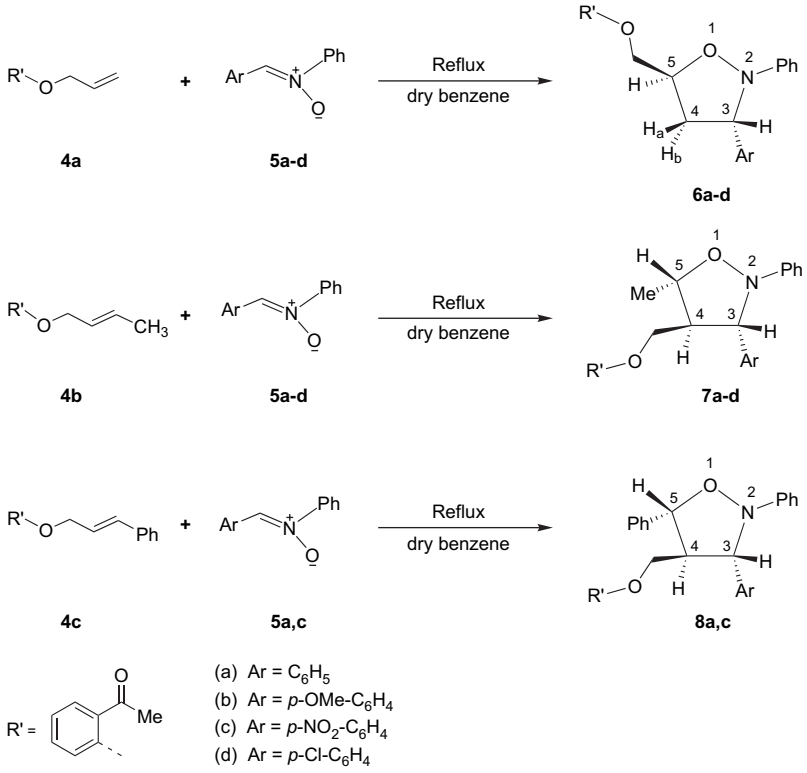
2. Results and discussion

Initially, cycloadditions of nitrones **5a–d** (prepared by the reaction of phenylhydroxylamine with the corresponding aldehydes and characterized spectroscopically), with *o*-allyloxy-/crotyloxy-/cinnamyloxy-acetophenones **4a–c** were carried out by refluxing (30–35 h) their equimolar solutions in dry benzene. After the completion of reactions (TLC), column chromatography afforded the isoxazolidines **6a–d**, **7a–d**, and **8a**,**c** (Scheme 2 and Table 1). The obtained isoxazolidines were characterized spectroscopically. The observed regio- and stereochemical outcomes of these cycloadditions were delineated by detailed NMR spectroscopic analyses involving extensive ^{1}H-decoupling experiments and establishing ^{1}H–^{1}H and ^{1}H–^{13}C connectivities by 2D NMR techniques.

The formation of the cycloadducts was established by the ^{1}H NMR and Mass spectra. The assigned regiochemistry of addition in the case of (**6a–d**) is based, besides ^{1}H NMR spectra, on the presence of two methine (*C*H–) resonances, one in the range of δ 69–70 (C3) and the other in the range

Table 1. Reaction times and yields of the products from cycloadditions of nitrones **5a–d** with dipolarophiles **4a–c**

Entry	Dipolarophile	Nitrone	Reaction time (h)	% Yields of adducts		
				6	**7**	**8**
1	**4a**	**5a**	30	65	—	—
2	**4a**	**5b**	32	63	—	—
3	**4a**	**5c**	30	70	—	—
4	**4a**	**5d**	35	60	—	—
5	**4b**	**5a**	32	—	64	—
6	**4b**	**5b**	33	—	62	—
7	**4b**	**5c**	31	—	68	—
8	**4b**	**5d**	35	—	60	—
9	**4c**	**5a**	33	—	—	65
10	**4c**	**5c**	31	—	—	67



Scheme 2.