SYNTHESIS OF NOVEL ISOXAZOLIDINES VIA 1,3-DIPOLAR CYCLOADDITION OF NITRONES TO OLEFINS

B. K. Vishu Kumar, K. Mantelingu, Basappa and **K. S. Rangappa***
Department of Studies in Chemistry, University of Mysore,
Manasagangotri, Mysore - 570 006, INDIA.
e-mail: rangappaks@yahoo.com

Abstract: C-anthranyl-N-3-methylphenyl nitrone has been discovered as new 1,3-dipole to form N-arylisoxazolidines via 1,3-dipolar cycloaddition reaction with olefins. Synthesized novel isoxazolidines were characterized by ^{1}H NMR, IR and C, H and N analysis.
Key words: nitrones, alkenes, isoxazolidines, cycloaddition, β-lactam, heterocycles

Introduction

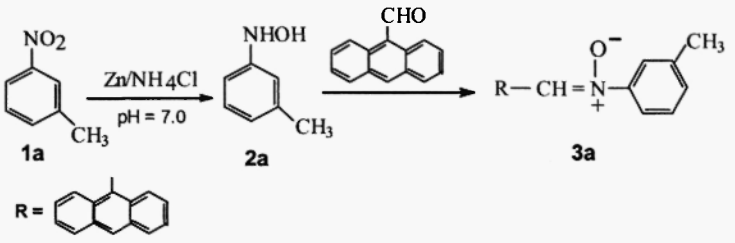
Cycloaddition reactions have figured prominently in both synthetic and biological chemistry.[1,2] Cycloaddition reactions of nitrones to unsaturated substrates constitute the best procedure for the construction of isoxazolidines ring system.[3] These are attractive intermediates for the synthesis of several class of biologically active compounds and natural products[3,4] such as Nujiromycin (antbiotics), Biotin (antibiotics, Vit-H) etc.

Since the nitrones are experiencing expanding application today as spin traps[5], very good potential therapeutic agents and as synthetic intermediates for the synthesis of ultimate carcinogens.[6] We further proceed to exploit its utility as synthetic tool, because our need was to develop a rapid procedure based on zinc/ammonium chloride reduction of nitro compounds and to synthesize biologically active nitrones.

In the present work, the presence of nitrogen atom within the isoxazolidine ring makes this novel heterocyclic moiety especially attractive for the synthesis of β-lactam ring,[7] which are used in the treatment of bacterial infections.[7] Most of the isoxazolidines synthesized are oily[8] in nature at room temperature.

---

* To whom the correspondence should be made.
Phone: 0821-412191, Fax: 0821-518835



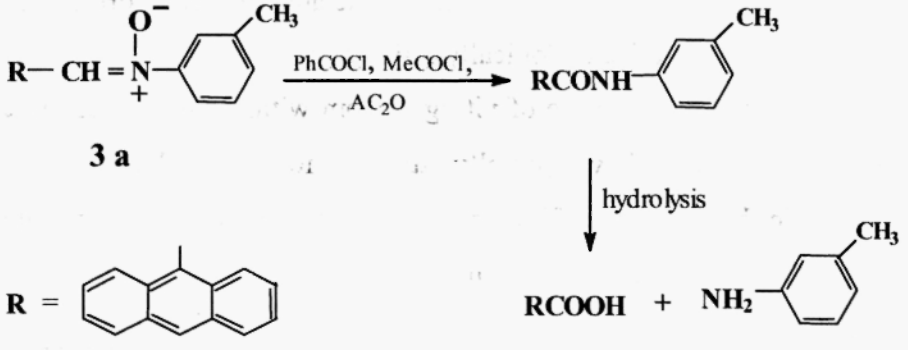
Scheme 1

Results and discussion

The usual synthesis of nitrones involve the oxidation of N-alkyl or aryl oximes with mild oxidizing agents. However, the nitrones so generated are unstable and usually reacted *insitu.* There are reports[9] only on the synthesis of isoxazolidines bycycloaddition of oximes with olefins via nitrones under thermal conditions. This prompted us to synthesize isoxazolidines by intramolecular cycloaddition of new N-aryl nitrones with monosubstituted olefins.

In the present study the new N-arylnitrone **3a** was obtained by the condensation of N-arylhydroxylamine **2a** with 9-anthraldehyde in dichloromethane at room temperature for 24 h. Obtained fine crystals on filtration were washed with minimum quantity of ether and hexane (1:1), got fine white cryastals of nitrone **3a** in high yield, 94.10%.

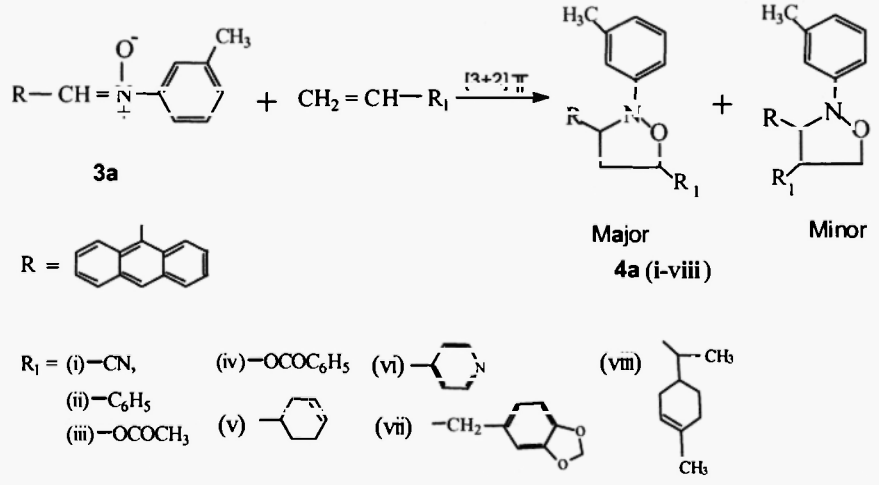
Stability and existence of **3a** was confirmed by their common characteristic reactions viz. compound **3a** rearranged to their isomeric amides[10] upon treatment with acetyl chloride / acetic anhydride / benzyl chloride in ether at room temperature. Amides on hydrolysis to give acid and amide fragments of original nitrone (Scheme 2).



Scheme 2

A considerable amount of work has been done on 1,3-dipolar cycloaddition.[9] However, this 1,3-dipolar cycloaddition reactions of new nitrones has attracted considerable attention as a convenient tool for the rapid construction of varied class of natural products.[11] For cycloaddition, both steric and electronic factors are important,[12] and in general the more hindered end of the dipolarophile adds to the nitrone oxygen atom. However, monosubstituted alkenes bearing a variety of groups afford 5-substituted isoxazolidines.[13]

Monosubstituted alkenes react with nitrones to give rise to diastereomeric ratio of cis and trans disubstituted isoxazolidines. The exo approach gives the cis product, provided that N-methylphenyl and C-anthracene are in a trans relationship, the endo approach gives the trans product. Inspections of the availability data tend to show that the exo approach is favoured in most cases when secondary orbital interactions are negligible. When R_1 = CO_2Me, CN, Ph, CO_2Ph, Pyridine, Cyclohexene etc. such secondary interactions could stabilize the transition state and give predominantly the trans adduct and this situation is favorable to our studies.



Scheme 3

In the present study we have used **3a** as new 1,3-dipole, which reacts with different alkenes to give isoxazolidines **4a(i-viii)** (Scheme 3). These reactions were carried out by refluxing the reactants in toluene and the products obtained are in good yield.

CONCLUSION

In conclusion we have shown that the 1,3-dipolar cycloaddition of nitrones to alkene derivatives results in the production of regioisomeric adducts of isoxazolidines. These isoxazolidines can be used for the synthesis of β-lactam by ring contraction.

Acknowledgement

We are grateful to the Department of University Grant Commission (UGC), Government of India, New Delhi, for financial support under the project vide No. f. 12-14/ 2002 (SR-1) and Sophisticated Instrument Facility (SIF), I I Sc, Bangalore for recording ^{1}H NMR spectra

References

(1) A. Wasserman, Diels-Alder reactions, Elseveir, New York, 1965.
(2) J. Sauer, Angew. Chem., Int. Engl. **6**, 16 (1967)
(3) A. Padwa, Intermolecular 1,3-dipolar Cycloadditions in Comprehensive Org. synthesis, press oxford, **4**, 1069-1109 (1991)
(4) K.B.G. Torsell, in Nitrile oxide, nitrones and nitronates in organic synthesis, (VCH, New York, Weinheim) 1988.
(5) B. H. R.Barton, J. M.Beaton, J. Am. Chem. Soc. **82**, 261(1990); ibid, **83**, 4083 (1961)
(6) H. Mallesha, K.R. Ravikumar, K. Mantelingu, and K.S. Rangappa, Synthesis. **10**, 1459-1461 (2001)

(6) A. Padwa, F. Konard, Kochler and Augusto Rodriguez, J. Am. Chem. Soc. **103**, 4974-4975 (1981)
(7) M. Ochiai, M. Obayashi and K. Morita, Tetrahedron. **23**, 2641-2648 (1967)
(8) A. Hasner and Lokanatha Rai, Synth. Commun. **26**(1994); ibid, **24**, 1669 (1994); ibid, **19**, 2799 (1989)
(9) J. S.Splitter and M. Calvin, J. Org. Chem. **23**, 651 (1958)
(10) M. J. Kamlet and L. A. Kaplan J. Org. Chem. **22**, 576 (1957); (b) H. Shindo, and B. Umezawa, Chem. Pharm. Bull. (Tokyo) **10**, 492 (1962)
(12) R. Huisgen, Angew. Chem. Int. Ed. **75**, 742(1963); Angew. Chem. Internat. Ed. **2**, 633 (1963)
(13) Czeslaw Belzecki and Trma Panfil. J. Org. Chem. **44**, 8 (1979)

Received on July 19, 2002