

## Synthesis of 1,2,4-Oxadiazolidine and Isoxazolidine Derivatives from Addition of Isocyanates and Alkenes to Nitrones

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### ABSTRACT

Some new heterocyclic compounds of 1,2,4-oxadiazolidine-5-one derivatives [3a-m] were synthesized from the reaction of nitrone compounds with some isocyanates of amino acid esters in good yields.

The reaction of nitrone compounds with cyclooctene and tetrahydrophthalic anhydride gave oxazolidine derivatives [4a-d]. The synthesized compounds were formed via 1,3-cycloaddition reaction of isocyanates and alkenes to nitrones. The I.R. spectral data of the synthesized compounds were also discussed.

-1,2,4

[3a-m] -5- -1,2,4

[4a-e]

1,3

### INTRODUCTION

The nitrone group play an important rules in the preparation of variety biologically active compounds which are antibacterial (Kametani *et al.*, 1985) and anticancer (Khallo et al., 2002).

Versatile heterocyclic compounds were synthesized from nitrones. Usually the reaction of nitrone with substituted isocyanate undergoes 1,3-dipolar cycloaddition reactions to give 1,2,4-oxadiazolidine-5-one. (Joachimi and Rolf, 1973; Utzinger and Regenass, 1954; Blanarikova et al., 2001)

Oxadiazoline compounds could be prepared from the reaction of substituted hydroxyl amine with isocyanate (Zinner and Dybowski, 1971; Gerwalt et al., 1981).

Furthermore, Helmat found that the N,N'-disubstituted hydroxyguanidine react with ethylchloroformate to give 1,2,4-oxadiazolin-5-one (Helmat and Gerwalt, 1972).

On the other hand, nitrones react with olefins to give isoxazolidine (Delpierre and Lamchen, 1963; Barker and Wierengo, 1975). The isoxazolidinyl moiety have been created by a wide range of synthetic pathways, including reactions of halotrinitromethane with alkenes (Altukhov *et al.*, 1973), thermal rearrangement of azetidine N-oxides (Teikoku Hormone Co. Ltd., 1974), reaction of hydroxyurea with  $\alpha,\beta$ -unsaturated carbonyl compounds (Jacquier *et al.*, 1975), Michael additions of hydroxylamine to  $\alpha,\beta$ -unsaturated ester (Ishikawa *et al.*, 1998).

Isoxazolidine derivatives are vastly applications in the biological fields as medical fungicides (Georgiev and Mullen, 1988; Mullen *et al.*, 1988).

## EXPERIMENTAL

Uncorrected melting points were determined using Electrothermal 9300 melting point apparatus. I.R. spectra were recorded by Pye-Unicam SP 1100 spectrophotometer as KBr disc. Nitron compounds [1a-c] were prepared according to the published procedure (Young *et al.*, 1970). Isocyanate of amino acid esters [2a-e] were prepared by following literature reported procedure (Basheer, 2000).

### **Synthesis of 2-phenyl-3-aryl-4-(ethoxy carbonyl substituted methyl)-1,2,4-oxadiazolidin-5-one (3a-m) (Utziger and Regenass, 1954)**

A mixture of (0.005 mole) nitron (1a-c) and (0.005 mole) of isocyanate amino acid esters (2a-e) in (100 ml) of dry benzene was heated at 70 °C for 1 hr. Evaporation of the solvent gave a solid product which was recrystallized from ethanol. The physical properties and I.R. spectral data were showed in (Table 1).

### **Synthesis of 2-phenyl-3-aryl-1,2-oxazolidine [1,2-b] cyclooctane [4a-b] (Delpierre and Lamchen, 1963)**

A mixture of (0.005 mole) of compound (1b-c) and 10 ml of cyclooctene was heated for 24 hrs (8 hrs. three time intervals) on a steam bath. The excess of alkene was removed by distillation and the residue was recrystallized from ethanol. The melting point and I.R. spectral data were indicated in (Table 2).

### **Synthesis of 2-phenyl-3-aryl-1,2-oxazolidine[4,5-c]hexahydro phthalanhydride [4c-d]**

A mixture of compound (1b-c) (0.002 mole) and (3.04 gm, 0.002 mole) of tetrahydrophthalic anhydride dissolved in (25 ml) tetrahydrofuran was heated to reflux for 14 hrs. Then the solvent was evaporated, the obtained product was recrystallized from ethanol. The physical constants and I.R. spectral data were indicated in (Table 2).

Table 1: Physical properties and spectral data of compounds (3a-m)

Comp. No.	Formula	M.P. °C	Yield %	I.R. $\nu$ $\text{cm}^{-1}$			
				C-O	C=C	C=O	C=O ester
3a	$\text{C}_{18}\text{H}_{18}\text{N}_2\text{O}_4$	135-136	75	1075	1605	1710	1770
3b	$\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_6$	248-250	71	1080	1600	1720	1765
3c	$\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_5$	240-242	78	1060	1600	1710	1770
3d	$\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_4$	260d.	60	1035	1610	1705	1760
3e	$\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_6$	105-107	81	1030	1620	1720	1775
3f	$\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_5$	36-38	65	1050	1605	1715	1780
3g	$\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$	74-76	73	1045	1600	1720	1760
3h	$\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_6\text{S}$	256d.	70	1060	1590	1695	1760
3i	$\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_5\text{S}$	250 d.	68	1070	1610	1710	1770
3j	$\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_4\text{S}$	225-227	74	1065	1615	1710	1750
3k	$\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_6\text{S}$	80-82	71	1040	1590	1710	1765
3p	$\text{C}_{22}\text{H}_{26}\text{N}_2\text{O}_5\text{S}$	186-188	82	1070	1610	1720	1760
3m	$\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_6$	162-164	84	1030	1600	1720	1765

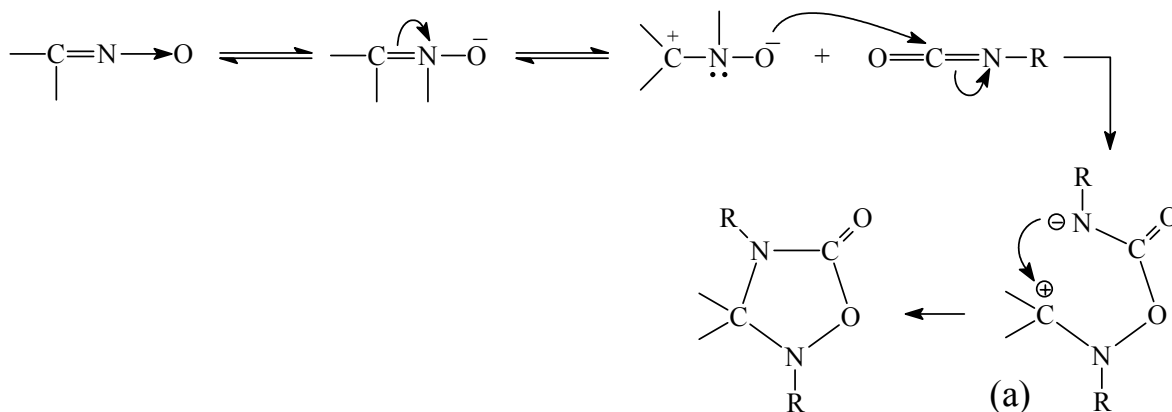
Table (2): Physical constant and spectral data of oxadiazolidine (4a-d)

Comp. No.	Formula	M.P. °C	Yield %	I.R. $\nu$ $\text{cm}^{-1}$			
				C-O	N-O	C=C	C=O sy/as.
4a	$\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_3$	122-124	81	1045	1345	1600	-
4b	$\text{C}_{22}\text{H}_{27}\text{NO}_2$	226 d	78	1060	1350	1590	-
4c	$\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_6$	138-140	86	1070	1345	1595	1755/ 1770
4d	$\text{C}_{24}\text{H}_{21}\text{NO}_5$	160-162	73	1065	1370	1590	1760/ 1780



## RESULTS AND DISCUSSION

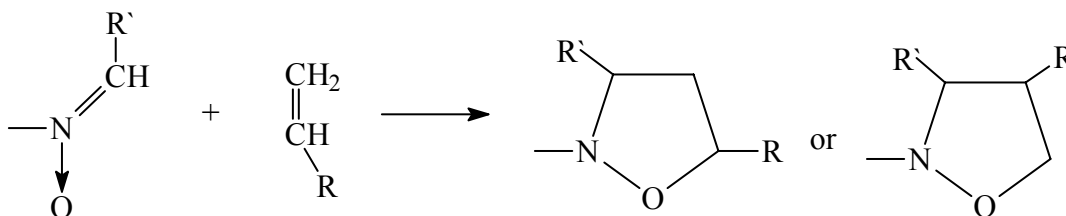
Compounds [3a-m] could be prepared by the reaction of nitrones with equivalent amount of the isocyanate of amino acid ester. The reaction was carried out through a nucleophilic addition from the oxygen of nitron at the carbon atom of isocyanato group to give the intermediate (a) which underwent intranucleophilic attack to give 1,2,4-oxadiazolidin-5-one, as follows:



The I.R. spectral data of these compounds showed the major absorption bands at (1030-1080  $\text{cm}^{-1}$ ), (1590-1620  $\text{cm}^{-1}$ ), (1695-1720  $\text{cm}^{-1}$ ) and (1750-1780  $\text{cm}^{-1}$ ) which are related to stretching vibrations C-O, C=C, C=O and C=O ester groups respectively.

The second part of this investigation is the preparation of isoxazolidine from the 1,3-dipolar cycloaddition of nitron with the corresponding olefin, as shown in the following equation.

Nitrones reacts with symmetrical olefin to produce one isomer. While unsymmetrical olefin gives two isomers of isoxazolidine.



The I.R. spectra of the compounds (4a-d) shows stretching vibration bands of C-O, N-O at (1045-1070 $\text{cm}^{-1}$ ) and (1345-1370 $\text{cm}^{-1}$ ). The C=O of anhydride were absorbed at (1755-1760  $\text{cm}^{-1}$ ) and (1770-1780  $\text{cm}^{-1}$ ) which related to symmetrical and asymmetrical stretching vibrations.

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