

SYNTHESIS OF NOVEL ISOXAZOLE DERIVATIVES FROM 1,3-DIKETONE DERIVATIVES

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Abstract : Condensation of β -diketone derivative with hydroxylamine hydrochloride ($\text{NH}_2\text{OH} \cdot \text{HCl}$) in pyridine results in the synthesis of isoxazole derivative. By washing with 15% glacial acetic acid and then recrystallization with 95% $\text{C}_2\text{H}_5\text{OH}$ led to crystal formation. Purity of the newly synthesized isoxazole derivative was checked by TLC. The structure of newly synthesized isoxazole derivative were established on the basis of IR, ^1H NMR, ^{13}C NMR and elemental analysis.

Key Words : β -Diketone, hydroxylamine hydrochloride, glacial acetic acid.

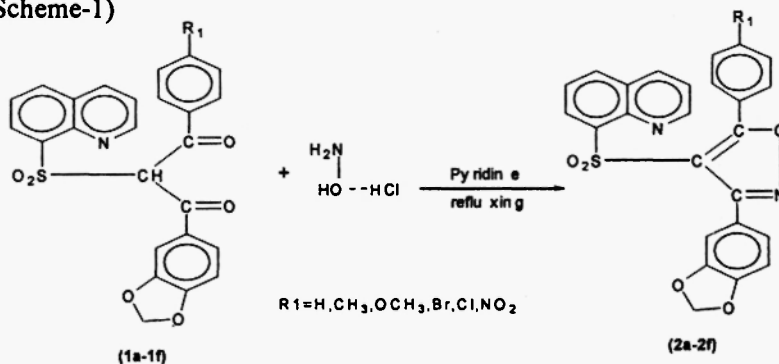
Introduction

Isoxazoles derivative represent a large group of compounds and display a number of medicinal¹ and agricultural properties²⁻⁵. The isoxazole derivatives are known to exhibit diuretic⁴, antifungal⁵, antiviral⁷, antihelmintic⁸, hypolipemic⁹, antibacterial¹⁰, cestoidal¹¹ and antiallergic¹² casting as histamine blocking agent's properties. Pharmacologically useful isoxazole¹³ includes semisynthetic penicillin's, semisynthetic lephalosporins, antibacterial sulfonamides, anabolic steroids, monoamine oxidase inhibitor used in psychotherapy etc. Beside these isoxazole derivatives are also employed in the treatment of leprosy¹⁴. Cycloserine¹⁵, an important isoxazole derivative shows antitubercular and antibacterial activity.

In synthetic organic chemistry isoxazole derivative were prepared by a number of synthetic way viz. Solid phase reaction of polymer bond with RCH_2NO_2 , RCHO and RNCS ¹⁶, by reaction of chalcone with phenyl cyanate in presence of triethylamin³, condensation of α,β -dibromochalcones with hydroxyl amine hydrochloride¹⁷, and by reaction of substituted 1,3-propane dione with hydroxyl amine hydrochloride in ethanol¹⁸⁻²¹. Various pharmacological activities associated with isoxazole derivative encourages us for synthesis of novel isoxazole.

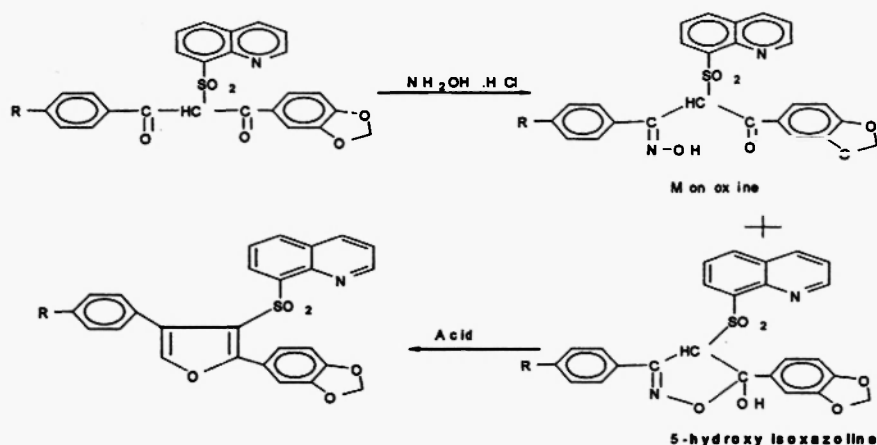
Result and Discussion

In this manuscript we report synthesis of novel isoxazole derivative via synthesis method¹⁸⁻²¹. β -diketone (1a-1f) on condensation with hydroxylamine hydrochloride ($\text{NH}_2\text{OH} \cdot \text{HCl}$) in presence of pyridine and refluxing the mixture for 3 hour on heating mentle led to synthesis of novel isoxazole derivatives. (Scheme-1)



Scheme -1

The reaction of β -diketone with hydroxyl amine first leads to the formation of monoxime of the respective β -diketone and then subsequently cyclise to form 5-hydroxy isoxazoline. Monoxime and 5-hydroxy isoxazoline are the intermediate products of the reaction. These monoxime and 5-hydroxy isoxazoline are readily converted into isoxazole derivatives by treatment with acid. (Scheme-2)



The structure of newly synthesized isoxazoline derivative were established on the basis of IR, ^1H NMR and ^{13}C NMR. The elemental analysis of data of titled compounds are given in Table 1.

Table-1: Analytical data of titled compounds

Compounds	M.F	Yields (%)	M.P ($^{\circ}\text{C}$)	Elemental analysis calc.(found)				
				C	H	N	S	X
2a	$\text{C}_{25}\text{H}_{16}\text{O}_5\text{N}_2\text{S}$	53	215	65.78 (65.73)	3.53 (3.51)	6.14 (6.13)	7.02 (7.00)	
2b	$\text{C}_{26}\text{H}_{18}\text{O}_5\text{N}_2\text{S}$	50	235	66.37 (66.33)	3.86 (3.83)	5.95 (5.93)	6.82 (6.81)	
2c	$\text{C}_{26}\text{H}_{18}\text{O}_6\text{N}_2\text{S}$	57	246	64.19 (64.20)	3.73 (3.72)	5.76 (5.74)	6.59 (6.57)	
2d	$\text{C}_{25}\text{H}_{15}\text{O}_5\text{N}_2\text{SBr}$	47	241	56.09 (56.04)	2.82 (2.81)	5.23 (5.23)	5.99 (5.97)	14.93 (14.91)
2e	$\text{C}_{25}\text{H}_{15}\text{O}_5\text{N}_2\text{SCl}$	50	227	61.16 (61.15)	3.08 (3.06)	5.71 (5.70)	6.53 (6.52)	7.22 (7.20)
2f	$\text{C}_{25}\text{H}_{15}\text{O}_7\text{N}_3\text{S}$	45	250	59.88 (59.86)	3.01 (3.00)	8.38 (8.36)	6.39 (6.38)	

Experimental

All the melting points were uncorrected. IR spectra were recorded on Perkin-Elmer Infrared spectrometer by using KBr pellets. The ^1H NMR and ^{13}C NMR spectra were recorded on DRX-300 MHz spectrometer using TMS as an internal standard. Elemental analysis was done using Perkin-Elmer CHNS/O Analyzer 2400. Purity of the compounds was checked by thin layer chromatography using silica gel 'G' as absorbent in suitable solvent system.

General procedure for synthesis of isoxazole derivatives (2a-2f)

The β -diketone derivative (0.005M) and hydroxyl amine hydrochloride (0.005 M) were placed in a round bottom flask and refluxed in pyridine for about 4-6 hours. The resultant mixture are poured onto crushed ice and washed thoroughly several times with 15% acetic acid so as to remove pyridine. The semisolid so obtained was then crystallized with 95% ethanol. Purity of the compound was checked through TLC using petroleum ether : acetone (8:2).

Spectral data:

- (2a) I.R. : 1156 & 1367 cm^{-1} (SO_2 vibrations), 1476-1635 cm^{-1} ($\text{C}=\text{C}$ vibration in Aromatic rings), 1095 ($\text{C}-\text{O}$ linkage).
 ^1H NMR: δ 6.02 (2H, s, OCH_2O), 6.83-8.67 (14H, m, aromatic protons).
 ^{13}C NMR: δ 99.97 (OCH_2O), 104 (carbon of isoxazole nucleus attached to $-\text{SO}_2-$) 115-156 (23 lines due to aromatic carbons).
- (2b) I.R. : 1152 & 1373 cm^{-1} (SO_2 vibrations), 1457-1625 cm^{-1} ($\text{C}=\text{C}$ vibration in Aromatic rings), 1074 ($\text{C}-\text{O}$ linkage).
 ^1H NMR: δ 6.00 (2H, s, OCH_2O), 6.80-8.56 (13H, m, aromatic protons), 2.14 (s, CH_3).
 ^{13}C NMR: δ 100.07 (OCH_2O), 106 (carbon of isoxazole nucleus attached to $-\text{SO}_2-$) 117-157 (23 lines due to aromatic carbons), 23.23 (CH_3).
- (2c) I.R. : 1134 & 1382 cm^{-1} (SO_2 vibrations), 1476-1627 cm^{-1} ($\text{C}=\text{C}$ vibration in Aromatic rings), 1064 ($\text{C}-\text{O}$ linkage).
 ^1H NMR: δ 5.99 (2H, s, OCH_2O), 6.77-8.59 (13H, m, aromatic protons), 3.83 (OCH_3).
 ^{13}C NMR: δ 99.96 (OCH_2O), 107 (carbon of isoxazole nucleus attached to $-\text{SO}_2-$) 113-155 (23 lines due to aromatic carbons), 57.87 (OCH_3).
- (2d) I.R. : 1165 & 1370 cm^{-1} (SO_2 vibrations), 1473-1626 cm^{-1} ($\text{C}=\text{C}$ vibration in Aromatic rings), 1105 ($\text{C}-\text{O}$ linkage).
 ^1H NMR: δ 6.00 (2H, s, OCH_2O), 6.90-8.54 (13H, m, aromatic protons).
 ^{13}C NMR: δ 100.23 (OCH_2O), 107 (carbon of isoxazole nucleus attached to $-\text{SO}_2-$) 119-151 (23 lines due to aromatic carbons).
- (2e) I.R. : 1150 & 1357 cm^{-1} (SO_2 vibrations), 1450-1625 cm^{-1} ($\text{C}=\text{C}$ vibration in Aromatic rings), 1079 ($\text{C}-\text{O}$ linkage).
 ^1H NMR: δ 5.97 (2H, s, OCH_2O), 6.87-8.52 (13H, m, aromatic protons).
 ^{13}C NMR: δ 100 (OCH_2O), 105 (carbon of isoxazole nucleus attached to $-\text{SO}_2-$) 115-157 (23 lines due to aromatic carbons).
- (2f) I.R. : 1154 & 1362 cm^{-1} (SO_2 vibrations), 1464-1627 cm^{-1} ($\text{C}=\text{C}$ vibration in

Aromatic rings), 1098(C-O linkage).

¹H NMR: δ6.00 (2H,S,OCH₂O), 7.01-8.79 (13H, m, aromatic protons).

¹³C NMR: δ100.02 (OCH₂O), 106 (carbon of isoxazole nucleus attached to -SO₂-)

118-154 (23 lines due to aromatic carbons).

Acknowledgement

The Authors are thankful to the Head, Department of Chemistry, University of Rajasthan, Jaipur, for providing laboratory facilities. One of us (Rajendra Kumar Saini) is thankful to the CSIR, New Delhi for award of a Senior Research Fellowship.

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Received on March 07, 2007