SOLID PHASE SYNTHESIS OF ISOXAZOLE DERIVATIVES FROM DIARYL 1,3-DIKETONES UNDER MICROWAVE IRRADIATION

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ABSTRACT

Reaction of various, diaryl 1,3-diketones with hydroxylamine hydrochloride on silica gel under microwave irradiation leads to the formation of corresponding isoxazole derivatives. Structures of these compounds were established on the basis of elemental analysis and spectral studies viz. IR, ^{l3}C NMR, ^{1}H NMR and Mass etc.

KeyWords: *1, 3-diketones, 1,3-benzodioxole, isoxazole, spectral studies.*

INTRODUCTION

Organic synthesis through microwave irradiation is a new and interesting technique and is becoming popular now. The reactions under microwave irradiation take place in few minutes and no solvent required or necessary. Thus this is time saving technique and the yield is higher than the reaction carried out under normal laboratory conditions. Furthermore, the solid-state reaction has many advantages: reduced pollution, low costs and simplicity in process and handling. These factors are especially important in industry.

The isoxazole nucleus is well known for its medicinal importance[1] and a number of related compounds are known to exhibit antitumor[2], anti-HIV[3]and cestoidal[4] agents. Diaryl isoxazole derivatives have a wide range of biological properties and commercial application in various realms of therapy, including antiinflammatory[5]and cytotoxic[6] agent. Isoxazole derivatives are also employed in the treatment of leprosy[7]and diabetes[8]. The marketed drugs of isoxazole, such as, Acetylsulfisoxazole, Cycloserine, Drazoxol on, Sulfisoxazole and Zonisamide have a great medicinal value. These drugs show antimicrobial[9-12], tuberculostatic[13], anticonvulsant[14], neurotoxic[15] and antiepileptic[16, 17] and these activities are also observed in their derivatives, led to the search for newer bioactive compounds of this class.

The 1,3-benzodioxole unit has shown interesting and diversified properties when used in new biologically active compound[18, 19]. Furthermore, these heterocycles are considered to be privileged structures by medicinal chemists. To gain accessible chemistry space not attainable by convert methods, the development of new synthetic methods will be very important to the chemistry community. Hence, investigation in to rapid means to synthesize isoxazole would be highly beneficial.

In this paper we wish to report reaction of diaryl-l,3-diketone(**la-1i**)[20] with hydroxylamine hydrochloride on silica gel under microwave irradiation to generate novel isoxazole derivatives.

EXPIRMENTAL

Melting points are uncorrected. The IR spectra were recorded in KBr disks on a, Nicolet-Megna-FT-IR 550 spectrometer. ^{1}H NMR and ^{13}C NMR were recorded on model DRX300 at 300.13 in

$CDCl_3$/DMSO-d_6 using TMS as internal standard. Mass spectra were recorded on, Jeol D-300 spectrometer. The microwave-induced reactions were carried out in a BMO-700 T modified domestic oven fitted with a condenser and a magnetic stirrer. The purity of the newly synthesized compounds were checked by TLC

Conventional Synthesis[21-23]

1,3-diketones (0.01 mole) were refluxed with hydroxylamine hydrochloride (0.02 mole) in pyridine for 10-34 h, depending on the nature of substitutents in the 1,3-diketones. The mixture was then poured into cold water and washed several time, with acetic acid (15%) to remove pyridine. The semisolid obtained was then triturated with aqueous ethanol (95%) and crystallized from absolute ethanol, yields varied from 55-70%. All the isoxazole give single spots in TLC.

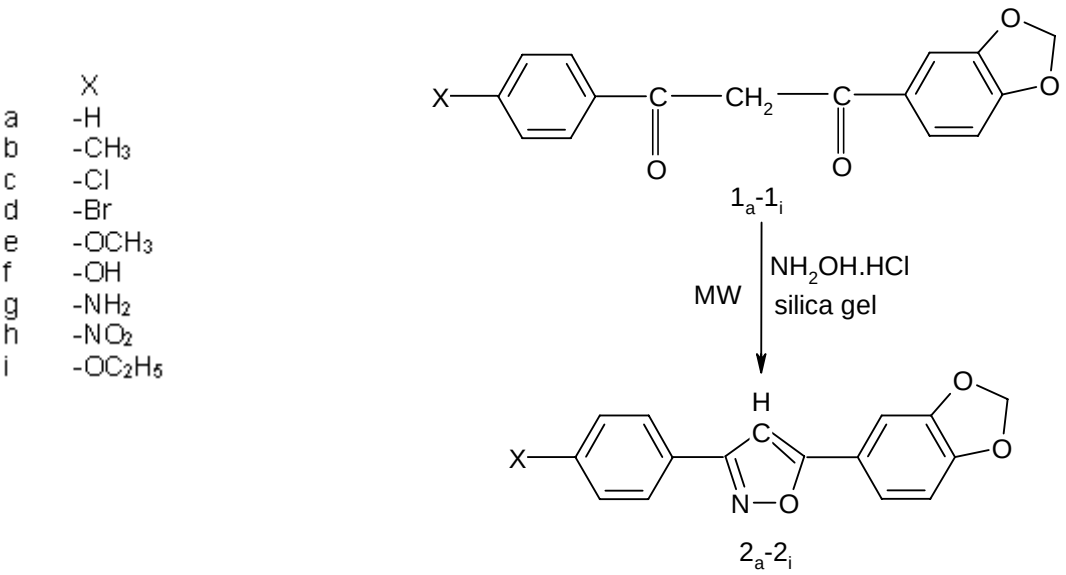
Microwave –assisted Synthesis[24-27]

Hydroxylamine hydrochloride (130 mg, 4 mmol), silica gel (2g) and diaryl-l, 3-diketone (la-1i) (2 mmol) were mixed in a mortar then transferred in to a beaker and irradiated for 2 min. The progress of reaction were monitored by TLC ($CHCl_3$: CH_3OH, 9 : 1) as mobile phase. The mixture was extracted in to $CHCl_3$ then filtered and washed with water, after drying, the organic phase was removed by a rotary evaporator. Further purification by column chromatography ($CHCl_3$ as eluent) and recrystallization give the desired products. All the isoxazole give single spot in TLC and yields varied from 82-93%.

RESULTS AND DISCUSSION

Microwave irradiation of propane-l-(1,3-benzodioxol-5-yl)-3-phenyl-l,3-dione (1a-1i) with hydroxylamine hydrochloride on silica gel gives some new 3,5-disubstituted isoxazole, with 1,3-benzodioxole unit as one substitutent. The Structure of the solid phase synthesized compound is well supported by spectroscopic data [Scheme-1, Tab1e-1].

	X
a	-H
b	$-CH_3$
c	-Cl
d	-Br
e	$-OCH_3$
f	-OH
g	$-NH_2$
h	$-NO_2$
i	$-OC_2H_5$



Scheme 1

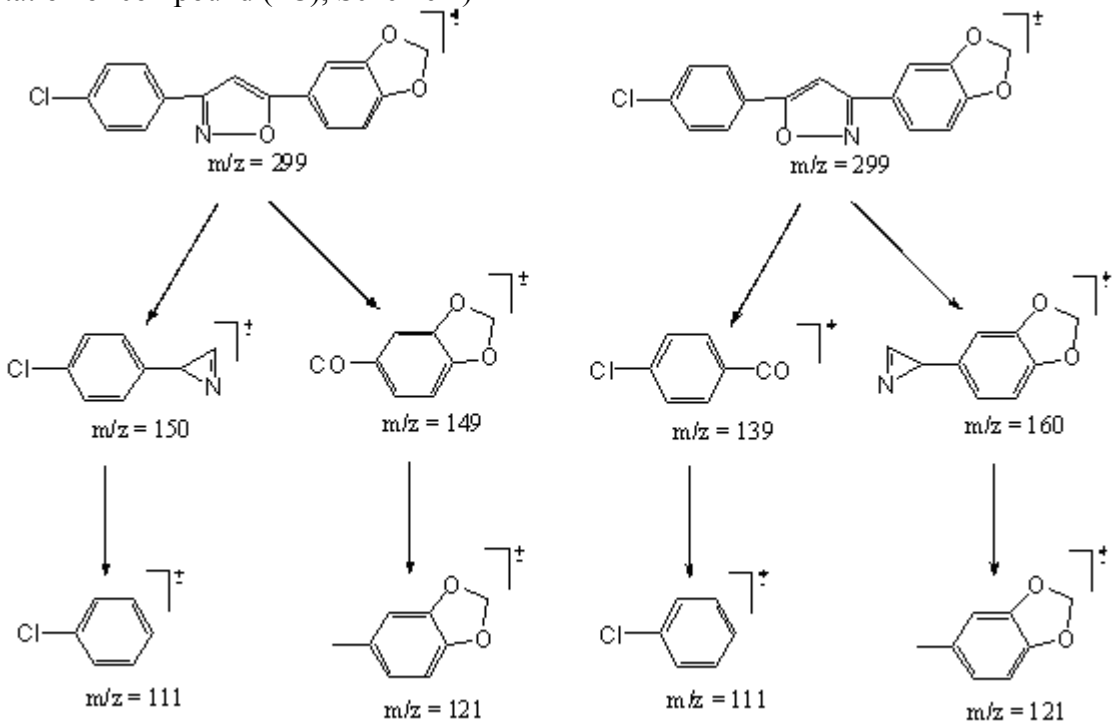
The IR spectra of the products (2a-i) indicated the completion of reaction as the characteristic

absorption in the range 1700-1640 cm^{-1} for C=O functional group was absent. The presence of a strong absorption signal in the range 1602-1572 cm^{-1} is characteristic of C=N .All of these compounds show absorption band at 3028-3015 cm^{-1}, which was due to Ar-H stretching vibration. The sharp peak observed at 1600 cm^{-1} (ring stretching band), 1500-1400cm^{-1} (ring stretching mode) has been assigned to isoxazole ring of the compounds.

The 1H NMR spectra of compound 2a-i showed a complicated pattern in the aromatic regin at δ 6.7-7.8 ppm indicates the presence of seven aromatic protons. A singlet is obtained for dioxymethylene (O-CH2-O) protons at δ 6.04. Compound (3e) also exhibited a singlet for three proton of O-CH3 group at δ 3.85. .In compound (2i), a quartet was observed at δ 3.92 (J=7Hz)for methylene protons (2H) in the ethoxy (O-CH2-CH3) group and a triplet at δ 1.76 (J=7Hz) showed the presence of three protons of the methyl of ethoxy (O-CH_2-CH_3)group .In compound (2a-i) , a singlet is observed at δ 6.6-6.2 ppm, which is assigned to one proton of isoxazole ring indicated the completion of reaction.

The 13 C NMR spectral data for the compound (2a-2i) are presented in Table –3 and these data are in good agreement with their structures. Aromatic carbon of ring A andB are observed at around δ 162.7-114.3 and δ 149.4-106.0 respectively .The absorption signals observed at around δ 101.6-101.2 was observed due to O(C) O carbon. Absorption in the range δ 96.5-97.6 may be assigned to –CH= carbon.

In the mass spectra all these compounds shows molecular ion peak. The mass spectrum of (2c) shows a cluster of absorption peak at m/z, 299 and 301 corresponds to M^+,$[M+2]^+$ respectively, with one third intensity of $[M+2]^+$ w.r.t. M^+,showing the presence of chlorine. (Mass fragmentation of compound (2C), Scheme 2)



Scheme 2

While in compound 2d, the intensity of [M+2]+ peak and M+ peak were found to be nearly equal, confirming the presence of bromine atom. In other compounds molecule A number of

workers[28, 29] observed that when isoxazoles are prepared by diaryl-1, 3-diketone, mixture of the two isomer are formed due to both eno1ic forms of β-diketone. In this paper, when the isoxazoles formed, were subjected to thin layer chromatography, in each case only one spot was observed showing the formation of only one product, but mass spectra showed the presence of two structural isomers.

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Table -1: Characterization Data of new 3,5-disubstituted isoxazoles

Compd.	M.F.	M.W.	Elemental Analysis Calcd. and (Found)				M.P. (°C)	Yield %
			C%	H%	N%	X%		
2a	$C_{16}H_{11}O_3N$	265	72.45	4.15	5.28	-	95°C	93
			(72.32)	(4.08)	(5.27)			
2b	$C_{17}H_{13}O_3N$	279	73.11	4.66	5.02	-	108°C	91
			(73.06)	(4.26)	(4.85)			
2c	$C_{16}H_{10}ClO_3N$	299.5	64.11	3.34	4.67	11.85	165°C	89
			(63.84)	(3.31)	(4.02)	(11.82)		
2d	$C_{16}H_{10}BrO_3N$	344	55.81	2.91	4.07	23.26	137°C	92
			(55.60)	(2.28)	(3.91)	(23.24)		
2e	$C_{17}H_{13}O_4N$	295	69.15	4.41	4.75	-	124°C	84
			(68.87)	(4.01)	(4.36)			
2f	$C_{18}H_{15}O_4N$	309	69.90	4.85	4.53	-	146°C	86
			(69.14)	(4.08)	(4.11)			
2g	$C_{16}H_{11}O_4N$	281	68.33	3.91	4.99	-	179° C	82
			(67.96)	(3.29)	(4.31)			
2h	$C_{16}H_{12}O_3N_2$	280	68.57	4.28	10.00	-	188° C	89
			(68.35)	(4.00)	(9.81)			
2i	$C_{16}H_{l0}O_5N_2$	310	61.93	3.23	9.03	-	193°C	87
			(61.42)	(2.99)	(8.89)			

Table –2: ^{1}H NMR data of title compounds (in δ, ppm)

Compd.	Ar-X	OCH_2O (2H, s)	Methine (lH, s)	Aromatic Proton (7H, m)
2a	-	6.03	6.62	6.85-7.71 (8H, m)
2b	3H, 2.41 s	6.04	6.66	6.89-7.75
2c	-	6.06	6.70	6.89-7.81
2d	-	6.02	6.65	6.83-7.74
2e	3H, 3.85 s	6.03	6.62	6.88-7.79
2f	1H, 4.05, s	6.02	6.61	6.78-7.78
2g	2H, 4.41(b), s	6.03	6.68	6.81-7.73
2h	-	6.05	6.66	6.83-7.82
2i	1.76 (3H, t, J = 7 Hz) 3.92 (2H, q, J = 7Hz)	6.04	6.69	6.80-7.76

Table- 3: ^{13}C NMR data of title compounds. (δ ppm)

Compd.	Ar-X	O(C) O	C=N	C–O	H C	Ring A *	Ring B**
2a	-	101.2	151.1	162.0	96.5	133.0-120.2	149.4-106.0
2b	CH_3; 21.4	101.4	151.4	162.9	96.7	140.1-120.5	149.2-106.2
2c	-	101.5	150.2	162.0	97.6	136.0-120.5	149.4-106.1
2d	-	101.6	151.4	162.4	97.2	135.8-119.3	148.9-106.6
2e	OCH_3; 55.9	101.4	150.3	162.3	96.3	162.3-114.3	148.2-106.1
2f	-	101.2	150.4	162.6	96.5	161.8-115.7	149.2-106.5
2g	-	101.5	150.4	162.0	97.1	151.5-117.6	148.9-106.0
2h	-	101.6	151.2	162.5	96.8	152.8-118.2	149.1-106.3
2i	OCH_2; 63.2, CH_3; 14.7	101.4	150.3	162.3	97.0	162.7-115.1	149.0-106.4

*Ring A - Benzene ring with various substitutents.
** Ring B - Benzene ring with dioxolane ring.

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A perfection of means, and confusion of aims, seems to be our main problem.
-Albert Einstein