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SYNTHESIS OF NOVEL SUBSTITUTED PYRAZOLES AND ISOXAZOLES CONTAINING 1, 4-BENZODIOXANE SULFONYL MOIETY

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ABSTRACT
Synthesis of substituted pyrazole (2a-e) and substituted isoxazole (3a-e) by the reaction of (1a-e) with hydrazine hydrate in absolute C_2H_5OH/Hydroxylamine hydrochloride in pyridine. The elemental analysis and spectral studies. IR, ^1H NMR, and ^{13}C NMR were performed for various pyrazole derivatives (2a-e) and isoxazole derivative (3a-e).
Keywords: β-diketone, β-ketoester, Hydrazine hydrate, Hydroxylamine, Sulfonyl Group, Spectral Studies.
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INTRODUCTION

Heterocycles and its derivatives have immense importance in pharmaceutical sciences and other industrial utilization. Unquestionably, these deeds are representing a significant role in the development of human society. The chemistry of condensed heterocyclic compounds, especially those containing isoxazole and pyrazole moieties have received much attention and reported to have significant pharmacological properties.[1-4] Pyrazoles contain two nitrogen atoms at ortho position with maximum unsaturation whereas isoxazoles have the five-membered heterocycles having one oxygen and one nitrogen at ortho position with maximum unsaturation.The pyrazole and isoxazole core are greatly referred to as its medicinal importance, and numerous related compounds are known with show antibacterial[5,6], antiviral[7,8], antifungal[9], antiinflammatory[10,11], and antitumor[12,13] properties.

Synthesize compounds also contain 1, 4-benzodioxane moiety which exhibits various biological activity such as antimicrobial and antioxidant activity[14], anti-inflammatory[15], α-2-adrenoreceptor antagonists and potential antidepressants[16], α_{1D}-adrenoreceptor antagonists and cytotoxic agents[17]. Apart from this accumulating compound additionally contain sulfonyl group which has been a focal point of interest for a long time due to their diversified biological function in the drug industry.[18, 19]

The packaged drugs of isoxazole such as *Acetyl Sulfisoxazole, Cycloserine, Sulfisoxazole, Zonisamide* and pyrazole such as *Novalgin, Isofezolac, Ampyrone* have great medicinal utilities, Prompted those search for newer bioactive compounds with containing 1, 4-benzodioxane sulfonyl moiety as one of the group.

EXPERIMENTAL

The melting points of the compounds were determined by the capillary tube method and may not found to be fully corrected. IR Spectra of the compounds were also recorded on Nicolet-Megna FT-IR 550 spectrometer by using KBr Pellets. The ^1H NMR and ^{13}C NMR spectra were operated on the BRUKER AVANCE II 400 NMR Spectrometer at 400.13 and 100.61 MHz, respectively with $CDCl_3$. The micro estimations of the analytical samples were carried out using Perkin Elmer CHNS/O Analyser 2400. Impurities in the synthesized compounds were segregated by TLC using suitable solvents systems.

Preparation of Substituted Pyrazoles (2a-e)[20-21]

In a dry flask placed a mixture of β-diketone/β-ketoester[22-23] (1a-e) (0.01M), silica gel (0.5gm) and hydrazine hydrate (0.48g., 0.01M) and refluxed it in C_2H_5OH (5-10 ml) for approximately 8-11 hours on

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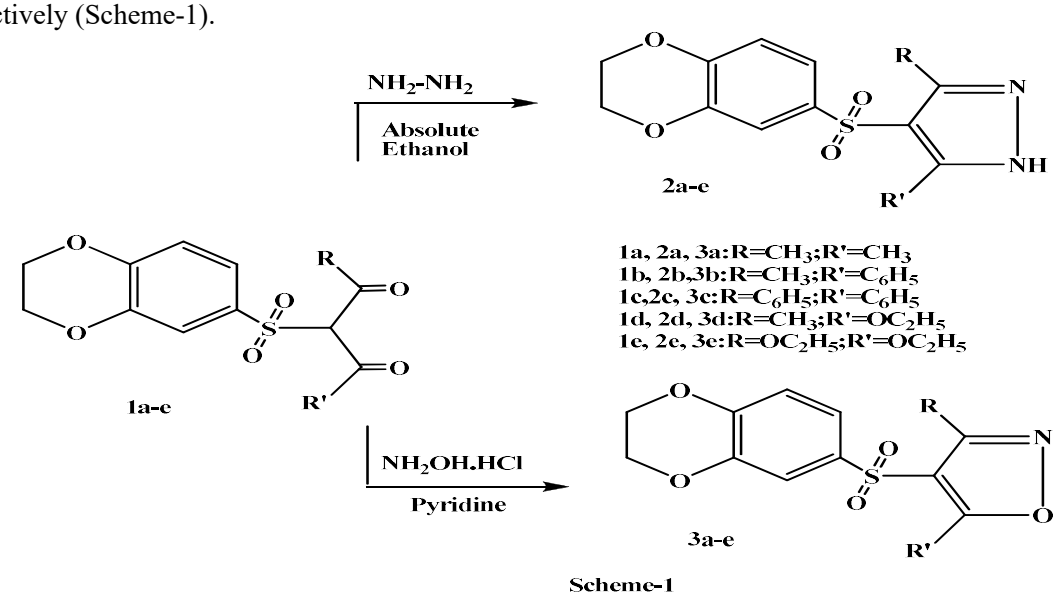
a heating mantle. The mixture was cooled and filtered. The product was recrystallized from ethanol. Impurity in the compound was checked by thin-layer chromatography using ethyl acetate: n-hexane (8:2) as the mobile phase.

Preparation of Substituted Isoxazoles (3a-e)[24]

$NH_2OH.HCl$ (0.7 g, 0.01M) and silica gel (0.5gm) were added to the stirred suspension of β-diketone/β-ketoester (1a-e) (0.01M) in pyridine (4 ml) and refluxed for 14-21 hours. The resulting mixture was cooled and poured into crushed ice and washed with 13% CH_3COOH. The produced precipitate was filtered and dried. The product was crystallized from aqueous C_2H_5OH. Impurity in the compound checked by thin-layer chromatography using pet ether: benzene (8:2) upper layer as mobile phase.

RESULTS AND DISCUSSION

The cyclocondensation of 1a-e synthesized pyrazole derivatives (2a-e) and isoxazole derivatives (3a-e) with NH_2-NH_2 in the presence of absolute ethanol/ Hydroxylamine hydrochloride in pyridine, respectively (Scheme-1).



Scheme-1

It is a simple condensation reaction which takes place through enol tautomer of the β-diketones and β-ketoesters (1a-e**)**. The pyrazole (2a-e) and isoxazole (3a-e) obtained by the reaction, were further purified through column chromatography. The structure of all the recently combine pyrazole and isoxazole subsidiaries (2a-e and 3a-e) was affirmed by the basic investigation, IR, ^1H NMR, and ^{13}C NMR.

Spectral Studies

In the IR spectrum of compound (2a-e and 3a-e), the C=N stretching mode appeared as strong absorption signal in the range of 1615-1600 cm^{-1} and C=O group range 1750-1690 cm^{-1} was absent which indicated the formation of the ring. Ar-H stretching vibrations were observed at 3050-3010 cm^{-1}. Symmetric and asymmetric $–SO_2$ stretching vibration also appeared at 1155-1135 and 1340-1310 cm^{-1}, respectively. The sharp peak observed in the range of 1500-1450 cm^{-1} as ring stretching mode to isoxazole ring in the compounds (3a-e) and stretching vibration for NH observed at 3245-3165 cm^{-1} confirming the presence of –NH group to pyrazole ring in the compounds (2a-e).

Table-1: Physical Data of Pyrazole and Isoxazole Derivatives (2a-e and 3a-e)

Compound	Molecular Formula	M.P. (°C)	Yield (%)	Elemental analysis Calculated (Found) %		
				C	H	N
2a	$C_{13}H_{14}O_4SN_2$	93	61	53.06 (52.83)	4.76 (4.13)	9.52 (9.13)
2b	$C_{18}H_{16}O_4SN_2$	105	52	60.67	4.49	7.86

				(59.89)	(4.20)	(7.10)
2c	$C_{23}H_{18}O_4SN_2$	157	58	66.02 (65.48)	4.30 (3.78)	6.69 (6.03)
2d	$C_{14}H_{16}O_5SN_2$	80	50	51.85 (51.23)	4.93 (4.23)	8.64 (8.15)
2e	$C_{15}H_{18}O_6SN_2$	85	49	50.84 (50.20)	5.08 (4.89)	7.90 (7.05)
3a	$C_{13}H_{13}O_5SN$	92	51	52.88 (52.03)	4.40 (4.02)	4.74 (4.36)
3b	$C_{18}H_{15}O_5SN$	103	49	60.50 (59.97)	4.20 (4.01)	3.92 (3.16)
3c	$C_{23}H_{17}O_5SN$	100	53	65.87 (65.48)	4.05 (3.78)	3.34 (3.09)
3d	$C_{14}H_{15}O_6SN$	189	50	51.69 (51.12)	4.61 (4.13)	4.30 (3.87)
3e	$C_{15}H_{17}O_7SN$	195	62	50.70 (50.25)	4.78 (4.06)	3.94 (3.25)

Table-2: IR Spectral Data (cm^{-1}) of Pyrazole and Isoxazole Derivatives (2a-e and 3a-e)

Compound	Ar-H	C-H	O-C		C=N	N-H	$-SO_2$	
2a	3010	2918	-		1615	3245	1155	1310
2b	3045	2885	-		1610	3165	1140	1340
2c	3030	2920	-		1612	3260	1150	1305
2d	3050	2890	1058	1248	1610	3240	1140	1326
2e	3035	2925	1060	1245	1615	3230	1155	1310
3a	3010	2850	-		1602	3165	1155	1310
3b	3015	2855	-		1600	-	1135	1340
3c	3030	2851	-		1610	-	1150	1305
3d	3019	2855	1058	1248	1615	-	1141	1326
3e	3045	2850	1060	1245	1603	-	1155	1310

In the ^1H NMR spectrum(2a-e and 3a-e), a broad singlet (unresolved, m) for four protons at δ 4.20-4.28 corresponding to the presence of the dioxane ring and not show the presence of methane proton as a singlet in the region δ 7.10-7.18 were absent, which confirmed the formation of the pyrazole and isoxazole ring. A signal at δ 8.11-8.41 showed the presence of one proton of –NH group in the pyrazole ring (2a-e). The ^{13}C NMR and elemental analysis data for the compound (2a-e and 3a-e) are dispense in Table-4,1 and these data suggest a valid positive argument for their structures.

Table-3: ^1H NMR Data (δ ppm) of Pyrazole and Isoxazole Derivatives (2a-e and 3a-e)

Compound	Ar-H	Dioxane ring	$-CH_3$	$O-CH_2-CH_3$	-NH
2a	7.06-7.98 (3H, m)	4.24-4.28 (4H,bs unresolved, m)	2.50 (6H,s)	-	8.29 (1H,s)
2b	7.49-7.86 (8H, m)	4.25-4.28 (4H,bs unresolved, m)	2.51 (3H,s)	-	8.11 (1H,s)
2c	7.06-7.80 (13H, m)	4.22-4.28 (4H,bs unresolved, m)	-	-	8.28 (1H,s)
2d	7.10-7.56 (3H, m)	4.25-4.28 (4H,bs unresolved, m)	2.45 (3H,s)	4.10(2H,q) 1.26(3H,t)	8.41 (1H,s)
2e	7.15-7.86 (3H, m)	4.20-4.28 (4H,bs unresolved, m)	-	4.12(4H,q) 1.29(6H,t)	8.30 (1H,s)
3a	7.26-7.84 (3H, m)	4.21-4.28 (4H,bs unresolved, m)	1.21 (6H,s)	-	-

3b	6.69-7.15 (8H, m)	4.20-4.28 (4H,bs unresolved, m)	1.25 (3H,s)	-	-
3c	6.56-7.26 (13H, m)	4.24-4.28 (4H,bs unresolved, m)		-	-
3d	7.20-7.28 (3H, m)	4.25-4.28 (4H,bs unresolved, m)	1.26 (3H,s)	4.21(2H,q) 1.21(3H,t)	-
3e	7.15-7.26 (3H, m)	4.21-4.28 (4H,bs unresolved, m)		4.18(4H,q) 1.17(6H,t)	-

Table-4: ^{13}C NMR Data (δ ppm) of Pyrazole and Isoxazole Derivatives (2a-e and 3a-e)

Compound	Ar-C	SO_2-C	O-C-C-O Dioxane ring	C=N	=C-O
2a	118.80-138-12	110.30	67.44	150.37	-
2b	118.70-138.10	108.22	67.35	151.42	-
2c	119.70-137.20	108.22	67.10	150.03	-
2d	116.70-138.10	108.34	67.10	151.42	-
2e	118.70-139.30	108.34	67.35	151.42	-
3a	118.85-138.08	110.30	66.56	150.38	162.12
3b	115.85-138.08	108.10	67.20	150.37	162.41
3c	118.85-138.10	108.18	67.35	151.20	162.30
3d	118.80-138.12	108.22	67.34	151.24	162.36
3e	118.85-138.10	108.22	67.36	151.38	162.36

CONCLUSION

The synthesis and characterization of substituted pyrazole (2a-e) and substituted isoxazole (3a-e) were adequately performed with provided conditions. A higher yield of compound (2a-e and 3a-e) was reported with refluxing through silica gel. Elemental analysis and spectral (IR, ^{1}H NMR and ^{13}C NMR) results were exhibiting a good agreement with predicted formulae.

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