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Synthesis of Isoxazolyl-benzenesulfonamide derived from N -[4-(2,3-dibromo-3-aryl-propanoyl)-phenyl]benzenesulfonamide

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ABSTRACT

N-[4-(2,3-dibromo-3-aryl-propanoyl)-phenyl]benzenesulfonamide on reaction with hydroxylamine hydrochlorde in ethanol in presence of catalytic amount of piperidine afforded N-(4-(5-arylisoxazol-3-yl)phenyl)benzenesulfonamides. Under microwave irradiation, reaction proceeds smoothly in ethanol without using piperidine. The reaction time was 4-5 minutes and yields were better. The synthesized compounds are characterized by elemental analysis, IR, ^{1}H NMR and Mass spectral data.

Key words- Microwave assisted synthesis, isoxazoles, benzenesulfonamides, chalcone-dibromides.

INTRODUCTION

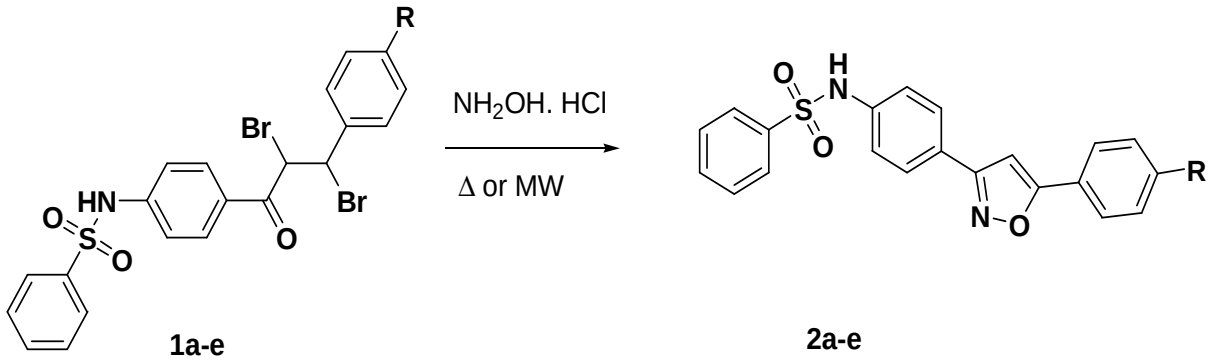
Isoxazoles are the important class of five member heterocycles and their bio-chemical behaviour have been studied over the years. Isoxazole derivatives have also proved to be a versatile building block for the synthesis of several important synthetic units such as β-hydroxy ketones [1], γ-amino alcohols [2], α,β-unsaturated oxime [3], and β-hydroxy nitriles [4]. Isoxazoles have long been popular moiety in synthetic organic chemistry for its known biological activities and pharmacological properties such as hypoglycaemic [5], anti-inflammatory [6], antivascular/ anticancer [7], antimycobacterial [8] and anti-microbial activity [9].

Many synthetic methods have been employed in the synthesis of isoxazoles including reactions of hydroxylamine with 1,3-dicarbonyl compounds [10], α,β-unsaturated carbonyl compounds [11] and α,β-unsaturated nitriles [12]. The reaction of an oxime-derived dianion and an ester [13] or amide [14] also provides isoxazoles. [3 + 2] Cycloaddition reactions between alkynes and nitrile oxides have also been developed [15].

Fokin et al [16] synthesized 3,5-disubstituted isoxazoles by a convenient one-pot, three-step procedure utilizing a regioselective copper(I)-catalyzed cycloaddition reaction between in situ generated nitrile oxides and terminal acetylenes. Gallardo et al [17], reported the synthesis of liquid crystals based on unsymmetrical 3,5-disubstituted isoxazole using 1,3 dipolar addition of chloro oximes and phenyl acetylenes. Reddy et al [18], reported isoxazolyl phenols from enaminoketones using montmorillonite K-10 as a heterogeneous catalyst. Larock et al [19], synthesised 3,5-disubstituted 4-halo(seleno)isoxazoles by the reaction of 2-alkyn-1-one O-methyl oximes with ICl, I_2, Br_2 , or PhSeBr. Katritzky et al [20], reported regioselective synthesis of 3,5-disubstituted isoxazoles from α-benzotriazolyl- α,β-unsaturated ketones and hydroxylamine. Recently, pharmaceutically important 3,5-disubstituted isoxazoles have been obtained by a simple cross-dehydrogenative coupling between nitrones and terminal alkynes using zinc triflate [21].

From the literature survey it is clear that synthesis of 3,5-diarylisoxazoles from chalcone dibromide is Prompted by these observations, it was contemplate to synthesize benzenesulphonamide derivatives, which is somehow linked to

isoxazole nucleus. We herein report the synthesis of N-[4-(5-aryl-1*H*/phenyl-isoxazol-3-yl)-phenyl]benzenesulfonamide under conventional heating conditions and microwave irradiation **(Scheme 1)**.



R= H, OMe, Cl, F, NMe_2

Scheme 1: Synthesis of N-(4-(5-arylisoxazol-3-yl)phenyl)-benzenesulfonamides

MATERIALS AND METHODS

All common reagents and solvents were used as obtained from commercial suppliers without further purification. All melting points were taken in open capillary in silicon oil bath and are uncorrected. Homogeneity of the synthesized compounds was checked on pre-coated TLC plates & spots were visualized using UV chamber. IR spectra were recorded in 1% KBr on Perkin-Elmer PARAGON 1000 spectrometer. ^1H NMR spectra were recorded on Brucker spectrometer (300 & 500 MHz) using TMS as internal standard. Mass spectra were recorded on Brucker micrOTOF-Q spectrometer.

General Procedure for synthesis of N-[4-(5-arylisoxazol-3-yl)-phenyl]-benzenesulfonamide
Method A: Conventional heating
1-(4-phenylsulphonamidophenl)-3-aryl-2,3-dibromopropanone **(2a-e)** (25 mmol), hydroxylamine hydrochloride (37.5 mmol) and and 2-3 drops of piperidine was refluxed in ethanol medium (25mL) until the TLC reported the consumption of starting material i.e. for 6-8 hrs. The reaction mixture was cooled and poured into aq. HCl (1M, 30 mL). The solid obtained was filtered, dried & purified by crystallization / column chromatography using proper eluent to get **3a-e**.

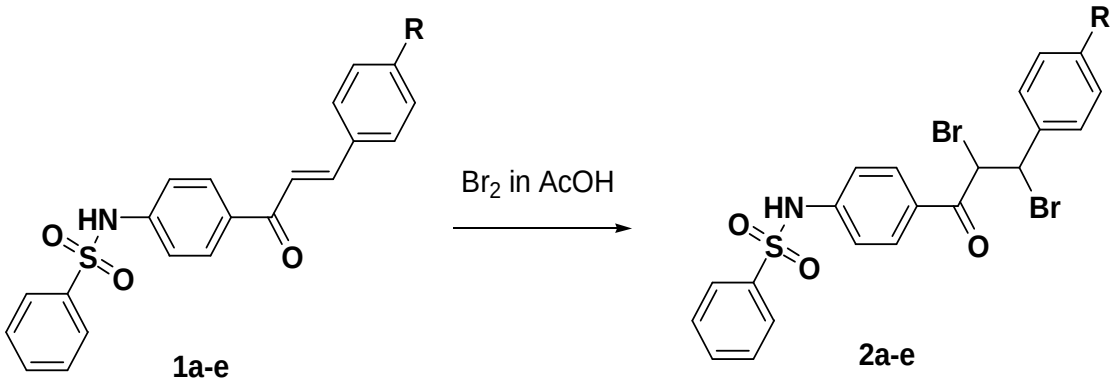
Method B: Microwave Irradiation
1-(4-phenylsulphonamidophenl)-3-aryl-2,3-dibromopropanone **(2a-e)** (25 mmol), hydroxylamine hydrochloride (37.5 mmol) and ethanol (2 mL) was irradiated with Microwave irradiation for 5-6 minutes. Then ethanol (10 mL) was added to it and it was stirred at room temp for 10 minutes. The reaction mixture was poured into crushed ice. The solid obtained was filtered, dried & purified by crystallization / column chromatography using proper eluent to get 3**a-d**.

N-[4-(5-Phenyl-isoxazol-3-yl)-phenyl]benzenesulfonamide 3a :
M.p. 70°C. Analysis calcd for $C_{21}H_{16}N2O_3S$: C, 67.01; H, 4.28; N, 7.44. Found C,; 66.97 H, 4.28; N, 7.39. IR (KBr) (vmax in cm^{-1}): 3244 (NH), 1597(C=N), 1339 & 1156 (SO_2 asymm. & symm.); ^1H NMR (DMSO-d_6) δ (ppm) : 7.11-8.05 (m, 15H, Ar-H+ =CH of isoxazole), 10.94 (s, 1H, SO_2NH; MS: m/z 377.4 [M+H]

N-[4-(5-(4-Chlorophenyl)-isoxazol-3-yl)-phenyl]benzenesulfonamide 3c
M.p. 120°C. Analysis calcd for $C_{21}H_{15}ClN_2O_3S$: C, 61.39; H, 3.86; N, 6.82. Found C, 61.23; H, 3.51; N, 6.79. IR (KBr) (vmax in cm^{-1}): 3245 (NH), 1608(C=N), 1332 & 1159 (SO_2 asymm. & symm.); ^1H NMR ($CDCl_3$) δ (ppm) : 7.18-8.11 (m, 14H, Ar-H+ =CH of isoxazole), 10.85 (s, 1H, SO_2NH); MS: m/z 411.1 [M+H]

RESULTS AND DISCUSSION

The starting material N- [4-(3-aryl-acryloyl)-phenyl]benzenesulfonamide **1a-e** were prepared by Claisen-Schmidt condensation of N-(4-acetyl-phenyl)-benzenesulfonamide with aromatic aldehydes in presence of NaOH / ethanol in good yields [22]. Compounds **1a-e** were treated with Br_2/AcOH to give N-[4-(2,3-dibromo-3-aryl-propanoyl)-phenyl]-benzenesulfonamide **2a-e** as per the reported procedure [23] **(Scheme 2)**.



R= H, OMe, Cl, F, NMe_2

Scheme 2: Bromination of N- [4-(3-aryl-acryloyl)-phenyl]benzenesulfonamide

Compounds **2a-e** were refluxed with hydroxyl amine hydrochloride in ethanol in presence of catalytic amount of piperidine to get **3a-d**. To demonstrate the utility of microwave irradiation in the synthesis of the titled isoxazoles, we attempted the successful synthesis of **3a-e** from **2a-e**. This method appeared to be fast, efficient and economical. The reaction was found to proceed smoothly with better yields under microwave irradiation within 5-6 minutes whereas under reflux conditions, 6-8 hrs were required **(Table 1)**

Table 1- Synthesis of N-[4-(5-aryl-isoxazol-3-yl)-phenyl]benzenesulfonamide under conventional heating conditions and microwave irradiation

Entry	R	Conventional Heating		Microwave Irradiation		Melting Point (° C)
		Time	% Yield	Time (min)	% Yield	
3a	H	6 h	71	5 min	84	70
3b	OCH_3	7h	58	4 min	74	140
3c	Cl	7h	74	5min	81	120
3d	F	8h	63	5 min	82	158
3e	NMe_2	7h	59	4 min	78	138

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