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Synthesis of novel 3-(4-methoxy benzene sulfonyl)-2-(1,3-benzodioxol-5-yl)-4-(substituted phenyl)-1,5-benzothiazepines

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ABSTRACT

An efficient synthesis of novel 2,3,4-trisubstituted 1,5-benzothiazepines **(4a-f)** incorporating 1,3-benzodioxol nucleus is described. Compound **(4a-f)** was synthesized by the reaction of substituted diketones **(3a-f)** with 2-aminothiophenol. Formation of compound **(3a-f)** was achived by the reaction of 4-methoxy benzene sulfonyl chloride **(1)** with substituted propane -1-(1,3-benzodioxol-5-yl)-3-phenyl-1, 3-dione **(2a-f)**. The structure of the compounds has been established by elemental, IR, ^{1}H NMR, ^{13}C NMR and Mass spectral analyses.

KEYWORDS

Chlorosulfonic acid;
2-Aminothiophenol;
1,3-Benzodioxol;
1,5-Benzothiazepine.

INTRODUCTION

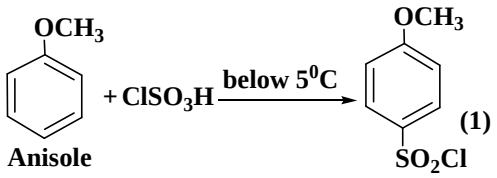
Development of new drugs with better activity is always required for clinical trial. Some of the most exciting and important advancements in organic chemistry are occurring in heterocyclic compounds. The utility of 1,5-benzothiazepines and its derivatives as medicament is well explored. A literature survey reveals the enhanced bioactivity of annulated benzothiazepines, such as antimicrobial[1,2], antipsychotropic[3] antihypertensive[4], cardiovascular[5], antiasthemic[6], platelate aggregation inhibitor and Ca antagonist[7]. The protective effect of *diltiazem* against the ischemia was flow independent[8]. Recently Ahmed et al.[9,10] patented 1,5-benzothiazepine derivatives as potential anticancer drugs. The superiority of *diltiazem* over other conventional vasodilators has resulted in to discovery of other useful compounds in recent years.

The research on the compounds containing sulfonyl group have been a focus of attention for a long time due to their diversified biological activities. Sulfones occupy a unique position in the drug industry with their antimalarial[11], bactericidal[12] and antitubercular activity against *Mycobaacterium tuberculosis*[13]. Antimalarial activity of *Acedapson* (sulfone) has been studied against *plasmodium berghii*[11]. The sulfone *Depsone* (sulfone) is well known antileprotic drug[14,15]. The 1,3-benzodioxole units can also be identified in some clinical antitumor agents like etoposide and teniposide[16]. Several heterocycles containing a dioxolane ring has been shown to possess antiviral activities[17]. Ayapin is a heterocycle containing dioxolane ring which shows antifungal[18], trypanomicidal[19] and hemocoagulant activities[20].

The presence of methoxy groups in phenyl ring located at position -2 in 1,5-benzothiazepine-4(5H)-one in the popular drug "diltiazem" attracted the attention to

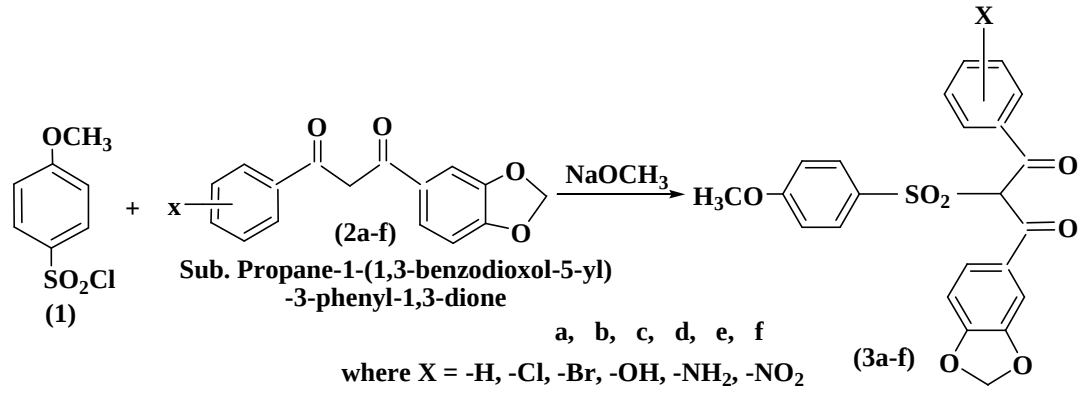
synthesize 1,5-benzothiazepines having methoxy group at position-4 in the phenyl ring. Recently, Nigam et al.[21], reported the synthesis of few derivatives of 2,4-disubstituted 1,5- benzothiazepines. Relatively large number of 1,5- benzothiazepine derivatives having various substituents at position-2,3,4,5 have been reported in the literature[22-24]. This resulted in a process of numerous surprising discoveries and persistent development pursuits took place for a long period of time before a leading compound was first discovered and then established as a drug.

To the best of our knowledge, there is no report on the synthesis of 2,3,4 tri substituted 1,5-benzothiazepine, incorporating 1,3-benzodioxol unit. Hence for the above mentioned reason and in a continuous to our research for better and improved cardiovascular drugs, we investigated the synthesis of novel 3-(4-methoxy benzene sulfonyl)-2-(1,3-benzodioxol-5-yl) -4-(substituted phenyl)-1,5-benzothiazepines with the assumption that the incorporation of more than one bioactive heterocyclic moiety in to a single framework may result in to the production of novel heterocycles with enhanced bioactivity.

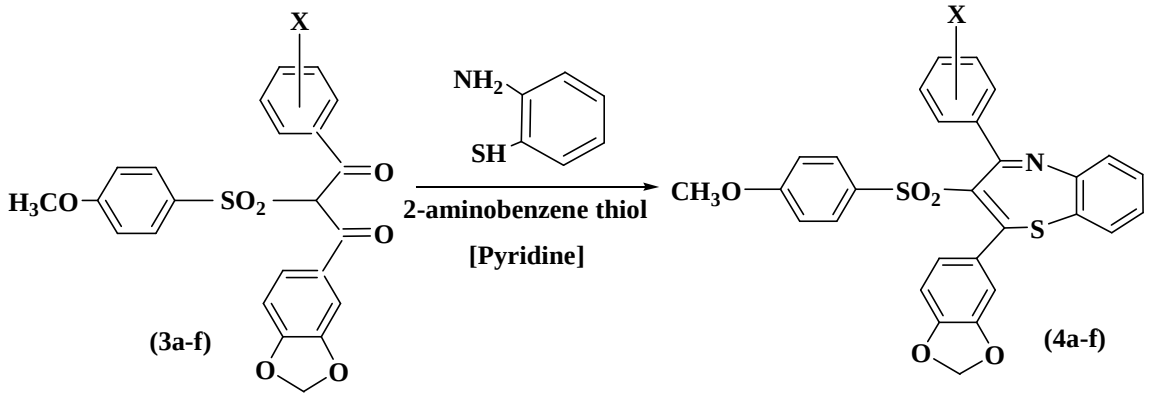


RESULT AND DISCUSSION

Anisole was first sulphonated with $ClSO_3H$ (chlorosulphonic acid) to afford the 4-methoxy benzene sulfonyl chloride which was condensed with substituted propane-1-(1,3-benzodidioxol-5-yl)-3-phenyl-1,3-dione **(2a-f)** in the presence of sodium methoxide to yield **(3a-f)**. The condensation of **(3a-f)** with 2-amino thio phenol in presence of pyridine afforded **(4a-f)**(SCHEME 1-3). It appears that the reaction is initi-



SCHEME 3



SCHEME 3

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TABLE 1: Elemental analysis data of title compounds

Compd. no.	M.F.	M.W	Elemental analysis calcd. (found)				M.P. (^{0}C)	Yield (%)
			C %	H %	N %	X %		
(4a)	$C_{29}H_{21}NO_5S_2$	528	65.90(65.59)	4.16(3.95)	2.65(2.41)	-	143	53
(4b)	$C_{29}H_{20}NO_5S_2Cl$	561.5	61.97(61.64)	3.73(3.52)	2.49(2.31)	6.32(6.07)	164	49
(4c)	$C_{29}H_{20}NO_5S_2Br$	606	57.42(57.03)	3.46(3.24)	2.31(2.03)	13.03(12.81)	132	59
(4d)	$C_{29}H_{21}NO_6S_2$	544	63.97(63.66)	4.04(3.81)	2.57(2.32)	-	172	34
(4e)	$C_{29}H_{22}N_2O_5S_2$	543	64.08(63.74)	4.23(4.04)	5.15(4.92)	-	157	39
(4f)	$C_{29}H_{20}N_2O_7S_2$	573	60.73(60.34)	3.66(3.44)	4.88(4.65)	-	148	35

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

Compd. no.	X	Ar-OCH_3	OCH_2O (2H,S)	Methine (1H,S)	Aromatic protones(15H,m)
(4a)	-H	3H,3.85s	6.04	6.64	6.84-7.72(16H,m)
(4b)	-Cl	3H,3.81s	6.07	6.72	6.78-7.93
(4c)	-Br	3H, .85s	6.02	6.66	6.81-7.95
(4d)	-OH	3H,3.85s	6.02	6.65	6.75-7.92
(4e)	$-NH_2$	3H,3.84s	6.04	6.71	6.83-7.99
(4f)	$-NO_2$	3H,3.85 s	6.05	6.68	6.71-7.96

TABLE 3 : ^{13}C NMR data of the title compounds(in δ ppm)

Compd. no.	X	O-C	O(C)O	C2	C3	C4	Aromatic carbons
(4a)	-H	55.4	101.6	136.1	91.5	150.9	159.0-109.2
(4b)	-Cl	55.4	101.2	138.6	92.2	151.0	160.1-107.5
(4c)	-Br	55.7	101.4	136.9	91.0	151.1	159.2-105.0
(4d)	-OH	55.3	101.8	138.3	91.5	151.7	159.1-107.2
(4e)	$-NH_2$	55.4	101.3	136.5	92.3	151.3	159.7-106.2
(4f)	$-NO_2$	55.4	101.7	137.0	92.0	150.8	159.3-107.0

ated by nucleophilic attack of sulphydryl electrons rather than by lone pair of electron of amino group, at enolic carbon of β -diketone and than dehydrative cyclisation results in 1,5- benzothiazepines.

The IR spectra of the compounds **(4a-f)** indicated the completion of reaction as the characteristic absorption band in the range 1700-1640 cm^{-1} for C=O functional group was absent. The weak bands were observed in the region 680-660 cm^{-1} may be assigned to C-S linkage[25]. All of these compounds show absorption band at 3028-3015 cm^{-1}, which was due to Ar-H stretching vibration. Strong absorption bands appeared at 1145 and 1305 cm^{-1}accounting for the symmetric and asymmetric $-SO_2$ stretching vibrations. All these compounds showed absorption in the range 1615-1600cm^{-1} due to stretching vibration of C=N in benzothiazepine ring. The absorptions at 1260-1230 cm^{-1} and 1050-1028cm^{-1} may be assigned to C-O-C stretching vibrations.

The ^{1}H NMR spectra of compounds **(4a-f)** showed a complicated pattern in the aromatic region at δ 6.71-7.99 ppm indicates the presence of aromatic protons. A singlet is obtained for dioxymethylene (O-CH_2-O) protons at δ 6.02-6.07. Compound also exhibited a singlet for three proton of O-CH3 group at δ 3.81-3.85 (TABLE 2).

The 13C NMR spectral data for the compound **(4a-f)** are presented in TABLE 3 and these data are in good agreement with their structures. Aromatic carbon of ring A, B and C are observed at around δ 162.7-114.3, δ 149.4-106.0 and δ148.4-126.0 respectively .The absorption signals observed at around δ101.6-101.2 was observed due to O(C) O carbon. Absorption in the range δ 96.5-97.6 may be assigned to -CH= carbon(TABLE 3).

In the mass spectra all these compounds shows molecular ion peak. The mass spectrum of 4b shows a cluster of absorption peak at m/z, 561 and 563 corresponds to M^+,$[M+2]^+$ respectively, with one third intensity of $[M+2]^+$ w.r.t. M^+, showing the presence of chlorine. While in compound **(4c)**, the intensity of [M+2]+ peak and M+ peak were found to be nearly equal, confirming the presence of bromine atom. The structure of newly synthesized compound is well supported by spectroscopic data (SCHEME 1-3, TABLES 1-3).

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on a Nicolet-Megna FT-IR 550 spectrophotometer in KBr pellets. The ^{1}H NMR and ^{13}C NMR spectra were scanned in $CDCl_3$ on an DRX-300 spectrometer at 300.13, using TMS as an internal standard. The Mass spectra were recorded on a Jeol D-300 spectrometer. TLC checked the purity of compounds.

Synthesis of 4-methoxy benzene sulphonyl choride (1)

Pure chlorosulphonic acid (11.9 ml, 0.05 M) was taken in a three necked round bottomed flask (500 ml)

fitted with a reflux condenser, dropping funnel and mercury seal with mechanical stirrer. The temperature of the flask was maintained below 5^0C by placing it in an ice bath (ice-salt mixture). To this anisole (methoxy benzene) (5.44 ml., 0.05 M) was added dropwise using dropping funnel with continuous stirring. The excess of HCl gas was removed during the reaction.

After the complition of the reaction, mixture was kept overnight in refrigerator. The reaction mixture was poured into crushed ice. The white solid obtained was filtered, washed 4-5 times with ice-cold water and dried. The crude solid was dissolved in a mixture of equal volume of benzene and acetone. The solution was filtered, concentrated and then kept at room temperature overnight. Crystalline 4-methoxy benzene sulphonyl chloride separated out. (m.p. 41^0C, yield 8.36g, 81 %)

Preparation of substitued β-diketones(3a-f)

Placed substitued propane-1-(1,3-benzodioxol-5-yl)-3-phenyl-1,3-dione (0.01 M) and sodium methoxide (0.54 g., 0.01M) in a dry round bottomed flask fitted with a guard tube and stirred for one hour on a magnetic stirrer at 50^0C-60^0C, until a creamy mass was obtained. The sulphonyl chloride derivative (1) (2.06 g., 0.01 M) was then added in small portion and dry toluene (5 ml) was added as solvent to effect proper stirring of the reaction mixture. The reaction mixture was refluxed at a temperature of 110^0C for about thirty-two hours. The completion of the reaction was monitored through TLC. After the reaction was completed the reaction mass was cooled and toluene was removed under reduced pressure. The reaction mixture was extracted using chloroform and then washed with water. The chloroform layer was then dried over anhy. Na_2SO_4. The chloroform was distilled off and purification of the compound was done by column chromatography using silica gel as absorbent and $CHCl_3$: MeOH (9:1) as mobile phase. The product was recrystallized from pet ether. Purity of the diketone was checked through TLC using (petroleum ether: acetone: 7:3) upper layer as mobile phase.

Preparation of substitued 1,5-benzothiazepines

2-Aminobenzenethiol (0.05m mol) was added to the stirred suspension of β-diketone **(3a-f)** (0.05m mol) in pyridine and the resulting mixture was refluxed for 5≈h. The mixture was cooled and poured on to crushed ice dropwise with vigorous stirring. The pale yellow precipitate formed was filtered, dried and crystallized from methanol. Purity of the compounds were checked by TLC using ($CHCl_3$:CH_3OH, 8:2) as mobile phase.

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