

Silica Sulfuric Acid를 이용한 효율적인 1,4-diazepine and 1,5-benzodiazepine 유도체의 합성

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Silica Sulfuric Acid as a Mild and Efficient Reagent for the Synthesis of 1,4-Diazepine and 1,5-Benzodiazepine Derivatives

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요약. Silica sulfuric acid (SSA)를 이용하여 ethylenediamine (EDA)과 *o*-phenylenediamine (*o*-PDA)을 2-(4-methylthio benzenesulfonyl)-1,3-dimethyl/1-methyl-3-phenyl/1,3-diphenyl/1-methyl-3-ethoxypropane-1,3-dione **3a-d**과의 헤테로고리화 반응을 통하여 좋은 생리활성을 나타내는 1*H*-1,4-diazepines **4a-d**과 3*H*-1,5-benzodiazepines **5a-d**을 좋은 수율로 합성하였다. 이 반응에서 β -diketones/ β -ketoesters **3a-d**는 4-methylthiobenzenesulfonyl chloride **1**과 다양한 β -diketones/ β -ketoesters **2a-d**과의 축합반응으로 합성하였으며, 합성한 **4a-d**와 **5a-d** 화합물들에 대해서 antimicrobial, antifungal 및 anthelmintic 활성을 측정하였다.

주제어: 3*H*-1,5-Benzodiazepines, 1*H*-1,4-Diazepines, Ethylenediamine, *o*-Phenylenediamine, Silica sulfuric acid

ABSTRACT. The synthesis of biologically active 1*H*-1,4-diazepines **4a-d** and 3*H*-1,5-benzodiazepines **5a-d** in good yields, from the heterocyclization reaction of 2-(4-methylthio benzenesulfonyl)-1,3-dimethyl/1-methyl-3-phenyl/1,3-diphenyl/1-methyl-3-ethoxy propane-1,3-dione **3a-d** with ethylenediamine (EDA) and *o*-phenylenediamine (*o*-PDA), respectively, in the presence of silica sulfuric acid (SSA) is described. The novel β -diketones/ β -ketoesters **3a-d** were synthesized by the condensation reaction of 4-methylthiobenzenesulfonyl chloride **1** with various β -diketones/ β -ketoesters **2a-d**. All structures of the newly synthesized compounds were elucidated by elemental analysis and spectral studies. The compounds **4a-d** and **5a-d** have been screened for antimicrobial, antifungal and anthelmintic activity.

Keywords: 3*H*-1,5-Benzodiazepines, 1*H*-1,4-Diazepines, Ethylenediamine, *o*-Phenylenediamine, Silica sulfuric acid

INTRODUCTION

Heterocyclic compounds have recently attracted attention as an important class of organic chemistry in the field of drugs and pharmaceuticals.¹ A large number of heterocyclic compounds derived from β -diketones have been reported as active entities.² β -Diketones are important precursors for the synthesis of pharmacologically active heterocyclic compounds as 1,4-diazepines and 1,5-benzodiazepines. These compounds are widely used as anticonvulsant,³ anti-HIV,⁴ CNS activity,⁵ anti-ulcer,⁶ anti-proliferative,⁷ antitumor agents,⁸ antianxiety,⁹ and HDM2 antagonists.¹⁰ These were also inhibitor of the bacterial

enoyl-ACP reductase, FabI,¹¹ antidepressive¹² as well as anti-inflammatory agents.¹³ Other than their biological importance, benzodiazepines derivatives are also commercially used as dyes for acrylic fibers.¹⁴

There are various methods for the synthesis of diazepines and benzodiazepines by the condensation of *o*-phenylenediamines with α,β -unsaturated carbonyl compounds, β -haloketones, or ketones in the presence of acid.¹⁵ A variety of reagents, such as BF₃-etherate, NaBH₄, polyphosphoric acid, or SiO₂, MgO/POCl₃, Yb(OTf)₃, Sc(OTf)₃, Al₂O₃/P₂O₅, (bromodimethyl) sulfonium bromide or under microwave irradiation are utilized for condensation reactions.¹⁶ However, these methods are associated with sev-

eral drawbacks such as harsh reaction conditions, complex and tedious experimental procedures and low yields. In recent years the use of organic-inorganic hybrid immobilized solid support reagents have received great interest. Such reagents not only simplify the purification process but also provide help in preventing the release of reaction residues into the environment.¹⁷ Furthermore, from the synthetic point of view, these reagents significantly reduce reaction time and make the workup easier. Recently, silica and sulfuric acid in dichloromethane have been reported for the oxathioacetalization of carbonyl compounds.¹⁸ The efficiency of silica sulfuric acid (SSA), under operationally simple conditions, has prompted us to explore the possibility of using this reagent for the synthesis of 1*H*-1,4-diazepine and 3*H*-1,5-benzodiazepines from the reaction of β -diketones/ β -ketoesters with ethylenediamine (EDA) and *o*-phenylenediamine (*o*-PDA), respectively.

In continuation of our ongoing research program to develop new reagents and synthetic procedure for the synthesis of novel heterocyclic compounds,¹⁹⁻²¹ we report here a new convenient method for the synthesis of 2-(4-methylthiobenzenesulfonyl) containing 1*H*-1,4-diazepines and 3*H*-1,5-benzodiazepines due to their importance in medicinal chemistry. To achieve this target, we had synthesized β -diketones/ β -ketoesters **3a-d** which were condensed with EDA and *o*-PDA in the presence of SSA, to obtain the corresponding substituted 1*H*-1,4-diazepines **4a-d** and 3*H*-1,5-benzodiazepines **5a-d**, respectively, in high yields.

RESULTS AND DISCUSSION

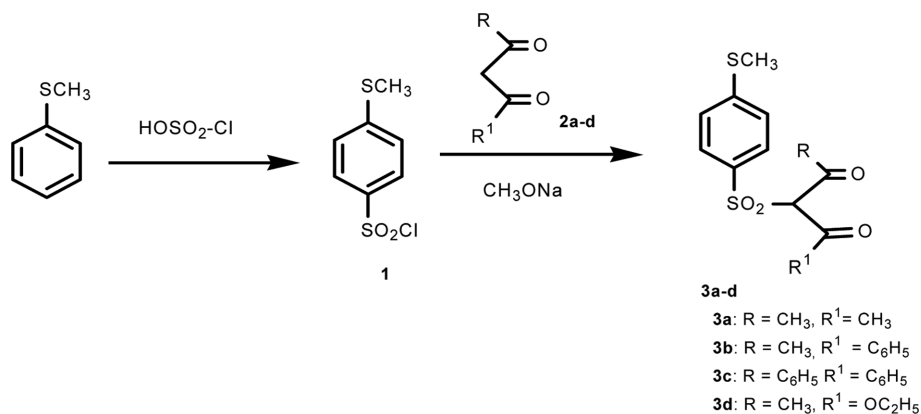
Thioanisole was sulfonated with chlorosulfonic acid, to obtain 4-(methylthio)benzenesulfonyl chloride **1**. This compound **1**, on condensation with various β -diketones/ β -

ketoesters **2a-d** in the presence of sodium methoxide yielded corresponding substituted β -diketones/ β -ketoesters **3a-d** (Scheme 1). All newly synthesized compounds were characterized by elemental analysis and spectral studies (experimental section). When compounds **3a-d** were treated with ethylenediamine in the presence of SSA underwent dehydrative annulation to afford novel substituted 1*H*-1,4-diazepines **4a-d**. Further **3a-d** were treated with *o*-phenylenediamine on similar reaction conditions, to obtain 3*H*-1,5-benzodiazepines **5a-d** (Scheme 2). SSA was prepared by reported method.²²

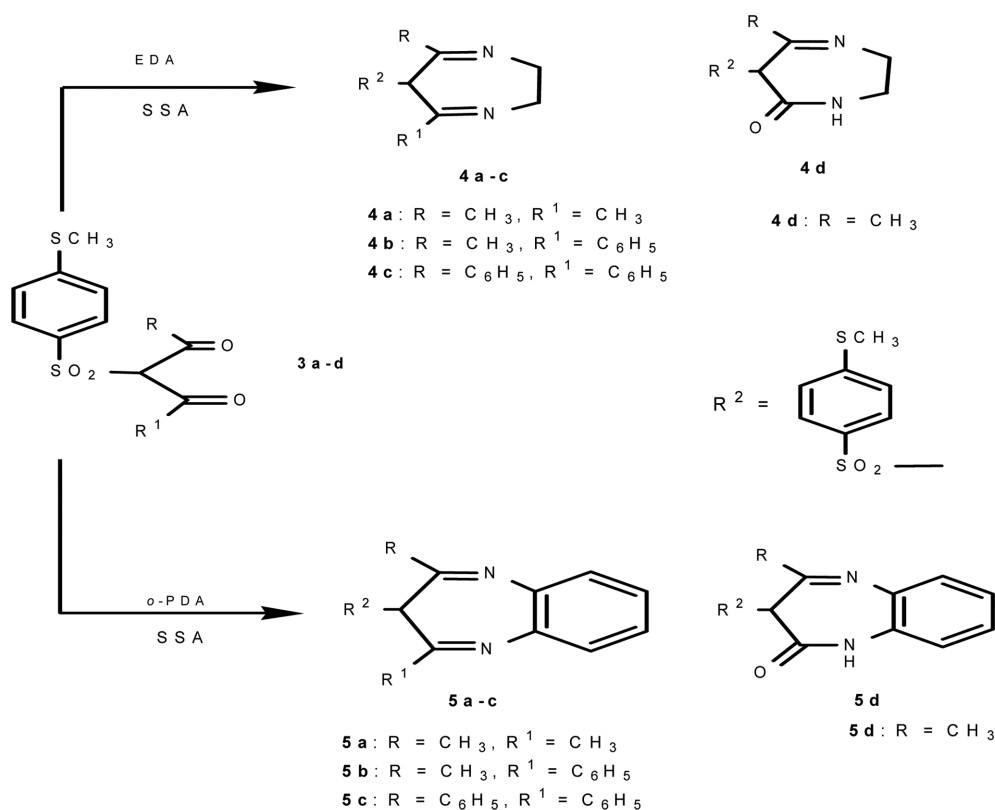
Antimicrobial, antifungal and anthelmintic activities of compounds **4a-d** and **5a-d**

The newly synthesized diazepines **4a-d** and benzodiazepines **5a-d** were evaluated for the antibacterial activity against *Staphylococcus aureus*, *Klebsiella pneumoniae* and antifungal activity against *Aspergillus niger*, *Candida albicans* by the cup-plate method.²³ Ciprofloxacin and ciclopiroxolamine were used as standards for comparison of antibacterial and antifungal activities, respectively. The results indicate that these compounds were active against all the four organisms. The anthelmintic activity was carried out on earth worms *Pheritima posthuma*, by a technique as described by Bagavant *et al.* with slight modification.²⁴ Piperazine citrate was used as standard drug. The values of antimicrobial and anthelmintic activity are terms of mean \pm SEM of results done in triplicate, reported in Table 1. The compounds **4a-c** and **5a-c** exhibited antimicrobial as well as antifungal activities, but **4d** and **5d** showed significant anthelmintic activity due to presence of more electronegative groups.

From these results it is apparent that attempts to introduce functionality methyl/phenyl at position 5 and 7 resulted in significantly increased antibacterial and antifungal



Scheme 1.



Scheme 2.

Table 1. Antimicrobial, antifungal and anthelmintic activities of compounds 4a-d and 5a-d

Compd.	Antibacterial activity zone of inhibition in mm ^a			Antifungal activity zone of inhibition in mm ^a		Anthelmintic activity in min. ^a	
	<i>S. aureus</i>	<i>K. pneumoniae</i>	<i>A. niger</i>	<i>C. albicans</i>	Paralysis	Death	
4a	21±0.57	20±0.65	19±0.58	21±0.58	92±0.65	103±0.48	
4b	19±0.48	19±0.57	18±0.54	19±0.57	93±0.69	110±0.57	
4c	21±0.65	18±0.85	20±0.57	20±0.54	91±0.57	111±0.54	
4d	15±0.75	16±0.54	17±0.55	16±0.48	101±0.85	121±0.48	
5a	22±0.57	21±0.65	19±0.58	21±0.58	92±0.65	99±0.48	
5b	20±0.48	20±0.57	18±0.54	19±0.57	93±0.69	103±0.57	
5c	21±0.65	18±0.85	20±0.57	20±0.54	92±0.57	104±0.54	
5d	16±0.75	17±0.54	16±0.55	16±0.48	98±0.85	115±0.48	
Ciprofloxin	24±0.57	26±0.24	--	--	--	--	
Ciclopirox-olamine	--	--	22±0.44	24±0.74	--	--	
Piperazine citrate	--	--	--	--	100±0.57	125±0.57	

^aValues are in terms of Mean±SEM of results done in triplicate.

activities due to its electron donating character but steric hindrance also played a major important role. The diazepam-5-one and benzodiazepam-2-one showed more anthelmintic activity than others due to more electronegativity of oxygen. This result implies that the presence of electron withdrawing groups at position 5 in diazepam and position 2 of benzodiazepam can increase anthelmintic activity.

CONCLUSION

In conclusion, this new method for the synthesis of 1*H*-1,4-diazepines and 3*H*-1,5-benzodiazepines using silica sulfuric acid (SSA) offers significant improvement over existing method. Also, this simple and reproducible method affords various 1*H*-1,4-diazepines and 3*H*-1,5-benzodiazepines with short reaction times, high yields and with-

out the formation of undesirable by products. Among the synthesized compounds evaluated (**4a-d** and **5a-d**), compound **4a-c**, **5a-c** exhibited antimicrobial as well as anti-fungal activities in comparison the standard drug but compounds **4d** and **5d** showed significant anthelmintic activity. More extensive study is needed to confirm the preliminary results and mode of action studies are required to be able to optimize the effectiveness of this series of compounds **4a-d** and **5a-d**.

EXPERIMENTAL

Instrumentation

All the melting points were determined in open capillary tubes and are uncorrected. The purity of the newly synthesized compounds was checked by TLC on aluminum oxide 60 F₂₅₄ plates (Merck) and spots were visualized by exposing the dry plates in iodine vapor. The IR spectra were recorded on a Nicolet-Magna-FT-IR-550 spectrometer in using KBr pellets. ¹H NMR and ¹³C NMR spectra were run on model DRX 300 at 300.13 MHz and 75 MHz, respectively, in CDCl₃ and mass spectra on a LCMS instrument. The elemental analysis (C, H, N) of compounds was performed on Carlo Erba-1108 element analyzer. Their results were found to be in good agreement with the calculated values.

General procedure for the preparation of 2-[(4-methylthio)benzenesulfonyl]-1,3-dimethyl/1-methyl-3-phenyl/1,3-diphenyl/1-methyl-3-ethoxypropane-1,3-dione (**3a-d**)

Sodium methoxide (0.54 g, 10.0 mmol) and β-diketones (10.0 mmol) were placed in a dried round bottom flask and stirred for 1 h on a magnetic stirrer at 50 °C, after which a creamy mass was obtained. The 4-(methylthio)benzenesulfonyl chloride **1** (2.22 g, 10.0 mmol) was taken in dry toluene and added drop by drop in above said reaction mass. The reaction mixture was refluxed for 7 h at 100 °C with stirring. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled and toluene was removed under reduced pressure. The reaction mixture was extracted using chloroform and washed with water. The chloroform layer was dried using anhydrous sodium sulfate and distilled to yield the solid compound. The product was purified by column chromatography over silica gel using pet ether: ethyl acetate (1:2) as an eluent. It was purified by recrystallization from absolute ethanol. Purity of the compound was checked by TLC on aluminum oxide 60 F₂₅₄ plates (Merck) in a 7:2:1 (ben-

zene:ethanol:ammonia) upper layer using as a mobile phase. The yield and spectral data were reported in experimental section.

2-[(4-Methylthio)benzenesulfonyl]-1,3-dimethylpropane-1,3-dione (3a). 2.23 g (78%), mp 145 °C; Anal. Calcd. C₁₂H₁₄O₄S₂: C, 50.33; H, 4.93; S, 22.39. Found: C, 50.35; H, 4.90; S, 22.40. IR (KBr): 3025 (Ar-H), 2915 (C-H), 1700 (C=O), 1290, 1415 (S-CH₃), 1345, 1140 (-SO₂) cm⁻¹; ¹H NMR (CDCl₃): δ 1.58 (s, 6H, CH₃), 2.46 (s, 3H, S-CH₃), 6.07 (s, 1H, -CH=), 7.40 (dd, *J* = 7.46, 6.89 Hz, 2H, Ar-H), 7.55 (dd, *J* = 7.45, 6.89 Hz, 2H, Ar-H); ¹³C NMR (CDCl₃): δ 18.9, 19.3, 106.2, 127.6, 129.0, 136.9, 198.4; MS (*m/z*): 287 (M+H⁺).

2-[(4-Methylthio)benzenesulfonyl]-1-methyl-3-phenylpropane-1,3-dione (3b). 2.56 g (74%), mp 145 °C; Anal. Calcd. C₁₅H₁₆O₄S₂: C, 58.60; H, 4.63; S, 18.41. Found: C, 58.57; H, 4.62; S, 18.40. IR (KBr): 3030 (Ar-H), 2919 (C-H), 1715 (C=O), 1295, 1410 (S-CH₃), 1345, 1140 (-SO₂) cm⁻¹; ¹H NMR (CDCl₃): δ 1.58 (s, 3H, CH₃), 2.45 (s, 3H, S-CH₃), 6.08 (s, 1H, -CH=), 7.40-7.86 (m, 10H, Ar-H); ¹³C NMR (CDCl₃): δ 18.9, 19.2, 101.2, 125.7, 127.6, 128.4, 128.6, 129.0, 132.9, 136.9, 137.5, 198.4; MS (*m/z*): 349 (M+H⁺).

2-[(4-methylthio)benzenesulfonyl]-1,3-diphenylpropane-1,3-dione (3c). 3.54 g (82%), mp 155 °C; Anal. Calcd. C₂₂H₁₈O₄S₂: C, 64.37; H, 4.42; S, 15.62. Found: C, 64.35; H, 4.40; S, 15.63. IR (KBr): 3020 (Ar-H), 2915 (C-H), 1710 (C=O), 1300, 1420 (S-CH₃), 1345, 1140 (-SO₂) cm⁻¹; ¹H NMR (CDCl₃): δ 2.46 (s, 3H, S-CH₃), 6.10 (s, 1H, -CH=), 7.65-7.80 (m, 14H, Ar-H); ¹³C NMR (CDCl₃): δ 19.8, 101.2, 125.7, 127.6, 128.4, 128.6, 129.0, 132.9, 136.9, 137.5, 198.4; MS (*m/z*): 411 (M+H⁺).

2-[(4-Methylthio)benzenesulfonyl]-1-methyl-3-ethoxypropane-1,3-dione (3d). 2.42 g (73%), mp 105 °C; Anal. Calcd. C₁₃H₁₆O₅S₂: C, 49.35; H, 5.10; S, 20.27. Found: C, 49.36; H, 5.13; S, 20.25. IR (KBr): 3030 (Ar-H), 2915(C-H), 1720 (C=O), 1297, 1415 (S-CH₃), 1350, 1145 (-SO₂), 1210, 1240 (C-O-C) cm⁻¹; ¹H NMR (CDCl₃): δ 1.30 (t, *J* = 7.25 Hz, 3H, CH₃CH₂-), 2.08 (s, 3H, CH₃), 4.12 (q, *J* = 7.26 Hz, 2H, O-CH₂CH₃), 2.45 (s, 3H, S-CH₃), 6.15 (s, 1H, -CH=), 7.40 (dd, 2H, *J* = 7.46, 6.89 Hz, Ar-H), 7.55 (dd, *J* = 7.25, 7.09 Hz, 2H, Ar-H); ¹³C NMR (CDCl₃): δ 14.7, 18.9, 19.3, 59.5, 106.2, 127.6, 129.0, 136.9, 198.4; MS (*m/z*): 317 (M+H⁺).

General procedure for the preparation of 1*H*-1,4-diazepine **4a-d** and 3*H*-1,5-benzodiazepine **5a-d** derivatives

An equimolar ratio of β-diketones/β-ketoesters (10 mmol) **3a-d**, and EDA/*o*-PDA (10.0 mmol) in ethyl ace-

tate (50 mL) in the presence of silica sulfuric acid (10.0 mmol) was stirred 50 °C for 2 h. The progress of reaction was monitored by TLC using 7:2:1 (benzene:ethanol: ammonia) upper layer as mobile phase. Upon completion of reaction, the mixture was extracted with ethyl acetate (2 × 25 mL) and the solvent was removed. The crude product was washed with dry ether and recrystallized from pet ether:ethyl acetate (1:1). The product was purified by column chromatography over silica gel using pet ether:ethyl acetate (40: 60) as an eluent.

6-[(4-Methylthio)benzenesulfonyl]-5,7-dimethyl-2,3-dihydro-1H-1,4-diazepine (4a). 2.35 g (76%), mp 160 °C; Anal. Calcd. C₁₄H₁₈N₂O₂S₂: C, 54.17; H, 5.84; N, 9.02. Found: C, 54.15; H, 5.85; N, 9.03. IR (KBr): 3050 (Ar-H), 2895 (C-H), 1580 (C=N), 1290, 1415 (S-CH₃), 1345, 1140 (-SO₂) cm⁻¹; ¹H NMR (CDCl₃): δ 2.07 (s, 6H, CH₃), 2.46 (s, 3H, S-CH₃), 3.10 (t, *J* = 6.98 Hz, 4H, N-CH₂-CH₂-N), 6.05 (s, 1H, -CH=), 7.43 (dd, *J* = 7.46, 6.89 Hz, 2H, Ar-H), 7.59 (dd, *J* = 7.46, 6.89 Hz, 2H, Ar-H); ¹³C NMR (CDCl₃): δ 12.7, 18.9, 48.5, 70.3, 114.5, 125.7, 127.6, 127.9, 128.4, 134.3, 140.5, 164.7; MS (*m/z*): 311 (M+H⁺).

6-[(4-Methylthio)benzenesulfonyl]-5-methyl-7-phenyl-2,3-dihydro-1H-1,4-diazepine (4b). 2.39 g (69%), mp 145 °C; Anal. Calcd. C₁₉H₂₀N₂O₂S₂: C, 61.26; H, 5.41; N, 7.52. Found: C, 61.28; H, 5.40; N, 7.50. IR (KBr): 3030 (Ar-H), 2919 (C-H), 1580 (C=N), 1295, 1410 (S-CH₃), 1350, 1145 (-SO₂) cm⁻¹; ¹H NMR (CDCl₃): δ 2.10 (s, 3H, CH₃), 2.50 (s, 3H, S-CH₃), 3.10 (t, *J* = 6.90 Hz, 4H, N-CH₂-CH₂-N), 6.10 (s, 1H, -CH=), 7.45-7.88 (m, 10H, Ar-H); ¹³C NMR (CDCl₃): δ 15.3, 18.9, 47.9, 48.5, 70.3, 114.5, 125.7, 126.5, 127.6, 127.9, 128.7, 130.7, 135.3, 140.9, 164.8; MS (*m/z*): 378 (M+H⁺).

6-[(4-Methylthio)benzenesulfonyl]-5,7-diphenyl-2,3-dihydro-1H-1,4-diazepine (4c). 5.36 g (83%), mp 175 °C; Anal. Calcd. C₂₄H₂₂N₂O₂S₂: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.33; H, 5.08; N, 6.47. IR (KBr): 3030 (Ar-H), 2920 (C-H), 1585 (C=N), 1295, 1410 (S-CH₃), 1345, 1140 (-SO₂) cm⁻¹; ¹H NMR (CDCl₃): δ 2.45 (s, 3H, S-CH₃), 3.15 (t, *J* = 7.05 Hz, 4H, N-CH₂-CH₂-N), 6.09 (s, 1H, -CH=), 7.65-7.80 (m, 14H, Ar-H); ¹³C NMR (CDCl₃): δ 18.9, 47.9, 72.3, 114.5, 125.7-137.9, 164.7; MS (*m/z*): 435 (M+H⁺).

6-[(4-Methylthio)benzenesulfonyl]-7-methyl-2,3,4,6-tetrahydro-1H-1,4-diazepine-5-one (4d). 2.46 g (78%), mp 140 °C; Anal. Calcd. C₁₃H₁₆N₂O₃S₂: C, 49.98; H, 5.16; N, 8.97. Found: C, 50.00; H, 5.15; N, 8.95. IR (KBr): 3350 (N-H), 3030 (Ar-H), 2915 (C-H), 1740 (C=O), 1630 (C=N), 1295, 1410 (S-CH₃), 1345, 1140 (-SO₂) cm⁻¹; ¹H NMR (CDCl₃): δ 1.83 (s, 3H, CH₃), 2.48 (s, 3H, CH₃),

2.46 (s, 3H, S-CH₃), 2.95-3.10 (m, 4H, N-CH₂-CH₂-N), 4.09 (s, 1H, -CH=), 7.45 (dd, *J* = 7.46, 6.89 Hz, 2H, Ar-H), 7.60 (dd, *J* = 7.46, 6.89 Hz, 2H, Ar-H), 8.30 (br s, 1H, NH); ¹³C NMR (CDCl₃): δ 13.7, 18.9, 43.8, 50.9, 64.9, 126.7, 127.6, 134.5, 140.6, 164.6, 170.8; MS (*m/z*): 313 (M+H⁺).

3-[(4-Methylthio)benzenesulfonyl]-2,4-dimethyl-3H-1,5-benzodiazepine (5a). 2.49 g (70%), mp 165 °C; Anal. Calcd. C₁₄H₁₈N₂O₂S₂: C, 60.31; H, 5.06; N, 7.81. Found: C, 60.30; H, 5.07; N, 7.80. IR (KBr): 3050 (Ar-H), 2895 (C-H), 1580 (C=N), 1290, 1415 (S-CH₃), 1345, 1140 (-SO₂) cm⁻¹; ¹H NMR (CDCl₃): δ 1.60 (s, 6H, CH₃), 2.45 (s, 3H, S-CH₃), 6.07 (s, 1H, -CH=), 7.65-7.80 (m, 8H, Ar-H); ¹³C NMR (CDCl₃): δ 12.7, 18.9, 70.3, 114.5, 123.7, 127.9, 128.4, 134.3, 140.6, 142.5, 164.7; MS (*m/z*): 358 (M+H⁺).

3-[(4-Methylthio)benzenesulfonyl]-2-methyl-4-phenyl-3H-1,5-benzodiazepine (5b). 2.64 g (63%), mp 185 °C; Anal. Calcd. C₂₃H₂₀N₂O₂S₂: C, 65.69; H, 4.79; N, 6.66. Found: C, 65.70; H, 4.80; N, 6.65. IR (KBr): 3030 (Ar-H), 2919 (C-H), 1583 (C=N), 1295, 1413 (S-CH₃), 1345, 1140 (-SO₂) cm⁻¹; ¹H NMR (CDCl₃): δ 1.70 (s, 3H, CH₃), 2.47 (s, 3H, S-CH₃), 6.10 (s, 1H, -CH=), 7.65-7.80 (m, 13H, Ar-H); ¹³C NMR (CDCl₃): δ 15.3, 18.7, 70.8, 114.6, 125.7, 126.5, 127.6, 127.9, 128.4, 130.7, 133.8, 140.5, 142.7, 164.9; MS (*m/z*): 421 (M+H⁺).

3-[(4-Methylthio)benzenesulfonyl]-2,4-diphenyl-3H-1,5-benzodiazepine (5c). 3.47 g (72%), mp 175 °C; Anal. Calcd. C₂₈H₂₂N₂O₂S₂: C, 69.68; H, 4.59; N, 5.80. Found: C, 69.67; H, 4.60; N, 5.83. IR (KBr): 3035 (Ar-H), 2915 (C-H), 1585 (C=N), 1295, 1410 (S-CH₃), 1345, 1140 (-SO₂) cm⁻¹; ¹H NMR (CDCl₃): δ 2.46 (s, 3H, S-CH₃), 6.09 (s, 1H, -CH=), 7.65-7.80 (m, 18H, Ar-H); ¹³C NMR (CDCl₃): δ 18.9, 72.3, 114.5, 125.7, 126.9, 128.3, 129.4, 130.5, 134.5, 142.4, 145.5, 146.9, 164.7; MS (*m/z*): 483 (M+H⁺).

3-[(4-Methylthio)benzenesulfonyl]-1,3-dihydro-4-methyl-3H-1,5-benzodiazepine-2-one (5d). 2.30 g (68%), mp 170 °C; Anal. Calcd for C₁₇H₁₆N₂O₃S₂: C, 56.65; H, 4.47; N, 7.77. Found: C, 56.63; H, 4.45; N, 7.80. IR (KBr): 3420 (N-H), 3025 (Ar-H), 2920 (C-H), 1745 (C=O), 1625 (C=N), 1300, 1415 (S-CH₃), 1350, 1145 (-SO₂) cm⁻¹; ¹H NMR (CDCl₃): δ 1.75 (s, 3H, CH₃), 2.50 (s, 3H, S-CH₃), 3.95 (s, 1H, -CH=), 7.65-7.80 (m, 8H, Ar-H), 8.30 (br s, 1H, NH); ¹³C NMR (CDCl₃): δ 13.7, 18.9, 64.9, 121.7, 125.4, 126.6, 127.6, 134.3, 134.7, 140.9, 164.6, 168.2; MS (*m/z*): 361 (M+H⁺).

REFERENCES

1. Landquist, J. K. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon: Oxford,

- U. K., 1984: Vol. 1, p166.
- Lioyed, D.; Marshall, D. R. *J. Chem. Soc.* **1956**, 2597.
 - Keshava Murthy K. S.; Edward, E. K. *Drug Dev. Res.* **1999**, 46(2), 155.
 - Gorlitzer, K.; Wilpert, C.; Rubsamen-Waigmann, H.; Suhartono, H.; Wang, L.; Immelmann, A. *Arch. Pharm.* **1995**, 328(3), 247.
 - Sprio, V.; Caronna, S.; Migliara, O.; Petruso, S.; Matera, M. *Farmaco. Sci.* **1989**, 44(9), 809.
 - Bianchi, M.; Butti, A. *Farmaco. Sci.* **1984**, 39(2), 162.
 - Ramajayam, R.; Giridhar, R.; Yadav, M. R.; Djaballah, H.; Shum, D.; Radu, C. *J. Enzyme Inhib. and Med. Chem.* **2007**, 22(6), 716.
 - Insuasty, B.; Orozco, F.; Quiroga, J.; Abonia, R.; Nogueras, M.; Cobo, J. *Eur. J. Med. Chem.* **2008**, 43(9), 1955.
 - DeWald, H. A.; Nordin, I. C.; Litalien, Y. J.; Parcell, R. F. *J. Med. Chem.* **1973**, 16(12), 1346.
 - Raboisson, P.; Marugan, J. J.; Schubert, C.; Koblish, H. K.; Lu, T.; Zhao, S.; Player, M.R.; Maroney, A. C.; Reed, R. L.; Huebert, N. D.; Lattanze, J.; Parks, D. J.; Cummings, M. D. *Bioorg. Med. Chem. Lett.* **2005**, 15(7), 1857.
 - Ramnauth, J.; Surman, M. D.; Sampson, P. B.; Forrest, B.; Wilson, J.; Freeman, E.; Manning, D. D.; Martin, F.; Toro, A.; Domagala, M.; Awrey, D. E.; Bardouniotis, E.; Kaplan, N.; Berman, J.; Pauls, H. W. *Bioorg. Med. Chem. Lett.* **2009**, 19(18), 5359.
 - DeWald, H. A.; Lobbstaal, S.; Poschel, B. P. H. *J. Med. Chem.* **1981**, 24(8), 982.
 - De Baun, J. R.; Pallos, F. M.; Baker, D. R. U. S. Patent 3,978,227, 1976; *Chem. Abstr.* **1977**, 86, 5498d.
 - Haris, R. C.; Straley, J. M. U. S. Patent 1,537,757, 1968; *Chem. Abstr.* **1970**, 73, 100054w.
 - Ried, W.; Torinus, E. *Chem. Ber.* **1959**, 92, 2902.
 - (a) Balakrishna, M. S.; Kaboudin, B. *Tetrahedron Lett.* **2001**, 42, 1127. (b) Curini, M.; Epifano, F.; Marcotullio M. C.; Rosati, O. *Tetrahedron Lett.* **2001**, 42, 3153. (c) Sabita, G.; Reddy, G. S. K.; Reddy, K. B.; Reddy, N. M.; Yadav, J. S. *Adv. Synth. Catal.* **2004**, 346, 921. (d) Kaboudin, B.; Naveen, K. *Heterocycles* **2001**, 55, 1443. (e) Pozaretzi, M.; Stephanatou, J. S.; Tsoleridis, C. A. *Tetrahedron Lett.* **2002**, 43, 1755. (f) Reddy, B. M.; Sreekant, P. M. *Tetrahedron Lett.* **2003**, 44, 4447. (g) Yadav, J. S.; Reddy, B. V. S.; Eshwaraiah, B.; Auradha, K. *Green Chem.* **2002**, 4, 592. (h) Jarikote, D. V.; Siddiqui, S. A.; Rajagapol, R.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *Tetrahedron Lett.* **2003**, 44, 1835. (i) De Surya, K.; Gibbs, R. A. *Tetrahedron Lett.* **2005**, 46, 1811.
 - Wight, A. P.; Davis, M. E. *Chem. Rev.* **2002**, 102, 3589.
 - Shirini, F.; Sadeghzadeh, P.; Abedini, M. *Chin. Chem. Lett.* **2009**, 20(12), 1457.
 - Kumar, R.; Joshi, Y. C. *J. Chem. Sci.* **2009**, 121, 497.
 - Kumar, R.; Joshi, Y. C. *ARKIVOC* **2007**, XIII, 142.
 - Saingar, S.; Kumar, R.; Joshi, Y. C. *Med. Chem. Res.* DOI 10.1007/s00044-010-9430-2, 2010.
 - Salehi, P.; Zolfigol, M. A.; Shirini, F.; Baghbanzadeh, M. *Curr. Org. Chem.* **2006**, 10, 2171.
 - Saundane, A. R.; Satyanarayan, N. D.; Rudresh, K.; Hiremath, S. P. *Indian J. Pharm. Sci.* **1998**, 60, 379.
 - Bagvant, G.; Gole, S. R.; Joshi V. W.; Soni, S. B. *Indian J. Pharm. Sci.* **1994**, 56, 80.