

## Syntheses of 1,5-Benzothiazepines. Part 20. Syntheses of 8-Substituted-2,5-dihydro-2-(4-N-dimethylaminophenyl)-4-(4-methoxyphenyl)-1,5-benzothiazepines

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**Abstract:** 8-Substituted-2,5-dihydro-2-(4-N-dimethylaminophenyl)-4-(4-methoxyphenyl)-1,5-benzothiazepines (**5a-e**) have been synthesized by reacting 5-substituted-2-aminobenzene-thiols (**1a-e**) with 4-N-dimethylaminobenzal-4-methoxy acetophenone (**2**) in dry ethanol saturated with hydrogen chloride gas. The products were tested for purity by tlc and characterized by elemental analysis for carbon, hydrogen and nitrogen and IR, <sup>1</sup>H NMR and mass spectral studies.

**Keywords:** 1,5-Benzothiazepine, hydrogen chloride gas.

### Introduction

The coveted drug ‘diltiazem’ being used as a calcium channel blocker [1], calcium channel modulator [2], calcium channel antagonist [3], vasodilator [4], antihypertensive [5,6], blood platelet aggregation inhibitor [7], antiarrhythmic [8], antithrombotic [9], antianginal [10], antiischemic [11] etc., possesses a 1,5-benzothiazepine nucleus having a p-methoxy phenyl group at position-2, a 4-oxo group with no substituent in the fused benzene ring.

In continuation of our studies [12] on the syntheses of 1,5-benzothiazepine derivatives having a p-N-dimethylaminophenyl group at position-2, a phenyl group at position-4 and an ethoxyl group at position-8 which showed mild stimulant and antihypertensive activities, it was thought interesting to carry out the syntheses of a series of compounds having a p-methoxy phenyl group at position-4, a p-N-dimethylaminophenyl group at position-2

and a halogeno-chloro, bromo; alkyl-methyl and alkoxy-methoxyl, ethoxyl at position-8, in the 2,5-dihydro-1,5-benzothiazepine nucleus.

### Results and Discussion

In recent years, one of the methods used for the syntheses of 1,5-benzothiazepines has been the reaction of  $\alpha,\beta$ -unsaturated carbonyl compounds, such as chalcones with 2-amino benzenethiols.

We have studied such reactions under various reaction conditions by using i) acidic medium-methanol/ethanol containing glacial acetic acid [13,14]; ethanol saturated with hydrogen chloride gas [15]; toluene containing traces of trifluoroacetic acid [16], ii) basic medium-pyridine [17] or toluene containing piperidine [18] and iii) neutral medium-anhydrous toluene [19,20] or o-xylene [21,22]. Since the yields of the products were found satisfactory in acidic medium containing hydrogen chloride gas [23,24],

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this method was used for the syntheses of 2-(p-dimethylaminophenyl)-4-methoxyphenyl-8-substituted-1,5-benzothiazepines (**5a-e**).

The 5-substituted-2-aminobenzenethiols having substituents such as chlorine, bromine, methoxyl, ethoxyl and methyl (**1a-e**) were prepared by methods reported earlier [25,26] and p-N-dimethylamino benzaldehyde was reacted with p-methoxy acetophenone to obtain the chalcone, 4-N-dimethyl aminobenzal-4'-methoxyacetophenone (**2**). 5-Substituted-2-aminobenzenethiols (**1a-f**) and 4-N-dimethylaminobenzal-4-methoxy acetophenone (**2**) were dissolved in dry ethanol and mixed in equimolar quantities. Dry hydrogen chloride gas was passed into the reaction mixture until it was saturated. The reaction mixture was then refluxed for about 3 hrs after which no further colour change was perceived. On concentrating the reaction mixture by distilling out ethanol, a coloured crude product was obtained which on re-crystallisation from dry ethanol afforded the title compounds (**5a-e**).

The products **5a-e** were tested for their purity by tlc and their  $R_f$ , yield, melting points and elemental analysis were carried out (Table 1). In elemental analyses, the % of elements was found to be satisfactory within the permissible limits of error of their calculated values.

In the literature, 2-amino benzenethiol has been reported to react with  $\alpha,\beta$  unsaturated ketones or chalcones to give a Michael addition type adduct [27], formed by the nucleophilic attack of the electron rich S of the thiol on the  $\beta$ -carbon atom of the chalcone, rendered electrophilic by a carbonyl group, when the reaction is carried out under milder conditions by using a neutral medium such as toluene [19,20]. It has also been reported that a mixture of intermediate and final products or only final products are obtained under acidic or basic reaction conditions. The Michael addition products, when isolated, were cyclized to obtain the final product thereby establishing the reaction product as formed in two steps, the Michael addition product is an intermediate which is subsequently cyclized to give the final product. We identified one product exclusively, based on our analytical and spectral observations.

### Spectral Studies

Appearance of single broad absorption at 3440-3415  $\text{cm}^{-1}$  ( $\nu$  N-H) and absence of absorptions around 3400-3100  $\text{cm}^{-1}$  (two peaks due to asymmetric and symmetric stretching of  $\text{NH}_2$  group), 1680-1650  $\text{cm}^{-1}$  ( $\nu$  C=O) and also no absorption at around 2550  $\text{cm}^{-1}$  ( $\nu$  S-H) indicated the absence of the formation of the intermediate. C-H stretching at 3050-3000  $\text{cm}^{-1}$ , C-C skeletal vibrations at 1600 to 1430  $\text{cm}^{-1}$  and absorptions at 2900-2800  $\text{cm}^{-1}$  showed the presence of aromatic and aliphatic compounds. Also, bands around 1265-1245  $\text{cm}^{-1}$ , 1035-1015  $\text{cm}^{-1}$  showed C-O-C absorptions. The absence of absorption in

the range 1615-1600  $\text{cm}^{-1}$ , characteristic of C=N absorption in heterocyclic compounds [25] negated the presence of C=N in the compounds. Thus the IR spectra of the products (**5a-f**) indicated the absence of Michael adduct type product i.e. intermediate (**3**).

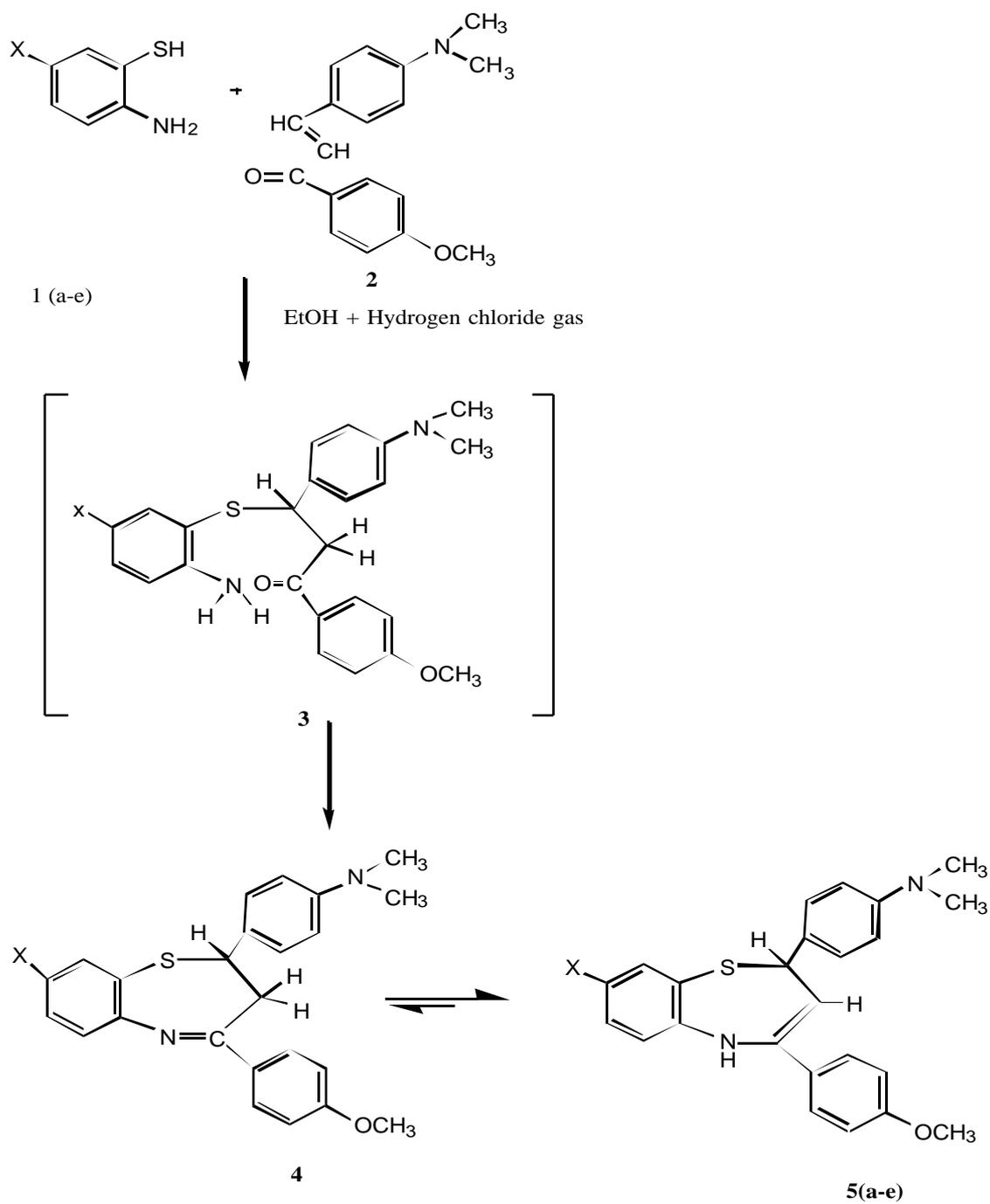
In  $^1\text{H}$  NMR spectra of all the compounds two characteristic singlet peaks at 3.48-3.64 integrated for three protons and at 2.76-2.4 integrated for six protons indicated the presence of three methoxyl protons and six methyl protons of the dimethylamino group respectively. Two doublets, one at 5.6-6.0 ( $J=7-8$  Hz) and other at 6.0-6.4 ( $J=7-8$  Hz) were assigned to the  $\text{C}_2$ -H and  $\text{C}_3$ -H protons respectively. The down field absorption of the  $\text{C}_2$ -H proton is explained by its attachment to the electronegative sulphur, a phenyl group and a carbon atom having unsaturation with conjugation. A singlet 3H absorption in the spectra of **5c** at 1.92 shows the presence of a methyl group. In **5d**, an additional singlet of 3H absorption at 3.6 was assigned to the methoxyl protons at C-8. The presence of an ethoxyl group is indicated by the absorption in the spectra of **5e** as a triplet of three protons at 1.2 with  $J=7$  Hz due to methyl protons and a quartet at 3.5 ( $J=7\text{Hz}$ ) due to the methylene protons. In all the compounds absorption as multiplets at 6.04-7.42 was assigned to aromatic protons.

The  $^1\text{H}$  NMR spectra of the products are characteristic of the enamino structure (**5**). The imino structure (**4**) formed instantaneously from the intermediate structure (**3**, not isolated), would have given three distinct double doublets in the ABX pattern in the range of 2.5-5.0 as has been observed in 2,3-dihydro-1,5-benzothiazepines [23,24]. The enamino structure is, therefore, a 2,5-dihydro-form instead of 2,3-dihydro-form (imine).

In the mass spectra of the compound **5c** having In the mass spectra of the compound **5c** having a dimethylaminophenyl group at position-2, the molecular ion peak [ $\text{M}^+$ ] was not observed at 402. Instead the peak at 282 (19.8%) may have been formed by the elimination of the dimethylaminophenyl fraction (120) at 282. Loss of a proton may result in the formation of an anion radical at  $m/z$ , 282 (100%) which is the base peak.

### Experimental

All melting points reported are uncorrected. TLC was used to monitor the progress of reactions and to test the purity of the compounds on silica gel 'G' coated glass plates with solvent system, benzene: ethanol ammonia (7:2:1), upper layer). IR spectra (KBr) were recorded on a Perkin-Elmer infracord 577 spectrophotometer,  $^1\text{H}$  NMR on a Jeol FT 90 MHz spectrophotometer using TMS as internal standard and mass on a varian Match-7 instrument at 70 eV.



Scheme

X=Cl, Br, CH<sub>3</sub>,  
 OH<sub>3</sub>, OC<sub>2</sub>H<sub>5</sub>

**Table 1.** Physical constants and analysis data of 2,4-diaryl-2,5-dihydro-8-substituted-1,5-benzothiazepines (**5a-e**).

Cpd.	X	M.p. (°C)	R <sub>f</sub>	yield	Molecular formula (Mol. Wt.)	Elemental Analysis(%), Found (calcd.)		
						C	H	N
<b>5a</b>	Cl	102	0.79	57	C <sub>24</sub> H <sub>23</sub> N <sub>2</sub> SO Cl (422.5)	- (68.16)	- 5.44	6.40 (6.62)
<b>5b</b>	Br	160	0.74	61	C <sub>24</sub> H <sub>23</sub> N <sub>2</sub> SO Br (466)	- (61.8)	- 4.93	5.98 (6.00)
<b>5c</b>	CH <sub>3</sub>	136	0.76	59	C <sub>25</sub> H <sub>26</sub> N <sub>2</sub> SO (402)	74.09 (74.62)	6.39 6.46	6.12 (6.96)
<b>5d</b>	OCH <sub>3</sub>	114	0.78	54	C <sub>25</sub> H <sub>26</sub> N <sub>2</sub> SO <sub>2</sub> (418)	71.22 (71.77)	6.34 6.22	6.15 (6.69)
<b>5e</b>	OC <sub>2</sub> H <sub>5</sub>	120	0.69	53	C <sub>26</sub> H <sub>28</sub> N <sub>2</sub> SO <sub>2</sub> (432)	71.93 (72.22)	6.62 6.48	6.39 (6.48)

**Table 2.** Characteristic IR (cm<sup>-1</sup>), <sup>1</sup>H NMR ( scale; J in Hz, solvent CDCl<sub>3</sub>) signals of 2,4-diaryl-2,5-dihydro-8-substituted-1,5-benzothiazepines (**5a-e**).

Cpd.	ν (NH)	C <sub>2</sub> -H (1H,d,J=7)	C <sub>3</sub> -H (1H,d,J=7)	OCH <sub>3</sub> (3H,s)	N(CH <sub>3</sub> ) <sub>2</sub> (6H,s)	CH <sub>3</sub> /OCH <sub>3</sub> / OC <sub>2</sub> H <sub>5</sub>	Aromatic
<b>5a</b>	34.65	5.68	6.04	3.56	2.44	-	6.12-7.40 (11H,m)
<b>5b</b>	34.70	5.80	6.12	3.62	2.64	-	6.14-7.42 (11H,m)
<b>5c</b>	3455	5.62	6.38	3.52	2.62	1.92 (3H,s)	6.40-7.04 (11H,m)
<b>5d</b>	34.20	6.00	6.24	3.60	2.40	3.60 (3H,s)	6.26-7.34 (11H,m)
<b>5e</b>	3415	5.82	6.01	3.48	2.76	1.20 (3H,t,J=7) 3.50 (2H,q, J=7)	6.04-7.32 (11H,m)

*General procedure for the preparation of 8-substituted-2-(4-dimethylaminophenyl)-4-(4-methoxyphenyl)-2,5-dihydro-1,5-benzothiazepines*

Equimolar quantities of 5-substituted-2-amino benzenethiols (1 mmol) and 4-dimethylaminobenzal-4'-methoxyacetophenone were dissolved in a minimum quantity of dry ethanol (10 ml). The reaction mixture was saturated with hydrogen chloride gas and then refluxed for a period of 3 hrs. Removal of the excess of solvent under reduced pressure gave crude solid, which on recrystallization from dry ethanol afforded the title products (**5a-e**).

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### References

- Belusa, J.; Hruskova, V.; Haas, Z.; Kaminska, Z.; Picha, F.; Dusek, J.; Trefulka, M.; Kysilka, V.; Wojnar, V. *Czech, CS 274,213* (1992); *Chem. Abstr.* **1992**, *118*, 2459706.
- Vaghy, L. P.; Williams, S. J.; Schwartz, A. *Am. J. Cardiol.* **1987**, *59*, 9A.
- Bacon, K.B.; Westwick, J.; Camp, R.D.R. *Biochem. Biophys. Res. Commun.* **1989**, *165(1)*, 349.
- Hirano, K.; Kamaide, H.; Abe, S.; Nakamusra, M. *Br. J. Pharmac.* **1990**, *101*, 173.
- Aoki, K.; Sato, K.; Kondo, S.; Yamamoto, M. *Eur. J. Clin. Pharmacol.* **1990**, *25*, 475
- Burris, J.; Weir, M.; Oparil, S.; Weber, S.; Cady, W.; Stewart, W. *JAMA, J. Aaam. Med. Assoc.* **1990**, *263*, 1507.
- Weiss, K.; Fitscha, P.; Gazso, A.; Gludovacz, D.; Sinzinger, H. *Prog. Clin. Biol. Res.* **1989**, *301*,353.
- Alonzo, D.; Allert, J.; Thomas, H.; Darbenzio, A.; Raymond, R.; Joseph, S.C. *J. Cardivasc. Pharmacol.* **1993**, *21*, 677.
- Myers, A.K.; Forman, G.; Duarte, A.P.T.; Penhos, J.; Ramwell, P. *Proc. Soc. Exp Biol. Med.* **1986**, *183*, 86.
- Stone, P.; Gibson, R.; Glaser, S.; Dewood, M.; Parker, J.; Kawanishi, D.; Crawford, M.; Messineo, F.; Shook, T.; Raby, K. *Circulation*, **1990**, *82*, 1962.
- Kuzelova, M.; Svec, P. *Cesk. Farm*, 1993, *42*, 124, *Chem. Abstr.* **1994**, *120*, 45561w.
- Pant, U.C.; Chugh, M.; Pant S.; Modwel, C. *J. Indian Chem. Soc.* **1992**, *69*, 342.
- Pant, U. C.; Gupta, A. K.; Singh, V. K. *Indian J. Chem.* **1983**, *22(b)*, 1057.
- Pant, S.; Sharma, B. S.; Sharma, C. K.; Pant, U. C. *J. Indian. Chem. Soc.* **1996**, *73*, 83.
- Pant, S.; Pant, U. C. *Indian. J. Chem.* **1994**, *33 b*, 988.
- Pant, S.; Joshi, B.C.; Pant, U.C. *Indian J. Chem.* **1993**, *32 B*, 869.
- Pant, S.; Sharma, A.; Sharma, C. K.; Pant, U. C.; Goel, A.K. *Indian J. Chem.* **1996**, *35B*, 794.
- Upreti, M.; Pant, S.; Dandia, A.; Pant, U.C. *Indian J. Chem.* **1997**, *36B*, 1181.
- Pant, U. C.; Chugh, M.; Pant, S.; Modwel, C. *J. Indian Chem. Soc.* **1991**, *68*, 418.
- Pant, U. C.; Chugh, M.; Pant, S.; Modwel, C. *J. Indian Chem Soc.* **1992**, *69*, 342.
- Pant, U.C.; Gupta, A.K. *Indian. J. Chem.* **1981**, *20*, 157.
- Pant, S.; Bhatia, A.; Sharma, A.; Pant, U. C. *Indian J. Chem.* **1994**, *33B* 885.
- Khanna, M. S.; Kumar, D.; Garg, C. P.; Kapoor, R. P. *Indian J. Chem.*, **1995**, *34B*, 333.
- Mushfiq, M.; Mudgal, G. *J. Chem. Res. Synop.* **1992**, *5*, 168.
- Upreti, M.; Pant, S.; Dandia, A.; Pant, U. C. *Phosphorous, Sulphur and Silicon.* **1996**, *113*, 165.
- Pant, U. C.; Upreti, M.; Pant, S.; Dandia, A.; Patnaik, G. K.; Goel, A. K. *Phosphorous, Sulphur and Silicon* **1997**, in press.
- Lancelot, J.C.; Letois, B; Saturnino, C; De Caprariis, P; Robba, M, *Org. Prep. Proceed. Int.* **1992**, *24*, 204.

*Sample Availability:* Available from MDPI. **5a**, MDPI 14710; **5c**, MDPI 14711; **5d**, MDPI 14710; **5e**, MDPI 14710.