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Syntheses of 1,5-Benzothiazepines: Part 51: Syntheses of 8-Substituted-2,5-Dihydro-4-(3-Nitrophenyl)-2-Phenyl-1,5-Benzothiazepines

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Abstract : The syntheses of novel six 8-substituted-2,5-dihydro-4-(3-nitrophenyl)-2-phenyl-1,5-benzothiazepines have been carried out by the reactions of six 5-substituted-2-aminobenzenethiols, the substituents being fluoro, chloro, bromo, methyl, methoxy and ethoxy, with the α–β-unsaturated carbonyl compound, 1-(3-nitrophenyl)-3-phenyl-2-propenone in dry ethanol saturated with dry HCl; and characterized by elemental and spectral data comprising IR, ^{1}H NMR, ^{13}C NMR and mass studies. On being screened for antimicrobial activity against the Gram-positive bacteria, *Staphylococcus aureus* and Gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa* and fungus, *Candida krusei* in 36 hrs. duration of incubation at 37ºC, it was found that 2,5-dihydro-8-ethoxy-4-(3-nitrophenyl)-2-phenyl-1,5-benzothiazepine displayed notable antibacterial activity against *Staphylococcus aureus*, which was higher than that of the reference standard Vancomycin. Other compounds having bromo, chloro and methoxy substituents showed significant antifungal activity against *Candida krusei*.

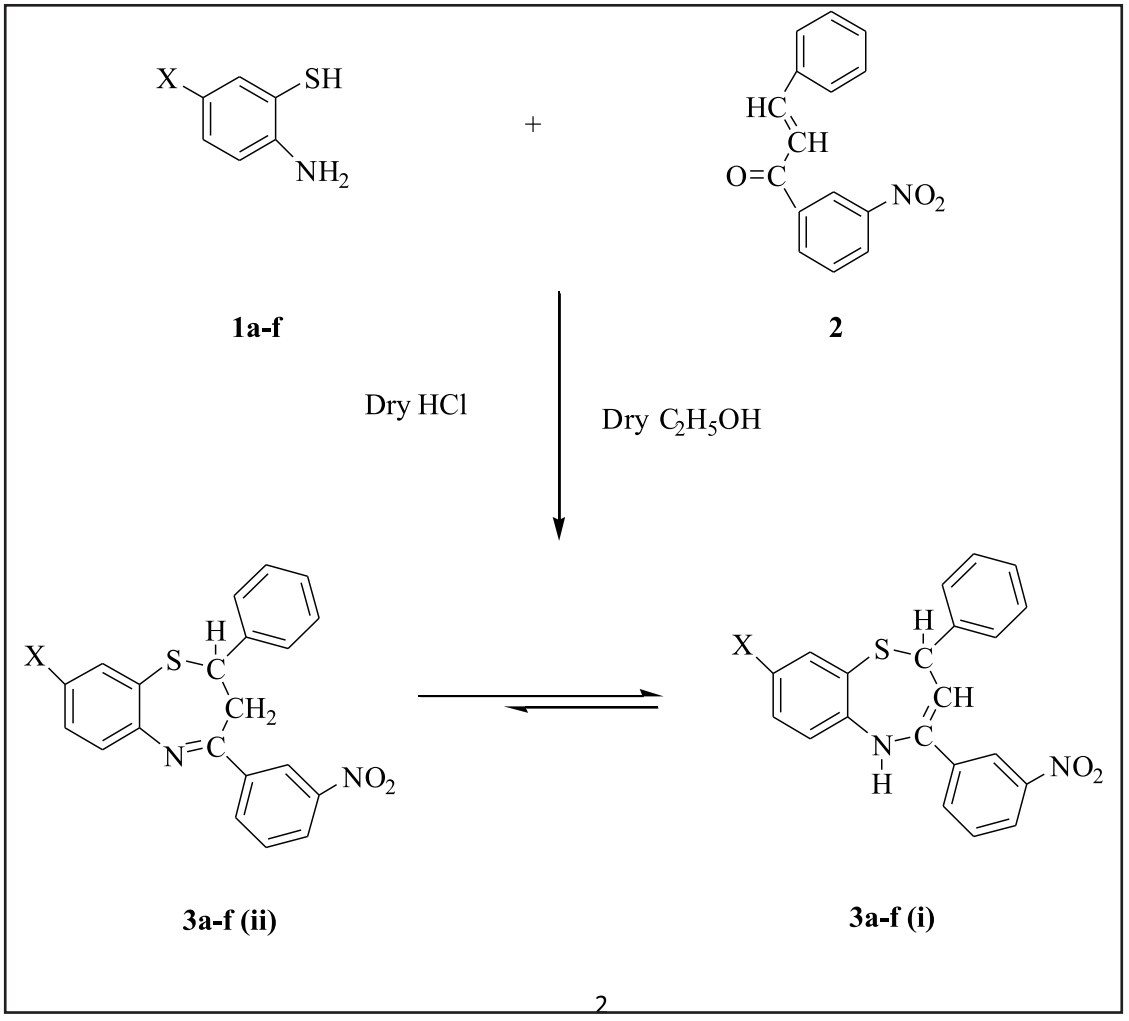
Keywords: α–β-unsaturated carbonyl compounds, Ethoxy, *Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Candida krusei*

Introduction

In the field of drug and pharmaceutical research benzothiazepine and its derivatives have received the considerable attention due to their wide range of pharmacological activities such as antimicrobial, antidepressant and anticancer. It has been observed that 1,4 or 1,5- benzodiazepine/benzothiazepine compounds having nitro substituent in the fused benzene ring show various types of chemotherapeutic activity (Tanaka *et al*., 2008). Patented drugs Nitrazepam, Nimetazepam, Clonazepam belonging to the 1,4-benzodiazepine class of compounds, having nitro substituents in the fused benzene ring, are known to show hypnotic, anxiolytic, amnesic and sedative activity (Moriya, 2003; Cloos and Marc, 2005). 1,5-benzodiazepines have recently attracted attention in the field of drugs and pharmaceuticals and are widely used as anti-depressive, hypnotic agents (Majid *et al*., 2012), anti-inflammatory (Pareek *et al*., 2013) and antibacterial agents (Micheli *et al*., 2001). In 2008, 1,5-benzodiazepine derivatives have been reported as a novel class of hepatitis C virus polymerase non-nucleoside inhibitors (Pauwels *et al.,* 2008). Some light sensitive 1,5-benzodiazepine compounds and their nitro derivatives have also been synthesized, reported and tested against breast cancer and have shown moderate biological activity (Rodriguez *et al*., 2004). It may thus be hypothesized that the introduction of nitro group as substituents in the benzodiazepine/ benzothiazepine nucleus may have led to the development of compounds having pharmacological/ biological activities (Barot *et al*., 2001). Analogous reactions of 5-substituted-2-aminobenzenethiols with nitro chalcones have been recently reported to give the respective 1,5-benzothiazepine compounds which exhibited very good antibacterial activity against *Staphylococcus aureus* (Pant *et al*., 2015). Considering the importance of the presence of nitro substituents, we herein report the syntheses of six new products, 8-substituted-2,5-dihydro-4-(3-nitrophenyl)-2-phenyl-1,5-benzothiazepines (3a-f) by the reactions of six 5-substituted-2-aminobenzenethiols (1a-f), the substituents being fluoro, chloro, bromo, methyl, methoxy and ethoxy, with 1-(3-nitrophenyl)-3-phenyl-2-propenone. These compounds have been screened for their antibacterial and antifungal activity by using Paper Disc Method (Smadi and Momani, 2008) against gram-positive bacteria, *Staphylococcus aureus*, gram-negative bacteria, *Escherichia coli* and *Pseudomonas aeruginosa* and fungus, *Candida krusei* with reference compounds Vancomycin, Gatifloxacin and Fluconazole respectively.

Materials and Methods

To have the substituents in the fused benzene ring of 1,5-benzothiazepine nucleus, two precursors were required. The first precursor required was 5-substituted-2-aminobenzenethiols **(1a-f),** which was prepared from readily available *p*-substituted anilines (Mittal and Taunk, 1971). The second precursor required, 1-(3-nitrophenyl)-3-phenyl-2-propenone **(2),** was prepared by the methods reported in literature (www.chemicalbook.com). The two categories of precursors were reacted to obtain six new products, 8-substituted-2,5-dihydro-4-(3-nitrophenyl)-2-phenyl-1,5-benzothiazepines **(3a-f)** in acidic medium, i.e. dry ethanol saturated with dry HCl. The reaction mixtures were refluxed for 7-10 hrs to obtain the products in single step in 50-54% yields. (Fig. 1, Scheme-1)



Comp. No.	3a	3b	3c	3d	3e	3f
X	F	Cl	Br	CH_3	OCH_3	OC_2H_5

Fig. 1 : Preparation of 8-substitute 2,5-dihydro-4-(3-nitrophenyl)-2-Phenyl-1, 5-benzothyiazetines (3a-f)

Scheme-1

The purity of final products was determined by TLC on silica gel 'G' coated glass plates, using benzene: ethanol: aq. ammonia (50%) (7:2:1) The structures of the final products were ascertained by microanalyses for C, H, N and S and spectral analyses comprising IR, ^{1}H and ^{13}C NMR and mass spectral studies (Table-1). All the compounds **3a-f** were then evaluated for antimicrobial activity, comprising antibacterial and antifungal.

Syntheses of 8-Ethoxy-2,5-dihydro-4-(3-nitrophenyl)-2-phenyl-1,5-benzothiazepine (3f)

Equimolar quantities of 2-amino-5-ethoxybenzenethiol (**1f**, 0.001 mol, 0.169 gm) and 1-(3-nitrophenyl)-3-phenyl-2-propenone (**2**, 0.001 mol, 0.253 gm) were dissolved in dry ethanol saturated with dry HCl (10 ml), and mixed with stirring. The reaction mixture was refluxed till the color changed to deep wine red. The crude obtained on concentration of resultant reaction mixture was crystallized from dry ethanol to afford 8-ethoxy-2,5-dihydro-4-(3-nitrophenyl)-2-phenyl-1,5-benzothiazepine.

The other compounds, **3a-e** were prepared on similar lines. Melting points of all the synthesized compounds are uncorrected. The IR spectra were taken in KBr pellets on Perkin Elmer RX1 FT IR Spectrophotometer.^{1}H NMR spectra were recorded on Bruker DRX-400 (400 MHz FT NMR with low and high temperature facility) using TMS as internal standard and $CDCl_3$ as solvent. The DART-MS spectra were recorded on a Jeol-AccuTOF JMS-T100LC Mass spectrometer having a DART source. Dry helium

was used with 4 LPM flow rate for ionization at 3500C. Micro estimation for carbon, hydrogen, nitrogen and sulphur of some of the compounds were carried out in an elemental analyzer, at the Sophisticated Analytical Instrumentation Facility, Central Drug Research Institute, Lucknow, India. (Tables 1, 2).

Results

Two precursors, 5-substituted-2-aminobenzenethiols (1a-f) and 1-(3-nitrophenyl)-3-phenyl-2-propenone (2)**,** were reacted with each other in equimolar quantities in acidic medium to give target compounds in a single step in 50-54% yields. (Table-1)

The IR spectra of **3a-f** showed a broad absorption in the region 3270-3100 cm^{-1}, which indicated the presence of a secondary amino group. Aliphatic and aromatic C-H stretching was found at around 2920-2950 cm^{-1} and 3060-3000 cm^{-1} respectively and aromatic skeletal vibrations, C=C were found at around 1600, 1590, 1490 & 1450 cm^{-1}.

Table1: Physical constants and antimicrobial data of compounds 3a-f

C. No.	M.P ˚C	R_f	Yield (%)	Antimicrobial Activity		
				Gram-positive bacteria	*Gram-negative bacteria*	*Fungus*
				Staphylococcus Aureus	*Escherichia coli*	*Candida krusei*
3a	138	0.70	54.16	14 (0.93)	14 (0.46)	----
3b	91	0.69	52.45	-----	----	11 (0.44)
3c	78	0.65	52.42	15 (1.00)	----	15 (0.60)
3d	104	0.62	53.44	13 (0.86)	----	----
3e	82	0.44	50.41	----	----	8 (0.32)
3f	90	0.72	50.36	16 (1.06)	14 (0.46)	----

Zones of inhibition are given in mm.

Values in parentheses represent activity index.

Zone of inhibition of Vancomycin for *Staphylococcus aureus* is15 mm.

Zone of inhibition of Gatifloxacin for *Escherichia coli* is 30 mm.

Zone of Inhibition of Fluconazole for *Candida krusei* is 25 mm.

Concentration of test and reference compounds were 100 µg/disc

The aralkoxyl linkage vibrations for C-O-C of methoxy and ethoxy group in the compounds **3e**,**3f,** were indicated by absorption in the region 1350-1150 cm^{-1}. All the products showed strong absorption band in the range of

1570-1500 cm^{-1} indicating the presence of Ar-NO_2. None of the spectra showed absorption band in the range 1675-1665 cm^{-1}, characteristic of carbonyl group C=O of α,β-unsaturated ketones. Two bands at around 3550 cm^{-1} (N-H asymmetric stretching) and 3450 cm^{-1} (N-H symmetric stretching), characterizing primary amino group and an absorption band at around 2600-2500 cm^{-1} due to S-H group were also found to be absent. These absorptions suggest that the two precursors have reacted to give the targeted 1,5-benzothiazepines in a single step.

The ^{1}H NMR spectra of the target compounds **3a-f** showed a doublet at 7.04-7.47 (d, 1H, J=7Hz) which may be due to C_2-H. The downfield absorption of C_2-H may be due to its presence in the deshielding zone of aryl ring and its attachment to electronegative sulphur atom. Another doublet at 7.88-8.01 (d, 1H, J= 7Hz) may be assigned to C_3-H vinylic proton. Absorption in the region 6.92-8.05 (m, 12H) appeared as multiplets, corresponding to the aromatic protons. All the synthesized compounds showed a broad singlet at around 4.00-4.09 (b, 1H) which may be assigned to secondary amino proton. (Table-2).

Table-2 Characteristic ^{1}H NMR ($CDCl_3$, values in ppm, J in Hz) signals of compounds 3a-f

C. No.	NH (br,1H)	C 2-H (1H, d, J=7Hz)	C 3-H (1H, d, J=7Hz)	C 8-XH	Aromatic protons (12H,m)
3a	4.06	7.14	7.90	__	6.96 -7.34
3b	4.08	7.04	7.96	__	7.72 -8.05
3c	4.09	7.37	8.01	__	7.53 -7.95
3d	4.00	7.14	7.88	2.53 (s, 3H)	6.92 -7.24
3e	4.02	7.47	7.93	3.70 (s, 3H)	7.26 -7.93
3f	4.01	7.42	7.96	1.40 (t, 3H, J=7) 4.03(q, 2H, J=7)	7.75 -8.04

In the ^{13}C NMR spectrum of **3f**, an absorption peak, found at 146.7 may be assigned to the ring carbon having the nitro group, at C-4. The absorption peak at 56 may be assigned to CH_2 of ethoxy group at C-8, while downfield absorption signal at 150.6 may be assigned to C-8 due to attachment of oxygen atom.

In the mass spectra of compound **3b,** the presence of molecular ion peaks, m/z $[M^+]$ and $[M+2]^+$ at 395 and 397 corresponded to the molecular mass of the products; the intensity of the $[M+2]^+$ peak was found nearly one third of the M^+ peak, which ascertained the presence of chlorine. The characteristic almost equal intensities of the $[M]^+$ and $[M+2]^+$ peaks in the spectrum of **3c** at 439 and 441, confirmed the presence of bromine.

Antimicrobial activity

Some of the compounds **3a-f** was found to show good antibacterial activity against the bacteria, *Staphylococcus aureus* and *Escherichia coli* but none of them exhibited any activity against the bacteria *Pseudomonas aeruginosa.* Against *Staphylococcus aureus,* compound **3f** showed maximum relative activity (activity index = 1.06) while compound **3c** showed relative activity equal to that of the reference compound.

All the synthesized compounds **3a-f** were investigated for antifungal activity. Compounds **3b, 3c** and **3e** showed moderate activity against *Candida krusei*. **(Table-1).**

Discussion

Literature studies (Stephens and Fiend, 1959) have revealed that when the reactions of 2-aminothiophenols are carried out with ketones in basic medium, an adduct is first formed, which on boiling with acid cyclises to the final product; whereas if the reactions are carried out in acidic medium, the final products are obtained in a single step (Reid and Marx, 1957). The acid catalyzed reaction is initiated by the nucleophilic attack of the sulphhydryl electrons to give the Michael type adduct, which then under the reaction conditions, undergoes dehydrative cyclisation to give the target compounds in a single step, which may exist in two tautomeric forms [Scheme 1, 3(i) or 3(ii)].

The IR spectra of **3a-f**, did not show absorption band in the range 1675-1665 cm^{-1}, characteristic of carbonyl group C=O of α–β-unsaturated ketones. Absorption bands at around 3550 cm^{-1} characterizing primary amino group and an absorption band at around 2600-2500 cm^{-1} due to S-H group were also found to be absent. These absorptions suggest that the two precursors have reacted the targeted 1,5-benzothiazepines in a single step. In the ^{1}H NMR spectra, the presence of one hydrogen at C_3 and –NH indicated the preferential formation of 2,5-dihydro

enamino form **3(i)**, as the continuation of p-π conjugation makes 2,5-dihydro form more stable than the tautomeric 2,3-dihydro form, **3(ii)**, whose formation would have been indicated by the appearance of a set of three double doublets in the upfield region corresponding to the C_2 and C_3 protons.

In a study on the antimicrobial activity of substituted 1,5-benzothiazepines, some compounds have been reported to exhibit good antibacterial activity against *Staphylococcus aureus* with Gentamycin as the reference drug (Ghotekar *et al.,* 2010). In our studies also, most of the newly synthesized compounds were found to show good activity w.r.t. the reference drug Vancomycin. Good antibacterial activity against *Staphylococcus aureus* has also been reported by Wang *et al.* (2009).

Conclusion

Presence of deactivating nitro group at benzene ring at C-4 in target compounds may have led to low percentage yields, in the range 50-54%.

Most of the compounds showed very good antibacterial activity for gram-positive bacteria *Staphylococcus aureus*.

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