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**RESEARCH ARTICLE**

# An Efficient Approach for the Synthesis of Various Substituted 1,5- Benzothiazepines.

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## *Abstract*

Single step synthesis of various substituted 1,5-benzothiazepines have been achieved by the reaction of different substituted chalcone with ortho-aminothiophenol in dry diethyl ether at room temperature just by swirling. This method provides mild reaction condition, shorter reaction time as compared to the conventional methods. The structural assignment of the final product has been done by spectral techniques.



## Introduction:-

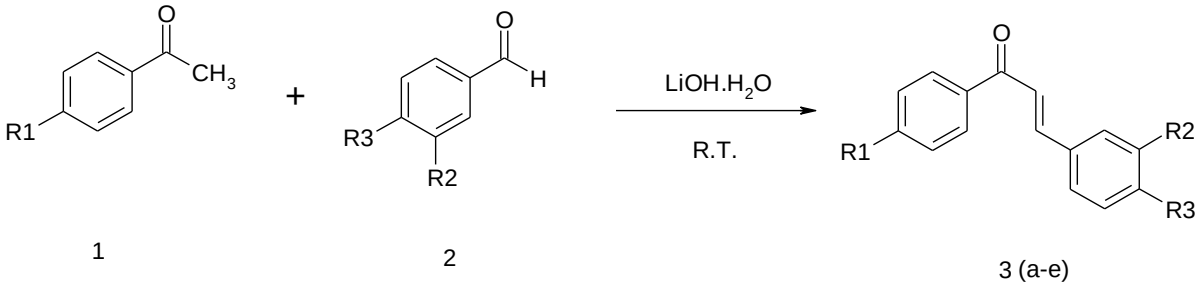
The biologically active shield structure of 1,5-benzothiazepine is found to be of immense chemotherapeutic applications especially in the treatment of ailments of cardiovascular system like coronary vasodialation[1], $Ca^{+2}$ channel antagonist[2], antidepressants[3] and other bioactivity of this molecule. This prompted us to search for improved synthetic routes and the study of various substituents in benzene nucleus of Chalcone.

Various methods are reported for the construction of substituted 1,5-benzothiazepine moiety. Common methods for the synthesis of this moiety include the reaction in which 2-amino 5-methoxy benzenethiol react with 4,4-dichlorobenzalacetophenone in a dry ether and dry hydrogen chloride gas reflux for 3 hrs.[4] An improved procedure for the synthesis of the same was recently reported in which the reaction was carried out under ultrasonic irradiation and it require 32 minutes for completion[5].

In present work the various substituted Chalcone were prepared by using $LiOH.H_2O$ in ethanol. This reaction completes within 2 minutes. So this could be the rapid step in constructing 1,5-benzothiazepine moiety. The prepared Chalcone then react with ortho-aminothiophenol in a dry ether at room temperature. The structure of final product were ascertained by the spectral studies comprising IR, and $^1H$ NMR.

The reaction of ortho-aminothiophenol with substituted Chalcone is initially a nucleophilic addition of sulphur over the β carbon of chalcone to give an adduct via a Michael addition. The amino group then get cyclised with keto functional group leading to the formation of benzothiazepine ring. The PMR spectral evidences favours the formation of benzothiazepine ring.

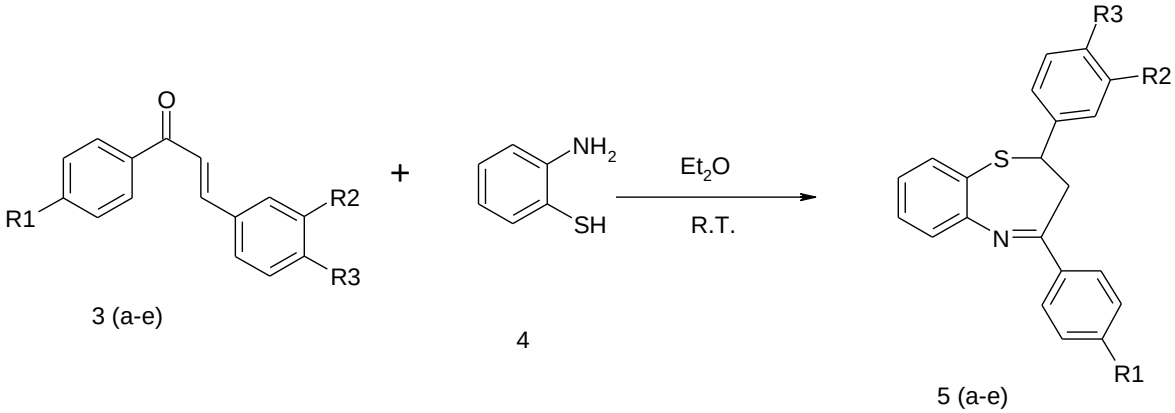
**Scheme-1**




1 2 3 (a-e)

| Comp. | R1 | R2 | R3 |
|---|---|---|---|
| 3a | H | $NO_2$ | H |
| 3b | H | H | $NO_2$ |
| 3c | Br | $NO_2$ | H |
| 3d | Br | H | $NO_2$ |
| 3e | Br | H | H |

**Scheme-2**




3 (a-e) 4 5 (a-e)

| Comp. | R1 | R2 | R3 |
|---|---|---|---|
| 5a | H | $NO_2$ | H |
| 5b | H | H | $NO_2$ |
| 5c | Br | $NO_2$ | H |
| 5d | Br | H | $NO_2$ |
| 5e | Br | H | H |

## Experimental:-

Melting points were determined in open capillaries in liquid paraffin bath and are uncorrected. Purity of the compound was routinely checked on silica gel TLC glass plates using $CHCl_3$ as a irrigant. $^1H$ NMR spectra were recorded on Bruker AV, 200 MHz spectrometers in appropriate solvents using TMS as internal standard or the solvent signals as secondary standards and the chemical shifts are shown in δ scales. Multiplicities of $^1H$ NMR signals are designated as s (singlet), d (doublet), dd (doublet of doublet), dt (doublet of triplet), t (triplet), quin (quintet), m (multiplet)… etc. IR data were recorded on Alpha-T ATR-FTIR Spectrometer.

**Substituted Chalcone were prepared by a method given below:-**
Substituted benzaldehyde (0.01 mol) and substituted acetophenone (0.01 mol) dissolve in 5 ml of ethyl alcohol and lithium hydroxide monohydrate (0.01 mol) was added. The reaction mixture was then stirred for 2 minutes, a solid was precipitated out. Crude product was crystallised from ethanol.
The result obtained for different products are recorded in Table-1.

**Substituted 1, 5-benzothiazepines (5a):-**
A substituted chalcones (0.01 mol), ortho-aminothiophenol (0.01 mol) were dissolved in 10 ml diethyl ether. The reaction mixture was swirled for about 15 minute and then concentrated to get a solid mass, which was then crystallised from ethanol, The completion of reaction was monitored by TLC (20:80 Ethyl acetate : Petroleum ether as eluent). m.p. 164-166$^0$C, yield (85%). IR: 1679 (C=N), 1332-1531 ($NO_2$); $^1$H NMR: δ 3.66 (2H, dd, $C_3$-H), 4.86 (1H, dd, $C_2$-H), 6.5-8.2 (13H, m, Ar-H).

Following the same procedure, the compounds 5b-e were prepared. Their characterization data are recorded in Table-2.

**Table-1:** Synthesis of Chalcone using $LiOH.H_2O$ / EtOH

| Comp. | R1 | R2 | R3 | Time | | M.P. ($^0$C) | Yield (%) |
|---|---|---|---|---|---|---|---|
| | | | | NaOH/EtOH In hrs.[4,7&8] | $LiOH.H_2O$/EtOH In min. | | |
| 3a | H | $NO_2$ | H | 48 | 2 | 142 | 97 |
| 3b | H | H | $NO_2$ | 48 | 2 | 152-154 | 83 |
| 3c | Br | $NO_2$ | H | 48 | 2 | 140-142 | 97 |
| 3d | Br | H | $NO_2$ | 48 | 2 | 122 | 93 |
| 3e | Br | H | H | 48 | 2 | 98 | 85 |

**Table-2**: Synthesis of various substituted 1, 5-benzothiazepines.

| Comp. | R1 | R2 | R3 | Time in min. | M.P. ($^0$C) | Yield (%) |
|---|---|---|---|---|---|---|
| 5a | H | $NO_2$ | H | 15 | 162-166 | 85 |
| 5b | H | H | $NO_2$ | 10 | 118 | 81 |
| 5c | Br | $NO_2$ | H | 10 | 122-124 | 88 |
| 5d | Br | H | $NO_2$ | 10 | 168 | 89 |
| 5e | Br | H | H | 5 | 122 | 81 |

## Conclusion:-
It is a new approach for the synthesis of 1,5-benzothiazepines with the features like high yield, very short reaction time, no side reactions, does not require critical purification and separation methods. The methodology employed is most superior over conventional methods of synthesis, since it is convenient and eco-friendly.

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## Spectral data:-
**(5b)** IR- 1679 (C=N), 1332-1531 ($NO_2$); $^1$H NMR- δ 3.66 (2H, dd, $C_3$-H), 4.86 (1H, dd, $C_2$-H), 6.5-8.2 (13H, m, Ar-H). **(5c)** IR-1679 (C=N), 650 (C-Br), 1332-1531 ($NO_2$); $^1$H NMR- δ 3.66 (2H, dd, $C_3$-H), 4.86 (1H, dd, $C_2$-H), 6.5-8.2 (12H, m, Ar-H). **(5d)** IR-1679 (C=N), 650 (C-Br), 1332-1531 ($NO_2$); $^1$H NMR- δ 3.66 (2H, dd, $C_3$-H), 4.86 (1H, dd, $C_2$-H), 6.5-8.2 (12H, m, Ar-H).

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