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PEG- 400 mediated synthesis of 1, 5-benzothiazepines

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Abstract: 1, 5-Benzothiazepines have been synthesized in one pot by condensing 2-propen-1-ones with 2-aminothiopheol in polyethylene glycol PEG-400 as a green reaction medium and catalyst. The merits of this protocol are ecofriendly, mild reaction conditions and use of non-expensive catalyst and non-hazardous solvent.

Keywords: PEG-400, 1, 5-Benzothiazipines, Chalcones, Aminothiophenol.

Introduction

1, 5-Benzothiazepines proved their ability as the clinical agents. They are of particular interest for drug discovery because they have been found active against different families of targets.[1] 1, 5-Benzothiazepine scaffold are useful in drugs that are used as vasodilator,[2]HIV-1reversetr anscriptaseinhibitor,[3]antiarrythmic agents,[4] and squalenesynthetase inhibitor,[5]V2 arginine vasopressin receptor antagonist,[6]HIV-1 reverse transcriptase inhibitor,[7] anticancer activity,[8] Ca^{2+}channel antagonist,[9] anti convulsant,[10] arginin vasopressin receptor antagonist,[11] antipsyshotic,[12] antifungal,[13] antibacterial[14] and anti-HIV.[15]

Recently, anticancer,[16] naemodynamic,[17] antiulcer[18,19] and spasmolytic activites[20-22] have also been reported for the 1,5-benzothiazepines. The clinically used diltiazem, as cardiovascular agent[23,24] is a 1,5-benzothiazepine derivative. The analogues of diltiazem have also been used clinically for CNS disorders which include clentiazem, thiazeim and quetiapinefumarate.[25] Owing to the interesting pharmacological features various groups were found to be devoted for the synthesis of this biodynamic scaffold. There are many reported methods in the literature for the synthesis of 1,5-benzothiazipines. Among these preferred and widely used route is cyclocondensation of 2-aminothiophenols with α, β-unsaturated ketones.[26]

Several attempts have been made to optimize the reaction conditions of the cyclocondensation to obtain high yields and to reduce condensation time. Cyclocondensations have been carried out in inert solvents such as ethanol using bi-catalysts, organic bases and acids[27] and it was noticed that the reaction time required for the completion of the condensation was longer and the product isolation was also tedious.

Literature revealed that polyethylene glycols have become a popular reaction media in the synthetic organic chemistry since last decade. PEGs are known as nontoxic, inexpensive, nonflammable, and nonionic liquid reaction media of low volatility.[28] This kind of solvent system fully meets the demands of green chemistry[29] and is found to be useful for various organic transformations.[30] PEG-400 has been found as an accelerator in various synthetic reactions.[31]

Considering the pharmacological importance of 1, 5-benzothiazipines, the drawbacks associated with existing methods and in continuation of our earlier interest,[32] towards the synthesis of 1,5-benzothiazepines, here we report a convenient synthesis of 1,5-benzothiazipines using reaction medium, PEG-400.

Result and Discussion

In the present work an attempt has been made to use inexpensive, benign and recoverable PEG-400 as solvent and catalyst for the synthesis of1, 5-benzothiazepines carried by condensation of 2-propene-1-ones (chalcones) and 2-amino benzenethiols in one pot. (**Scheme 1**).1,5-benzothiazepines have been synthesized by classical method by condensation of 2-aminothiophenol with 2-propene-1-ones in alcohol using dual catalysts piperidine and acetic acid. The same benzothiazepines have been obtained in short reaction time in absence of traditional acids and bases in presence of green medium and recyclable catalyst, PEG-

Scheme1. Synthesis of 1, 5-benzothiazipine using PEG-400

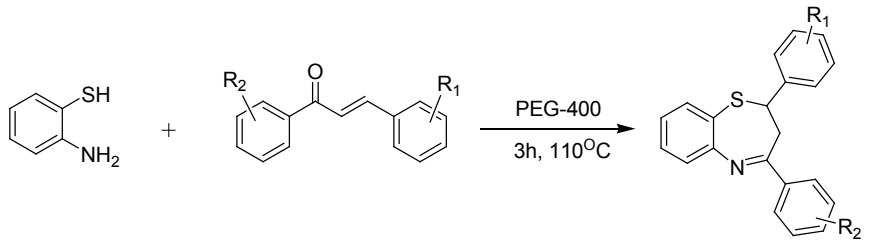

Table 1. Physical data of 1, 5-Benzothiazepines (Scheme 1).

Sr. No.	R_1	R_2	Yield (%)[a]		M.P. (°C)[b]
			Method A	Method B	
1	OH	OCH_3	51	67	153-154
2	H	H	57	76	112-113
3	OCH_3	H	54	71	105-106
4	CH_3	OCH_3	62	74	110-111
5	Cl	OCH_3	63	78	130-131
6	CH_3	H	46	68	135-136
7	F	H	42	64	101-102
8	OCH_3	OCH_3	49	61	106-107

[a]Isolated yields.
[b]Melting points of synthesized compounds are in good agreement with those reported in literature[33].

400. The experimental details are provided in the experimental part and physical data is incorporated in the Table1.

The rate acceleration recorded when the cyclocondensation was run in PEG-400 may be attributed to i) PEG-400 is nonvolatile unique solvent for many of the organic substrates as it has ability to dissolve hydrophilic and hydrophobic solutes. The solubility of reactants in PEG-400 form high concentrated homogenous mass which might have helped to accelerate the rate of the condensation. ii) Here PEG-400 might be enhancing the electrophilic character of carbonyl carbon of the 2-propene-1-ones (chalcones) by forming intermolecular H-bondings between the terminal H of hydroxyl group of PEG-400 and carbonyl oxygen of the chalcones. iii) It would be enhancing the nucleophilic character of sulphur atom of amino thiophenol forming intermolecular H- bonding between ethereal oxygen of PEG-400 and hydrogen atom of thiol of aminothiophenols. iv) This therefore might be helping to accelerate 1, 4-Micheal addition leading to 1, 5-benzothiazepines.

Experimental Details

Chemicals and solvents required were obtained from Merck, Spectorchem and S.D fine makes. ^{1}H-NMR spectra were recorded at 300 MHz on Bruker DRX-300. The mass spectra were recorded on JEOL–Accu TOF DART-MS-T 100Lc. The melting points were taken in open capillary and are uncorrected.

General reaction procedure for the synthesis of 1, 5-Benzothizepines

Method A) Classical Method of synthesis of 1, 5-benzothiazepines

To a mixture of chalcones (5 mmol) and 2-amino thiophenol (5 mmol) in alcohol (30 mL) few drops of piperidine were added and then it was refluxed for 2h. It was then acidified with glacial acetic acid and further refluxed for 3h and cooled. The reaction mixture was left overnight at room temperature. Then reaction mass was poured in ice cold water. The solid obtained was filtered and crystallized using proper solvents.

Method B) Synthesis of 1, 5-benzothiazepines using PEG-400 as medium and catalyst

A mixture of chalcones (5 mmol) and 2-aminothiophenol (5 mmol) was heated in PEG-400 (5 mL) at 110°C. Progress of reaction was monitored by thin layer chromatography. After completion of the reaction, the content of the reaction mass was cooled and then extracted by diethyl ether. Ether was removed from extract by distillation under vacuum and thus obtained residue of 1, 5-benzothiazepines were crystallized using proper solvents. (**Scheme 1)**

The comparative results of formation of 1, 5-Benzothiazepines by method A and B are recorded in T**able 1**

Recyclability study of PEG 400

PEG-400 obtained by separating ether layer was washed thrice with diethyl ether (15 mL) and was separated by using separating funnel. Thus obtained PEG-400 was reused for further reaction without significant loss of efficiency.

Conclusion

We have developed a one pot method for the synthesis of 1,5-benzothizipines using benign and recoverable PEG-400,avoiding bi-catalysts which would be a good addition to existing methods.

Spectral data of representative compound

2-(4-methoxy phenyl)-4-(2-hydroxy phenyl)-

2,3-dihydro-1,5-benzothiazepine.

Dart MS ESI$^+$ (M/Z, % Intensity): 362 (M^+, 100). IR: (KBr, cm $^{-1}$):3346 (OH str), 3219 (Ar-H str), 2890 (CH aliphatic str), 1630 (C=N str)1610 (C=C str), and 766 (C-S str).PMR (300 MHz, DMSO, δ ppm): 10.11 (br s, 1H, OH, exchangeable with D_2O), 6.43-8.05 (m, 12H, ArH), 3.73(d, 2H, methylene thiazepine), 3.33 (s, 3H, OCH3). ^{13}CMR (75 MHz, DMSO, δppm): 36.89, 55.12, 55.35, 59.16, 113.81, 114.37, 114.79, 115.45, 119.59, 122.19, 127.16, 128.22, 129.43, 129.79, 130.53, 131.02, 134.73, 136.52, 142.66, 158.59, 160.39, 187.04.

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