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Microwave Assisted Synthesis of 1,5-Benzothiazepines Using Greener Reaction Medium

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An efficient and eco-friendly synthesis of 1,5-benzothiazepines has been developed by the reaction of various 2-propen-1-ones with 2-aminothiophenol using microwave irradiation in greener reaction medium, glycerol. The clean reaction conditions, shorter reaction time, high yields and non-toxic, biodegradable reaction medium manufactured from renewable sources are unique features of this method.

Keywords: 1,5-Benzothiazepines, Chalcone, Glycerol, Microwave, Green synthesis.

INTRODUCTION

1,5-Benzothiazepines scaffold is a useful structural moiety in medicinal chemistry and has broad application in the drug development. 1,5-Benzothiazepine nuclei exhibits a number of biological properties, *e.g.*, anticonvulsant [1], calcium(II) channel antagonist [2], antianginal [3], anti-HIV [4], V_2 arginine vasoperssion receptor antagonist [5], antimicrobial [6] and anticancer [7]. The first molecule of 1,5-benzothiazepine used clinically was diltizem, followed by clentiazem, for their cardiovascular action. Some of the 1,5-benzothiazepine derivatives were also used clinically for CNS disorders which includes thiazesim and quetiapine fumarate.

Conventionally 1,5-benzothiazepines have been synthesized by condensing 2-propene-1-ones with *o*-aminothiophenol in organic solvent using acid or base catalyst like acetic acid, TFA [8,9], HCl [10], pyridine and piperidine [11]. The conventional synthetic routes has been modified to obtain high yields of the 1,5-benzothiazepines using solid supports [12]. Sharma *et al*. [13] have been synthesized 1,5-benzothiazepine using fluoroboric acid adsorbed on silica-gel (HBF_4-SiO_2) as a new heterogeneous catalyst. Khatik *et al*. [14] reported cyclocondensation of chalcones with *o*-aminothiophenol in the presence of magnesium perchlorate was carried in anhydrous DCE for 45 min under N_2 atmosphere. Recently 1,5-benzothiazepine moiety have been prepared by using gallium(III) triflate [15]. Environmentally benign synthetic routes have been receiving considerable attention and some solvent-free protocols [16,17] and use of greener medium have also been developed. Water mediated and nano-crystalline Al_2O_3 catalyzed at 110 °C for 12 h. has shown to be greener method for 1,5-benzothiazepines [18]. Enhance rate, formation of 1,5-benzothiazepines using non-conventional energy like microwave and ultrasound irradiation has also been reported [19,20].

However, many of these methods suffer from several drawbacks such as use of high boiling solvent (DMF, Toluene and DMSO) that is difficult to recover, use of corrosive and hazardous reagent like HCl gas, TFA, pyridine and piperidine, high cost metal catalyst, *etc*. In this context, more attention is found to be directed on the use of non-volatile organic solvents as an alternative medium like water, super critical liquid and ionic liquids. Water is the first solvent of choice, regarding the greener medium yet the negligible solubility of many organic compounds in water limits its application, super critical liquid CO_2 have also been reported as green solvent, but their high critical properties still limits their practical use and ionic liquid have been reported as recyclable environmentally bengin reaction media. However, ionic liquids are non-biodegradable and their production is also associated with use of high amount of hazardous and volatile organic solvents.

Organic reactions in glycerol have attracted increasing interest currently because of environmental issues. Recently,

glycerol has been received as greener medium for various organic transformations [21-24]. Radatz *et al*. [25] reported glycerol as recyclable solvent for synthesis of benzodiazepines and benzimidazoles. The unique physico-chemical nature of glycerol such as non-toxicity, biodegradability, polarity, recyclability, high boiling point, lower vapour pressure and ready availability from renewable feed stocks makes it an ideal reaction medium.

In recent year, considerable attention has been attracted towards the application of microwave irradiation to organic synthesis. Under microwave irradiation conditions, organic reactions can be accelerated and selectivity's of the ensuing products can be obtained by choosing appropriate microwave parameters, thus offering several advantages over conventional heating, such as instantaneous and rapid heating (deep inside heating), high temperature homogeneity and selective heating [26-28]. Since the first reports in 1986 [29,30] the use of the microwave heating technique has become an essential tool in all areas of synthetic chemistry, including solvent-free and water-mediated reactions [31-35]. Cabrera *et al*. [36] reported that the glycerol has proved to be an efficient solvent for the oxidation of aromatic, aliphatic and functionalized thiols under microwave irradiation.

Keeping in view as part of our interest in developing greener and efficient synthetic routes for biologically relevant compounds [37-40], herein we have synthesized 2,3-dihydro-1-5-benzothiazepines by employing glycerol under microwave irradiation.

EXPERIMENTAL

Chemicals and solvents required were obtained from Merck, Spectorchem and S.D. Fine. ^{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 procedure for the synthesis of 1,5-benzothiazepines (3a-h)

Conventional synthetic route: A mixture of prop-2-en-1-ones (0.002 mol) and *o*-aminothiophenol (0.0022 mol) was dissolved in glycerol (10 mL). Catalytic amount of glacial acetic acid was added to the solution and it was then warm on an oil bath at 120 °C for 4 h. The progress of the reaction was monitored on TLC plate using hexane: ethyl acetate. After completion, the reaction mass was poured in ice cold water and extracted with EtOAc. The solvent was removed and crude product was crystallized using proper solvents.

Microwave irradiation synthetic route (3a-h): In a conical flask, prop-2-en-1-ones (0.002 mol), *o*-aminothiophenol (0.0022 mol) and catalytic amount of glacial acetic acid was dissolved in glycerol. The reaction mixture was irradiated using microwave at 100 Watt for 3.5 min. The progress of the reaction was monitored on TLC plate. After completion, the reaction mixture was poured in ice cold water and was extracted with EtOAc. The solvent was removed and crude product was crystallized using proper solvents.

Characteristic absorption of **2a** as one of the representative product (**2a-h**) has been presented bellow MS ESI$^+$ (*m/z*, % Intensity): 316 (M^+, 100). ^{1}H NMR (DMSO-d_6) δ: 3.07 (t, 1H), 3.32 (dd, 1H), 4.99 (dd, 1H), 7.12-8.05 (m, 14H, Ar-H).

RESULTS AND DISCUSSION

In the present work, firstly we optimized cyclocondensation of prop-2-en-1-ones with 2-aminothiophenol in various solvent such as EtOH, DMF, toluene and water but we have not get satisfactory result in reaction time and yield of products whereas DMF and toluene are high boiling solvent and not recommendable from an environmental perspective. Ethanol gave good result as compare to DMF, toluene and water after long reaction time 7 h. When we carried reaction using glycerol gave better result as compared other solvent (Table-1: entry 1-5). In PEG-400 the reaction completed within 4 h with 78 % yield. Further, same reaction in glycerol was performed using a microwave irradiation, the reaction completed within 3-5 min with 78 % yield. Glycerol attributes more polar a reaction mixture, has greater ability to couple with the microwave energy and accelerate the rate of reaction comparing with conventional heating (Table-2: entry 6). The high viscosity of glycerol might be a disadvantage, yet increasing the temperature above 50 °C decreases their viscosity. Glycerol has three hydroxyl groups that are responsible for its solubility in water and has a higher boiling point, lower vapour pressure as compared with water, make it easy to isolate the reaction product by simple extraction. The key intermediates, chalcones (**1**) required for the synthesis were synthesized following literature procedure [41]. Compounds (**3a-h**) were prepared by the reaction of compound (**1**) with *o*-aminothiophenol (**2**) in presence of acetic acid in glycerol at 120 °C. under microwave irradiation with better yields. The reaction sequence is outlined in **Scheme-I**.

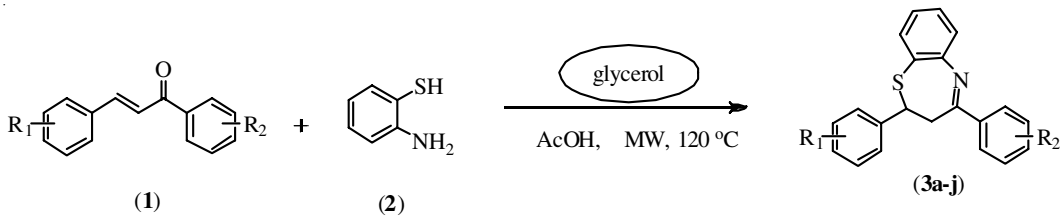
TABLE-1
OPTIMIZATION OF SOLVENT EFFECT
ON THE MODEL REACTION

Entry	Solvent	Reaction conditions	Time[a] (h)	Temp. (°C)	Yield[c] (%)
1	Ethanol	Reflux	7	78	73
2	DMF	Reflux	6	153	68
3	Toluene	Reflux	6	111	62
4	Water	Reflux	8	100	20
5	Glycerol	Warm	4	120	78
6	Glycerol	MW (100 W120 °C)	3-5 min[b]	120	78

[a]Reaction of chalcone with *o*-aminothiophenol in presence of acetic acid under conventional heating; [b]Reaction of chalcone with *o*-aminothiophenol in presence of acetic acid under microwave irradiation for 3-6 min; [c]Isolated yields.

Conclusion

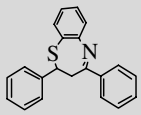
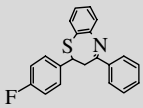
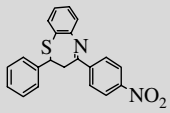
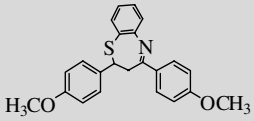
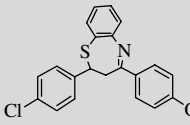
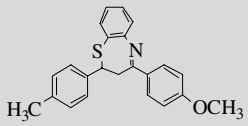
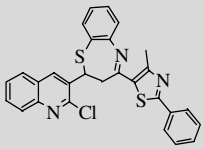
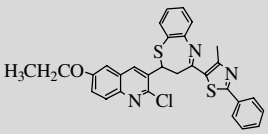
In conclusion, glycerol has proved an efficient solvent for the synthesis of 1,5-benzothiazipines under microwave irradiation. In the present study proposed method has advantage over existing conventional method with high yield and shorter reaction time with good to excellent yields. In addition glycerol, which is non-toxic, biodegradable and recyclable liquid manufactured from renewable sources.



(**1**) (**2**) (**3a-j**)

Scheme-I: Synthetic route for 1,5-benzothiazepines from chalcones and *o*-aminothiophenol

TABLE-2
PHYSICAL DATA OF 1,5-BENZOTHIAZEPINES (**3a-j**)

Compd.	Structure	Melting point (°C)	
		Obs.	Lit.
3a		114-116	114-116 [42]
3b		101-102	102-103 [42]
3c		116-118	116-118 [42]
3d		108-110	106-108 [42]
3e		130-132	132-134 [42]
3f		109-111	109-111 [42]
3g		158-160	158-160 [41]
3h		139-141	137-139 [41]

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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