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Research Article

ULTRASOUND PROMOTED ONE POT SYNTHESIS OF 1,5-BENZOTHIAZEPINES USING POLYETHYLENE GLYCOL (PEG-400)

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ABSTRACT

Synthesis of a variety of 1,5-benzothiazepines using polyethylene glycol PEG-400 as a medium and promoter. The synthesis is carried out using ultrasonic irradiation. The advantage of this protocol is that it eco-friendly, mild reaction conditions and the synthesis highlights the use of ultrasound irradiation.

Key words: 1,5-benzothiazepines, Polyethylene glycol (PEG-400), Ultrasound irradiation.

INTRODUCTION

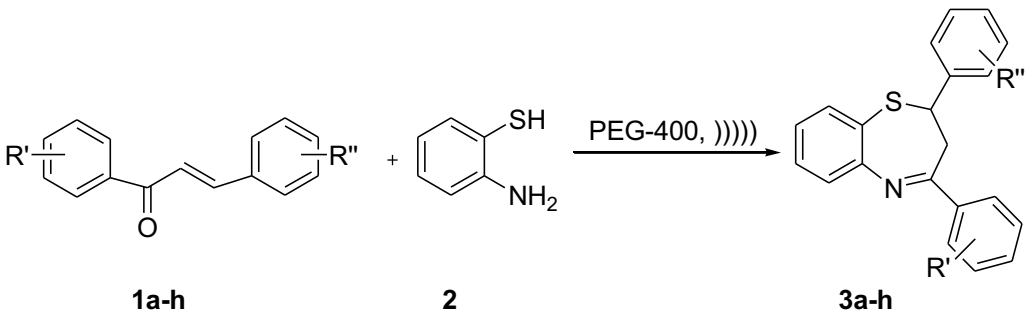
The 1,5-benzothiazepines are very versatile and are present in number of famous drugs. 1,5-benzothiazepines are used as a antidepressants, calcium antagonists and coronary vasodilators. The 1,5-benzothiazepine is a privileged group of pharmacophore, having a huge variety of biological activities like squalene synthetase inhibitor [1], anti-convulsant, anti-anginal [2,3], anti HIV [4],V_2 arginine [5], Ca^{+2} channel antagonist [6], HIV-1 reverse transcriptase inhibitor [7,8] etc. Thus looking towards its huge importance there is need to develop a green and efficient methodology for the synthesis of 1,5-benzothiazepines.

Nowadays the use of harmful, volatile, toxic organic solvents has been replaced by various alternatives. In which polyethylene glycols (PEGs) occupy an important part in organic synthesis, since last decade it has been accepted as reaction media. PEGs are nonflammable, nontoxic, inexpensive, and non-ionic liquid reaction media of low volatility [9]. Polyethylene glycol (PEGs) is a solvent which entirely fulfill the demands of green chemistry and are establishing to be helpful for a range of organic reactions [10,11]. PEG-400 has been used as promoter for a variety of synthetic reactions [12,13]. As our interested to develop green and efficient method for the synthesis, here we have used ultrasound irradiated which has been recognized as an important method in organic synthesis [14-18].

MATERIALS AND METHODS

Procedure for the Screening of solvents

A model reaction was performed at different reaction conditions, for the synthesis of 1,5-benzothiazepines **3c**, from the condensation of chalcone **1c** and o-aminothiophenol **2** (Scheme). Here we have observed the effect of various solvents like Water, Water-Ethanol, ethanol, methanol, THF, acetonitrile and PEG-400 where the reaction was performed using ultrasound irradiation (power intensity: 40% at rt). Considering all the solvent screened (entry 1-7, **Table 1**), the PEG-400 gave 93 % yield (entry 7, **Table 1**) of the desired product. Considering the result (**Table 1**) it is clear that PEG-400 the best media and promoter for the synthesis of 1,5-benzothiazepines and its derivatives.



1a-h **2** **3a-h**

Scheme: Synthesis of 1,5-benzothiazepines using PEG-400 under ultrasound irradiated.

General procedure for the synthesis of 1,5-benzothiazepines

A mixture of chalcone (**1a-h**) (1.0 mmol) and o-aminothiophenol (**2**) (1.0 mmol), was taken in RBF, to that mixture PEG-400 (5 ml) was added as a reaction medium and as a promoter and then after the RBF was kept into the ultrasonic water bath, and was irradiated at 40% of the power of the ultrasonic bath at rt. By using TLC the progress of the reaction was monitor. After complete conversion the product was extracted by diethyl ether. Then after with the help of vacuum distillation the ether was removed and thus the product was obtained and the product was recrystallized using (1:1) DMF-Ethanol. And then to extract PEG-400 from ether layer, the ether layer was washed three to four times with diethyl ether (25 mL) and at last separating funnel was used to separate PEG-400. The recycled PEG-400 was reused for further reaction.

Spectral data for representative compound 3c.

Compound 3c**:** IR (KBr): 3418, 2860, 1610, 1535, 1502, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.35 (s, 3H, CH_3), 3.02 (apparent triplet, J = 12Hz, 1H, C_3-H), 3.27 (dd, J = 12.4 Hz & 4.3 Hz, 1H, C_3-H), 5.05 (dd, J = 11.5 Hz & 4.5 Hz, 1H, C_2-H), 6.89-7.03 (m, 3H, Ar-H), 7.15-7.26 (m, 1H, Ar-H),7.27-7.32 (m, 3H, Ar-H), 7.43-7.52 (m, 2H, Ar-H), 7.63 (d, J = 7.3 Hz, 1H, Ar-H); MS (M+): m/z 396.5.

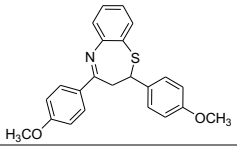
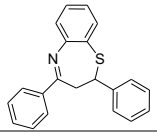
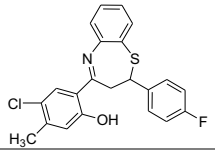
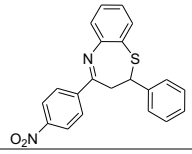
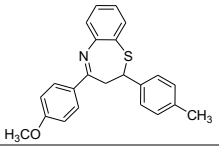
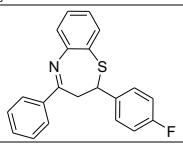
Table 1: Screening of solvents for the synthesis of 1,5-benzothiazepines (3c)[a]

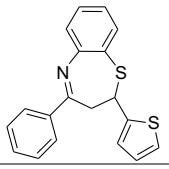
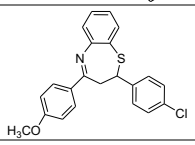
Entry	Solvent	Ultrasound Method	
		Time (min)	Yield (%)[b]
1	Water	60	trace
2	Ethanol	65	30
3	Methanol	70	28
4	CH_3CN	70	40
5	THF	70	38
6	H_2O-EtOH	78	28
7	PEG-400	**30**	**90**
[a]Reaction condition: chalcone (**1a-h**) (1.0 mmol) and o-aminothiophenol (**2**) (1.0 mmol), and PEG-400 (5 mL) under ultrasound irradiation. [b]Isolated yields.			

Table 2: Recyclability and reusability of PEG-400

Cycle	Yield [a]
Fresh	90
I[st]	86
II[nd]	82
III[rd]	76

Table 3: One pot Synthesis of 1,5-benzothiazepines (3a-h) using PEG-400 under ultrasound irradiated.

Comp.	Product	m.p °C	Time (min)	Yield (%)
3a		107 -109	25	92
3b		112 -116	25	93
3c		173 - 176	30	90
3d		116 - 118	30	92
3e		110 - 112	35	88
3f		101 - 103	35	92

3g		124-127	30	86
3h		133 - 135	30	88

[a]Reaction condition: chalcone (**1a-h**) (1.0 mmol) and o-aminothiophenol (**2**) (1.0 mmol), and PEG-400 (5 mL) under ultrasound irradiation.
[b]Isolated yields.

RESULT AND DISCUSSION

One pot cyclocondensation of chalcone (**1a-h**) (1.0 mmol) and o-aminothiophenol (**2**) (1.0 mmol), for the synthesis 1,5-benzothiazepines. Initially here we have screened various solvents like water, ethanol, methanol, CH_3CN, THF, H_2O-EtOH, PEG-400 (entry 1-7, **Table 1**), where we have observed that PEG-400 (entry 7, **Table 1**) gave good yield in less time as compared to other solvents screened. Also the product separation was easy, using PEG-400. It was also observed that product formation for compounds (compound 3a, 3b, 3e, 3g **Table 3**) was excellent in less time as compared to others (compound 3c, 3d, 3f, 3h **Table 3**). And the use of ultrasound irradiation as a non-conventional source has played a key role in the synthesis as compared to other conventional methods. The PEG-400 (**Table 2**) was recycled, simply by separating funnel and was reused. PEG-400 was recycled three to four times, every time there is a loss of 4-5 %.

CONCLUSION

In conclusion, we report the green and efficient method for synthesis 1,5-benzothiazepines and its different derivatives using PEG-400 as medium and promoter for the reaction. Were the method highlights the use ultrasound irradiation as a non-conventional source and also recycling and reuse of PEG-400. And the further use of the methodology for the synthesis of other useful heterocycles is going on our laboratory.

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