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Catalyst-free synthesis of 2,3-dihydro-1,5-benzothiazepines in a renewable and biodegradable reaction medium†

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A clean and efficient strategy for the synthesis of benzothiazepines from chalcone and *ortho*-aminothiophenol has been reported. Here, glycerol, a biodegradable and reusable promoting medium, has been utilized under acid, base or metal-free conditions. The significant features of the protocol include a one-pot eco-friendly approach, short reaction time, high atom economy, broad substrate scope, easy workup process and high yields.

Introduction

In recent years, many efforts have been devoted to developing new synthetic methodologies using renewable resources and trying to shift society's dependence away from fossil resources to environmentally benign biomass resources.[1–6] In all the experiments, solvents are needed in huge amounts for different applications including reaction media, dispersant media and cleaning agents.[7] Thus, organic chemists are continuously searching for the maximum use of eco-friendly and sustainable reaction media. Recently, glycerol has emerged as an efficient and convenient solvent in synthetic chemistry, as it meets with various standards such as non-flammability, low toxicity, non-volatility and ease of availability[8,9] thereby fulfilling most of the criteria of green chemistry. Since it is a biodegradable by-product generated from biodiesel, it is inexpensive, easy to handle and can be reused several times.[10] In addition, it has the potential to dissolve[11] several organic molecules that are immiscible in aqueous media and thus can accelerate reactions that generally do not occurr in low boiling point media. Thus, as suggested by Jérôme and co-workers, glycerol can be considered as "organic water" in chemical reactions.[12]

Fused heterocyclic compounds containing N and S atoms have received a great deal of attention because of their privileged role in nature and medicines.[13] Among these compounds, 1,5-benzothiazepines have attracted considerable interest.[14,15] For instance, 1,5-benzothiazepines have antibacterial,[16] analgesic,[17] anti convulsant,[18] anti-HIV and squalene synthase inhibitory activity.[19–21] In recent times, 1,5-benzothiazepines have been used in cardiovascular treatments (diltiazem, fluorodiazepam, *etc.*), as muscle relaxants, and as antibiotics.[22–25] For instance, the 1,5-benzothiazepine scaffold is extremely versatile and possesses various features in a number of clinically used drugs[26–29] (Fig. 1). To date, some synthetic approaches for the construction of 1,5-benzothiazepine derivatives have been developed.[30–33] However, all of these protocols suffer drawbacks such as harsh reaction conditions including high temperature, use of toxic agents, acid, base and metal catalysts, corrosivity, tedious workup and unsatisfactory yields.[34–36]

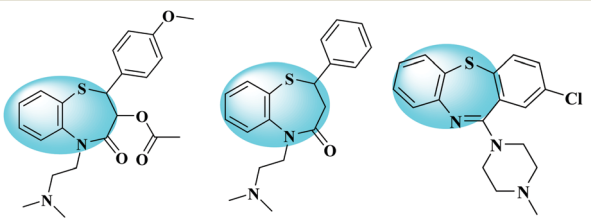

Fig. 1 Some clinically used drugs containing 1,5-benzothiazepine derivatives.

Therefore, new protocols for the preparation of 1,5-benzothiazepine scaffolds are still desirable for the development of an eco-friendly pathway for the synthesis of biologically significant heterocycles. Consequently, in continuation of our ongoing research program on the development of green synthetic routes to important heterocyclic scaffolds,[37,38] we herein report a new, catalyst-free, clean and efficient one-pot synthesis of 1,5-benzothiazepines using glycerol as a promoting medium (Scheme 1).

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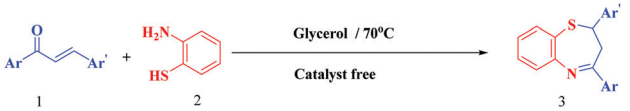
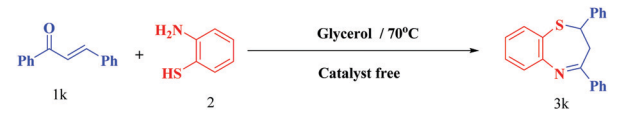


Scheme 1 General synthetic strategy.

Results and discussion

To initiate our study, we chose chalcone (**1**) and *ortho*-aminothiophenol (**2**) as the model substrates for the synthesis of 2,3-dihydro-1,5-benzothiazepine (**3k**) and examined the impact of various reaction conditions on the reaction outcome, including solvents, temperature and so on (Scheme 2).



Scheme 2 Model reaction for the synthesis of benzothiazepine **3k**.

Initially, we carried out the reaction in water at room temperature (r.t.) and observed that the product was not formed even after 12 h of stirring possibly due to limited solubility of the organic reactants in water (Table 1). To overcome this problem, we further performed the same experiment in the presence of CTAB and SDS, respectively (Table 1, entries 2–5) but it did not give a better yield even after 12 h. Further, the reaction was performed in different organic solvents like THF, DCM and toluene but the reaction did not give satisfactory yields. In our effort to increase the yield further, we carried out the reaction in ethanol and methanol without any catalyst. Pleasingly, the reaction occurred but with little success as there was only a minimal increase in the yield in this case (Table 1, entries 9 and 10). Surprisingly, instead of all these solvents when we used glycerol, it led to a remarkable improvement in the yield under the same conditions (Table 1, entry 11).

Table 1 Optimisation of the reaction conditions for the synthesis of 2,3-dihydro-1,5-benzothiazepines[a]

Entry	Solvent	Catalyst	Time (h)	Yield[b] (%)
1	Water	None	12	No reaction
2	Water	CTAB	12	No reaction
3	Water	CTAB	12	Trace[c]
4	Water	SDS	12	No reaction
5	Water	SDS	12	Trace[c]
6	THF	—	12	Trace
7	DCM	—	12	Trace
8	Toluene		12	Trace
9	Ethanol	—	12	30
10	Methanol	—	12	37
11	Glycerol	—	12	60

[a] Reaction conditions: all reactions were carried out at r.t. with **1** (1 mmol) and **2** (1 mmol) in glycerol. [b] Isolated yield of products. [c] Reaction performed at 60 °C.

Next, to evaluate the effect of temperature on this reaction, we performed a set of experiments under a diverse range of temperatures, *viz.* 60 °C, 70 °C, 80 °C and 90 °C in glycerol (Table 2). As expected, an improvement in the yield and reduction in the reaction time were observed upon increasing the temperature and the maximum yield of the product was obtained within the minimum time when we performed the reaction at 70 °C (Table 2, entry 3).

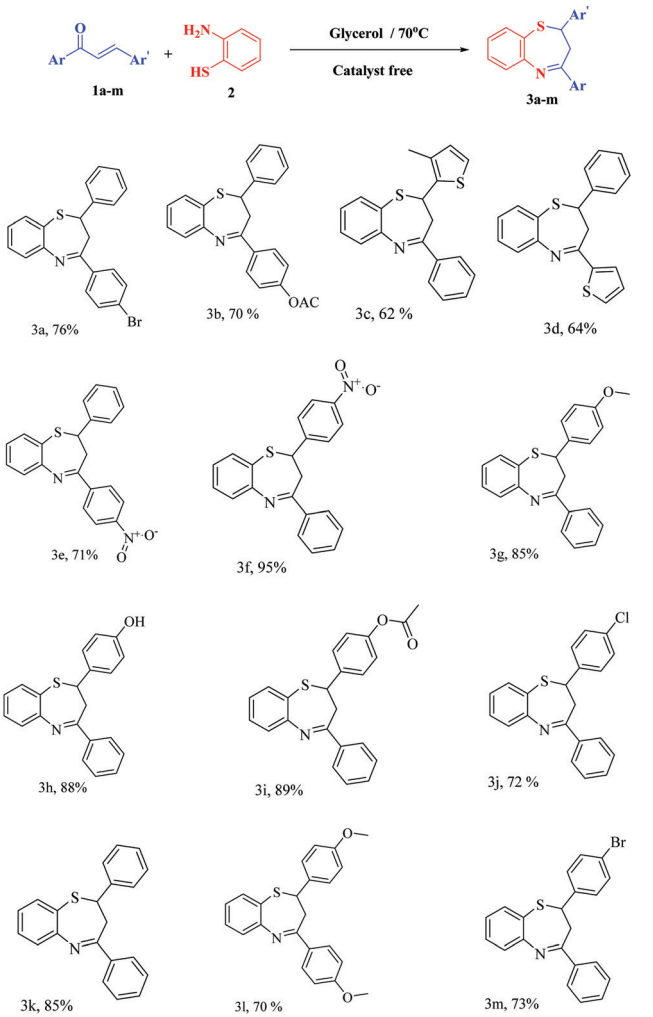
Table 2 Optimisation of the temperature for the synthesis of 2,3-dihydro-1,5-benzothiazepines[a]

Entry	Solvent	Temperature (°C)	Time (h)	Yield[b] (%)
1	Glycerol	r.t.	12	60
2	Glycerol	60	8	70
3	Glycerol	70	6	85
4	Glycerol	80	6	85
5	Glycerol	90	6	85

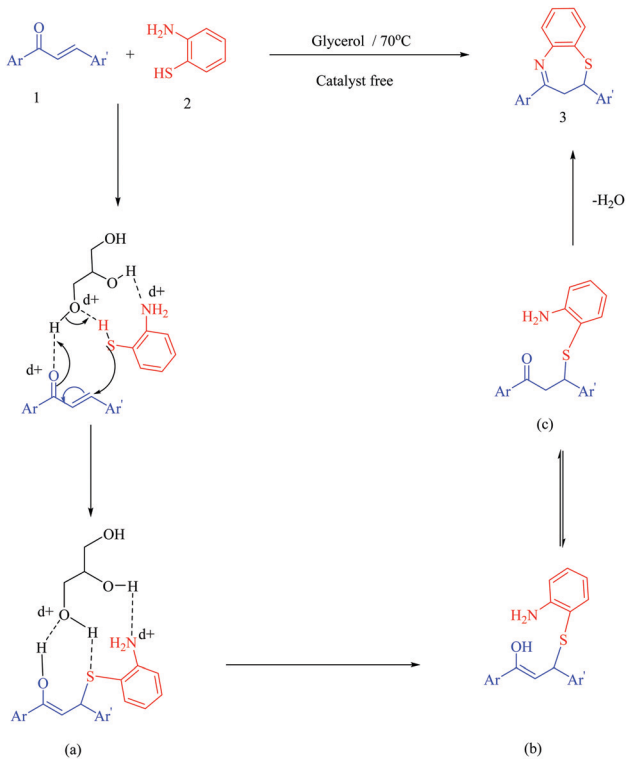
[a] Reaction condition: all reactions were carried out with **1** (1 mmol) and **2** (1 mmol) in glycerol. [b] Isolated yield of products.

After optimizing the reaction conditions, the substrate scope of this protocol was explored by employing *ortho*-aminothiophenol

Table 3 Substrate scope for the synthesis of substituted benzothiazepines[a]



[a] Reaction conditions: all reactions were carried out with **1** (1 mmol) and **2** (1 mmol) in glycerol.



Scheme 3 A plausible mechanism for the synthesis of 2,3-dihydro-1,5-benzothiazepines.

(**2**) and a series of substituted chalcones (**1**). The results clearly revealed that the present procedure is compatible with a wide range of substituents in the chalcones including both electron withdrawing and electron donating substituents at different positions and gave the corresponding products in good-to-excellent yield (Table 3).

A plausible mechanism for the synthesis of the reported heterocycles is depicted in Scheme 3. In the above reaction, the hydroxyl group of glycerol plays an important role. It activates the carbonyl group of chalcone through hydrogen bonding which facilitates the reaction pathway with 2-aminothiophenol leading to the formation of intermediate **(b)**. Subsequently, tautomerization of intermediate **(b)** results in thia-Michael adduct **(c)** which, on intramolecular nucleophilic attack by the NH_2 group, followed by dehydration, furnished the desired 1,5-benzothiazepines **3**.

Conclusion

In summary, we have reported a rapid and efficient method for the synthesis of 2,3-dihydro-1,5-benzothiazepines, a biologically significant scaffold. The key features of the present work are the use of bio-renewable and recyclable, eco-compatible solvent, catalyst-free mild reaction conditions and the use of readily available cost-effective starting materials, good yields of the desired products, operational simplicity and isolation of pure products through simple filtration thereby avoiding the need for column chromatography.

Conflicts of interest

There are no conflicts to declare.

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