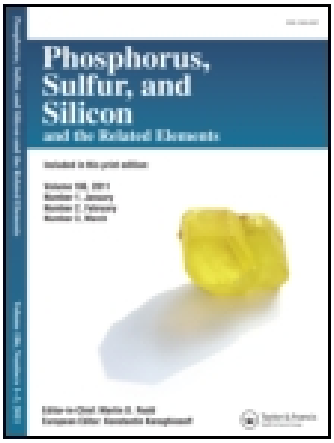

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Facile Synthesis of 1,5-Benzothiazepines in Water Using Tetrabutylammonium Tribromide

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FACILE SYNTHESIS OF 1,5-BENZOTHIAZEPINES IN WATER USING TETRABUTYLAMMONIUM TRIBROMIDE

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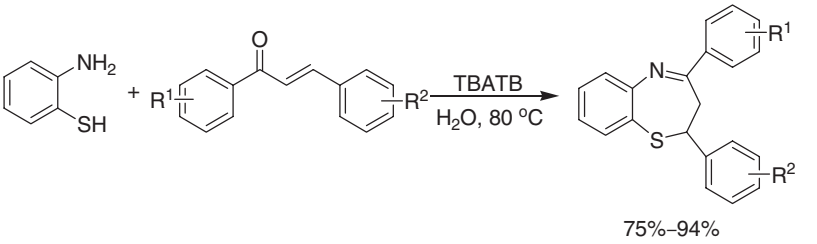
GRAPHICAL ABSTRACT



Abstract *A simple, environmentally benign, and efficient method was developed for the preparation of 1,5-benzothiazepines via a one-pot condensation reaction of 2-aminothiophenol with 1,3-diaryl- 2-propenones using tetrabutylammonium tribromide as an efficient and versatile catalyst in water.*

Keywords 1,5-Benzothiazepines; 2-aminothiophenol; 1,3-diaryl-2-propenones; tetrabutylammonium tribromide

INTRODUCTION

Organic reactions in water have become an important research area. Many reactions have been accomplished in aqueous medium.[1] Water has therefore become an attractive medium for many organic reactions, not only for the advantages concerning the avoidance of expensive drying reactants, catalysts, and solvents but also for some unique reactivity and selectivity.

1,5-benzothiazepines are an important class of heterocyclic compounds and exhibit a wide range of biological properties, such as antifungal,[2] antimicrobial,[3] anticonvulsant,[4] antibacterial,[5] anti-HIV,[6] Ca^{+2} channel antagonist,[7] V_2 arginine vasopressin receptor

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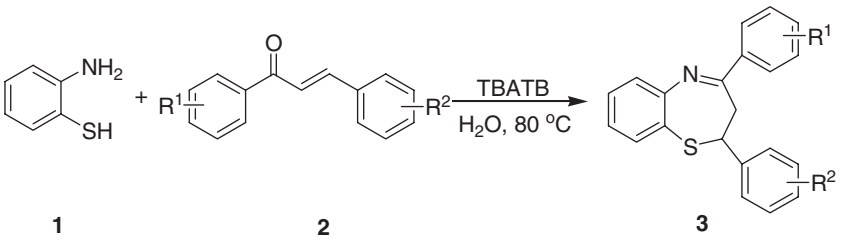
antagonist,[8] and HIV-1 reverse transcriptase inhibitor activities.[9] Various methods for the synthesis of 1,5-benzothiazepines have been reported. Among these methods, the most widely used are the reactions of 2-aminothiophenol with α, β-unsaturated carbonyl compounds in the presence of $Yb(OTf)_3$,[10] nanocrystalline aluminum oxide,[11] $Ga(OTf)_3$,[12] HBF_4-SiO_2,[13] sodium dodecyl sulfate,[14] $Mg(ClO_4)_2$,[15] $HClO_4$-SiO_2,[16] SmI_2,[17] and HCl.[18] However, still there remains a need to develop a more efficient method, particularly from the viewpoint of today's environmental concerns.

The use of organic molecules as catalysts has become an attractive alternative to traditional metal-catalysts. Interest in the field of organocatalysis has increased spectacularly in the last few years as the result of both the novelty of the concept and, more importantly, the fact that the efficiency and selectivity of many organocatalytic reactions meet the standards of established organic reactions.[19] Tetrabutylammonium tribromide (TBATB) is one such catalyst, which has recently received considerable attention as a catalyst in various organic transformations.[20] We now report a highly efficient procedure for the preparation of 1,5-benzothiazepines via a one-pot condensation reaction of 2-aminothiophenol with 1,3-diaryl-2-propenones using TBATB as an efficient and versatile catalyst in water (Scheme 1).



Scheme 1

RESULTS AND DISCUSSION

Initially, to optimize the reaction temperature, the reaction of 2-aminothiophenol with 1,3-diphenyl-2-propenones to the corresponding 2,3-dihydro-2,4-diphenyl-1,5-benzothiazepine was studied in water in the presence of 5 mol% TBATB at different temperatures. The results were summarized in Table 1. As shown in Table 1, the reaction at 80 °C proceeded in the highest yield.

The effect of amount of catalyst on the conversion and rate of the reaction was studied by varying the amount of TBATB in water at 80 °C (Table 2). It was found that 5 mol% of TBATB was sufficient to carry out this reaction smoothly. An increase in the amount of TBATB to more than 5 mol% showed no substantial improvement in the yield, whereas the yield was reduced by decreasing the amount of TBATB to 4 mol%.

These results encouraged us to investigate the scope and generality of this new protocol for various 1,3-diaryl-2-propenones under optimized conditions. As shown in Table 3, a series of 1,3-diaryl-2-propenones containing either electron-withdrawing or electron-donating substituents successfully react with 2-aminothiophenol and afforded good to high yields of products with high purity, at 80 °C in water.

A comparison of the efficiency of this method with selected previous methods is collected in Table 4. The results show that this method is superior to some previously

Table 1 Temperature optimization for the synthesis of 2,3-dihydro-2,4-diphenyl-1,5-benzothiazepine[a]

Entry	Temperature (°C)	Time (h)	Yield (%)[b]
1	25	12	38
2	50	10	56
3	60	8	67
4	70	6	79
5	80	6	87
6	90	6	85
7	100	6	83

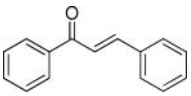
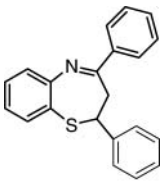
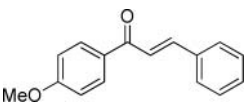
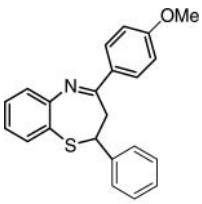
[a]Reaction conditions: 2-aminothiophenol (1 mmol); 1,3-dienyl-2-propenone (1 mmol); TBATB (0.05 mmol); H_2O (5 mL).
[b]Isolated yield based on three experiments.

Table 2 Amount of catalyst optimization for the synthesis of 2,3-dihydro-2,4-diphenyl-1,5-benzothiazepine[a]

Entry	TBATB (mol%)	Time (h)	Yield (%)[b]
1	0	12	15
2	1	10	46
3	2	8	55
4	3	8	68
5	4	6	76
6	5	6	87
7	6	6	86
8	7	6	87

[a]Reaction conditions: 2-aminothiophenol (1 mmol); 1,3-dienyl-2-propenone (1 mmol); H_2O (5 mL); 80 °C.
[b]Isolated yield based on three experiments.

Table 3 Preparation of 1,3-diaryl-2,3-dihydro-1,5-benzothiazepines[a]

Entry	1,3-diphenylprop-2-enone	Time (h)	Product	Yield (%)[b]	mp (°C) (lit.)
1		6	 **3a**	87	113–114 (114–115)[21]
2		8	 **3b**	84	106–107 (104–107)[21]

(Continued on next page)

Table 3 Preparation of 1,3-diaryl-2,3-dihydro-1,5-benzothiazepines[a] *(Continued)*

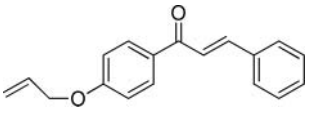
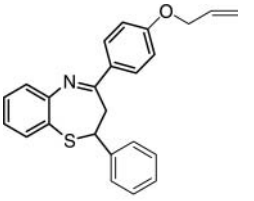
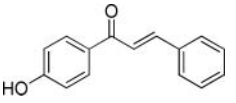
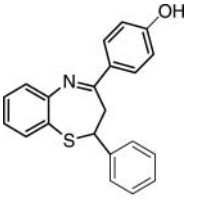
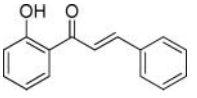
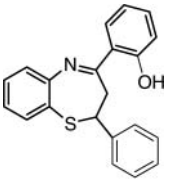
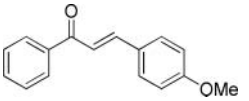
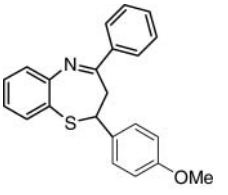
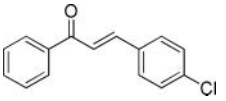
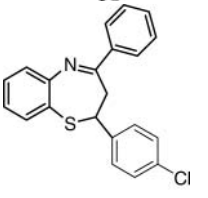
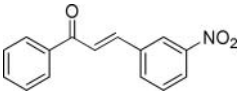
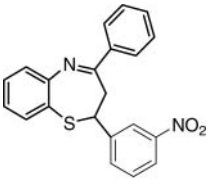
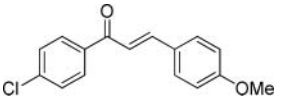
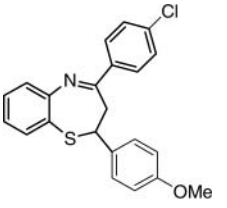
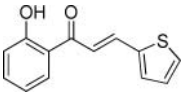
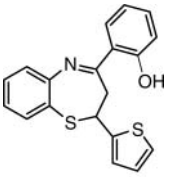
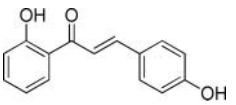
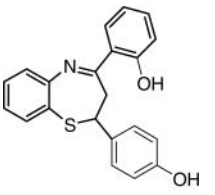
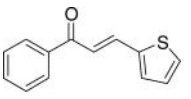
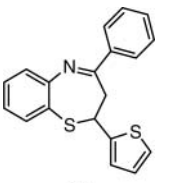
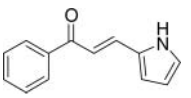
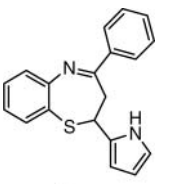
Entry	1,3-diphenylprop-2-enone	Time (h)	Product	Yield (%)[b]	mp (°C) (lit.)
3		7	 **3c**	85	80–81 (78–80)[21]
4		7	 **3d**	80	205–206 (200–204)[21]
5		8	 **3e**	84	154–156 (154–155)[12]
6		5	 **3f**	90	106–107 (106–108)[21]
7		5	 **3g**	88	129–130 (127–129)[21]
8		5	 **3h**	94	178–179 (178–180)[21]

Table 3 Preparation of 1,3-diaryl-2,3-dihydro-1,5-benzothiazepines[a] *(Continued)*

Entry	1,3-diphenylprop-2-enone	Time (h)	Product	Yield (%)[b]	mp (°C) (lit.)
9		7	 **3i**	87	132–133 (130–132)[21]
10		7	 **3j**	80	88–89 (88–89)[12]
11		7	 **3k**	80	171–172 (170–172)[12]
12		7	 **3l**	78	Oil
13		8	 **3m**	75	Oil

[a]Reaction conditions: 2-aminothiophenol (1 mmol); 1,3-diaryl-2-propenones (1 mmol); TBATB (0.05 mmol); 80 °C; H_2O (5 mL).

[b]*I*solated yield.

reported methods in terms of yields and reaction times. There are four new things in the present work when compared to previous publications: (a) Water is an environmentally friendly solvent; (b) The reaction temperature is lower than those reported in references 10 and 11; (c) The time is somewhat shorter than in the previous publication with

Table 4 TBATB-catalyzed synthesis of 2,3-dihydro-2,4-diphenyl-1,5-benzothiazepine in comparison with other literatures

Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield (%)	Ref.
1	$Yb(OTf)_3$ (5 mol%)	[bmim][BF_4]	25	0.5	84	10
2	nano-Al_2O_3 (3 mol%)	H_2O	110	12	71	11
3	$Ga(OTf)_3$ (10 mol%)	MeCN	60	4	30	12
4	SDS (10 mol%)	H_2O	100	12	65	14
5	TBATB (5 mol%)	H_2O	80	6	87	This work

comparative yields; and (d) The reaction using 5 mol% TBATB at 80 °C proceeded in highest yield.

CONCLUSION

We developed a simple, environmentally benign, and efficient method for the preparation 1,5-benzothiazepines using TBATB in water. The notable features of this procedure are the use of a cheap, easy to handle, and commercially available catalyst, and water as the reaction medium in place of harmful volatile organic solvents, which make it a useful and attractive process for the synthesis of 1,5-benzothiazepines.

EXPERIMENTAL

NMR spectra were determined on Bruker AV-400 spectrometer at room temperature using TMS as an internal standard, and coupling constants (J) were measured in Hz; Elemental analysis was performed by a Vario-III elemental analyzer; melting points were determined on a XT-4 binocular microscope and were uncorrected; commercially available reagents were used throughout without further purification unless otherwise stated.

General Procedure for the Synthesis of 1,5-benzothiazepines

A mixture of 1,3-diaryl-2-propenones (1 mmol) in water (5 mL) was heated at 80 °C until it formed a melt admixed with water as tiny liquid droplets, after which 2-aminothiophenol (1 mmol) was added followed by TBATB (0.05 mmol) and the mixture was stirred at 80 °C for the appropriate time (Table 3). The reaction was cooled to room temperature and extracted with EtOAc (3 × 5 mL). The combined EtOAc extracts were washed with brine, dried (Na_2SO_4), concentrated under rotary vacuum evaporation, and the crude product purified by column chromatography over silica gel using *n*-hexane/EtOAc (v:v = 2:1) as eluent to afford the pure product. The spectral data of some new 1,5-benzothiazepines are given below.

2-(2-thienyl)-4-phenyl-2,3-Dihydro-1,5-benzothiazepine (**3l**): IR (KBr) ν: 2926, 1658, 1594; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66–7.26 (m, 8H), 7.01–6.59 (m, 4H), 5.04 (dd, 1H, J = 4.8, 12.4, Hz), 3.42 (dd, 1H, J = 4.8, 13.2, Hz), 3.04 (t, 1H, J = 12.4 Hz); Anal. calcd for $C_{19}H_{15}NS_2$: C 70.99, H 4.70, N 4.36, S 19.95; found: C 71.10, H 4.72, N 4.20, S 20.01.

2-(1H-pyrrol-2-yl)-4-phenyl-2,3-Dihydro-1,5-benzothiazepine (**3m**): IR (KBr) ν: 2930, 1660, 1596; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.15 (brs, 1H), 7.64–7.49 (m, 5H), 7.23–6.99 (m, 4H), 6.42–5.81 (m, 3H), 5.01 (dd, 1H, J = 4.8, 12.8, Hz), 3.42 (dd, 1H,

$J = 4.8, 12.8$, Hz), 2.95 (t, 1H, $J = 13.2$ Hz); Anal. calcd for $C_{19}H_{16}N_2S$: C 74.97, H 5.30, N 9.20, S 10.53; found: C 75.06, H 5.23, N 9.30, S 10.48.

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