Synthesis of 1,5-benzothiazepines with microwave irradiation under solvent and catalyst-free conditions

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Microwave irradiation of α,β-unsaturated ketones (chalcones) and *o*-aminothiophenol in the absence of solvent and catalyst provides a highly efficient methodology for the synthesis of 1,5-benzothiazepines in moderate to good yields.

Keywords: microwave, α,β-unsaturated ketone, *o*-aminothiophenol

1,5-Benzothiazepines have anti-fungal, anti-bacterial,[1] anti-feedant,[2] analgesic,[3] anti-convulsant,[4] anti-HIV,[5] and squalene synthetase inhibitory activity.[6] Recently 1,5-benzothiazepin-2-ones have been used as calcium antagonists (*e.g.* Clentiazem), coronary vasodilators (*e.g.* Diltiazem) and antidepressants (*e.g.* Thiazesim). In addition to their biological activity 1,5-benzothiazepine are used as starting materials for the synthesis of fused ring heterocyclic compounds.[4]

The usual strategy to construct the ring skeletons of 1,5-benzothiazepine is via the reaction of 2-aminothiophenol with α,β-unsaturated carbonyl compounds.[7,8] Many of the methods cited in the literature employ catalysts such as $Mg(ClO_4)_2$ in DCE under reflux,[9] SiO_2,[10] AcOH (3 mL $mmol^{-1}$) in DMF under MW,[11] AcOH or TFA(1 mL $mmol^{-1}$) in EtOH or toluene under reflux for 3–6 h,[12] AcOH in DMF or EtOH at 60 °C for 5 h followed by treatment at room temperature overnight,[13] and EtOH/HCl under reflux for 3 h.[14] Piperidine(1 mL $mmol^{-1}$) in toluene under reflux for 8 h and pyridine (15 mL $mmol^{-1}$) under reflux for 3 h have also been used.[15]

These methods have some disadvantages such as a long reaction time, difficulties in the isolation of the products, strongly acidic medium and hazardous reagents. Recently two methods for the preparation of 1,5-benzothiazepines have been developed using $Ga(OTf)_3$ in MeCN at 60 °C[16] and SDS in water.[17] Though these methods are general for the preparation of 1,5-benzothiazepine but in the case of $Ga(OTf)_3$ in MeCN the reaction time is long and only chalcones with OH, OMe substituents were studied. The overall experimental procedure using SDS is little bit tedious.

As a part of our research to provide a greener methodology,[18-32] we have shown that the reaction of α,β-unsaturated ketones (chalcone) and *o*-aminothiophenol give 1,5-benzothiazepines with MW irradiation without any solvent or catalyst (Scheme 1).

A wide range of chalcones (see Table 1) were converted to the corresponding 1,5-benzothiazepines. There was no evidence for the formation of any side products. The reaction conditions were the same for all the substrates.

In a typical experimental procedure, a mixture of the α,β-unsaturated ketone (chalcone) (1 mmol), and *o*-amino-thiophenol (1.1 mmol), was irradiated under microwave radiation for 5-6 minutes to give the 1,5-benzothiazepine. Several sensitive functionalities such as –OH, OMe, NO_2, O-allyl, and ester were unaffected under the present reaction conditions. The yields of some products were verified by repeating some experiments for two to three times.

In conclusion microwave irradiation of chalcones and *o*-aminothiophenol provides a highly efficient methodology for the synthesis of 1,5-benzothiazepine with moderate to good yields. The procedure has the advantage of operational simplicity, solvent free and, mild reaction conditions. It is environmentally friendly, and it is compatible with various functional groups. We believe that this will present a better alternative to the existing methodologies for the synthesis of 1,5-benzothiazepines.

Experimental

Melting points were determined on a glass disk with an electric hot plate and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were run in $CDCl_3$ solutions. IR spectra were taken as KBr plates in a Shimazu 8400S FTIR. Elemental analyses were done by Perkin-Elmer autoanalyser.

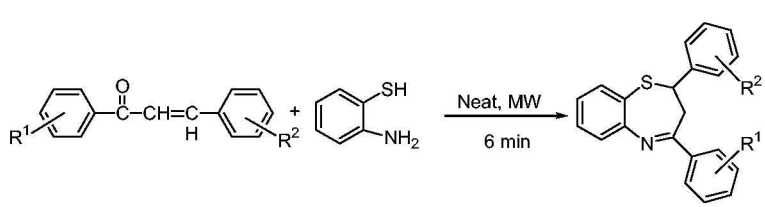
Synthesis of 1,5- benzothiazepine; general procedure

2,4-Diphenyl-2,3-dihydro-1,5-Benzothiazepines (entry 1): A mixture of α,β-unsaturated ketone (1,3-diphenylprop-2-enone,chalcone) (208 mg, 1 mmol), and *o*-aminothiophenol (137 mg 1.1 mmol), was irradiated under MW for 5–6 min to complete the reaction (TLC). The reaction mixture was then dissolved in ethyl acetate (20 mL). The ethyl acetate was washed with (5%) NaOH sol. (3 × 5 mL) and brine solution (2 × 5 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by column chromatography of the crude product over silica gel (hexane/ethyl acetate 98:2) furnished the pure product (220 mg, 70%) as a yellowish solid; m.p.114–115 °C, (Lit.[17] 114–116 °C) whose spectroscopic data (IR and NMR) were given below.

^{1}H NMR δ 3.01 (t, 1H, J = 12 Hz), 3.38 (dd, 1H, J = 4.5, 12.5 Hz), 5.05 (dd, 1H, J = 4.5, 12 Hz), 7.10–7.15 (m, 1H), 7.22–7.33 (m, 5H) 7.35–7.55 (m, 4H) 7.62 (d, 2H, J = 6 Hz) 8.02 (d, 1H, J = 7 Hz).

This ^{1}H NMR spectrum was in full agreement with an authentic sample.[9] This procedure is followed for the synthesis of all the substrates listed in Table 1. The known compounds have been identified by comparison of spectroscopic data (IR and ^{1}H NMR) and m.p. with those reported. The m.p. and spectral data of the new compounds are presented below in order of their entries.

2-Furan-2-yl-4-phenyl-2,3-dihydro-benzo[b][1,4]thiazepine (entry 2): Oily liquid; IR (cm^{-1}) 2923, 1650, 1596. ^{1}H NMR δ 3.01 (t, J = 12.9 Hz, 1H), 3.37 (dd, J = 4.8, 12.9 Hz, 1H), 5.06 (dd, J = 4.8, 12.9 Hz, 1H), 6.19–7.62 (m, 12H). ^{13}C NMR δ: 34.2, 53.0, 105.4, 110.4, 112.6, 116.1, 119.4, 125.0, 127.4, 128.7 (2C), 130.8, 132.7, 135.4, 141.9, 144.9, 151.7, 153.6, 168.7 with Anal. Calcd.



Scheme 1

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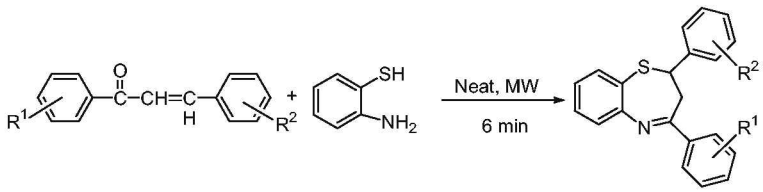
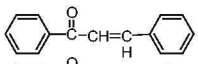
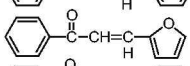
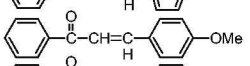
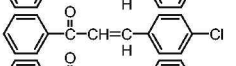
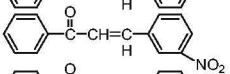
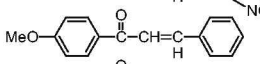
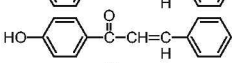
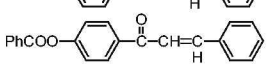
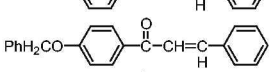
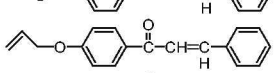
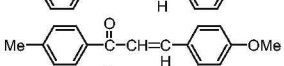
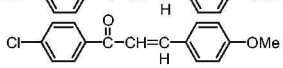
Table 1 Reaction of o-amino thiophenol with chalcone



Entry	Substrate	Yield[a]	Ref.	Obs. m.p./ °C	Lit m.p./ °C
1		70	17	114–115	114–116
2		70[b]	—	—	—
3		70	17	106–108	106–109
4		50	17	127–129	128–129
5		50	9	178–180	178–180
6		80	9	104–107	104–106
7		75	9	200–204	220–220
8		75	9	186–188	187–190
9		75	9	114–115	115–117
10		75	—	78–80	—
11		65	17	108–110	108–110
12		50	17	130–132	133–135

[a]Yield of pure product fully chacterised by IR and NMR spectroscopy and comparison with authentic samples. [b]Highly viscous oil.

Anal. Calcd for $C_{19}H_{15}NOS$: C, 74.72; H, 4.95; N, 4.59. Found: C, 74.70; H, 4.91; N, 4.62%.

4-(4-Allyloxy-phenyl)-2-phenyl-2,3-dihydro-benzo[b][1,4] thiazepine (entry 10): Colourless solid; m.p. 78–80 °C; IR (Cm^{-1}) 3557, 3058, 2923, 1662, 1602. ^1H NMR δ 3.04 (t, J = 12.9 Hz, 1H), 3.25 (dd, J = 4.8, 12.9 Hz, 1H), 4.61 (d, J = 3.9 Hz, 2H), 4.95 (dd, J = 4.8, 12.9 Hz, 1H), 5.33 (d, J = 10.5 Hz, 1H), 5.44 (d, J = 20.0 Hz, 1H), 6.01–6.12 (m, 1H), 6.99 (d, J = 8.7 Hz, 2H), 7.08–7.14 (m, 1H), 7.22–7.61 (m, 8H), 8.00 (d, J = 9.0 Hz, 2H). ^{13}C NMR δ 37.3, 60.3, 68.8, 114.5 (2C), 115.7, 122.75, 124.9, 125.25, 126.0 (2C), 127.1, 127.5 (2C), 127.7, 128.9, 129.1 (2C), 131.1, 137.6, 143.7, 152.6, 162.5, 168.1 with Anal. Calcd.

Anal. Calcd for $C_{24}H_{21}NOS$: C, 77.59; H, 5.70; N, 3.77. Found: C, 77.61; H, 5.74; N, 3.80%.

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