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Di-cationic Ionic Liquid Catalyzed Synthesis of 1,5-Benzothiazepines

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A simple and elegant method for the synthesis of 1,5-benzothiazepines has been developed using di-cationic liquid as a solvent cum catalyst by the reaction of *o*-aminothiophenol with a variety of chalcones under mild reaction conditions. Furthermore the reusability of the catalyst has also been studied for three cycles. All the reactions are proposed to proceed through a 1,4-conjugate Michael addition followed by a cyclo-condensation reaction.

Keywords: *gem*-Dicationic ionic liquids, 1,5-Benzothiazepines, 1,5-Benzodiazepines, Cyclo-condensation reaction, Reusability.

INTRODUCTION

1,5-Benzodiazepines and 1,5-benzothiazepines have continued to attract many researchers since they possess a wide range of pharmacological activities. They have been broadly used in many pharmaceutically active drugs such as antifeedants, tranquilizers, antidepressants, CNS stimulants, calcium channel blockers and antimicrobial agents [1-3]. Moreover, they have also been combined with other well-known benzofuran derivatives to form single molecule with improved pharmaceutical properties [4].

Several syntheses of 1,5-benzothiazepine and its other analogues have been reported including the reactions of *o*-aminothiophenol and *o*-phenylenediamines with ketones [5], α,β-unsaturated carbonyl systems like chalcones or β-haloketones [6]. In most of these syntheses, various catalysts have been used such as BF_3·Et_2O, Amberlyst-15, $Yb(OTf)_3$, $Ga(OTf)_3$, acetic acid and NBS [7-14]. However, these methods suffer from one or more of the following drawbacks such as expensive catalyst, low yields, harsh reaction conditions, long reaction times and non-environmentally friendly conditions. Therefore, a new facile and unprecedented synthetic methodology with more environmentally friendly method is required.

The ionic liquids (ILs) like imidazolium salt ionic liquids have been classified as an efficient and conventional organic solvent [15]. They are reported to be environmentally friendly, thermally stable, non-volatile, reusable catalysts and solvents. Owing to their application, they have been widely used in many different organic transformations such as isomerization, Claisen rearrangement [16], Friedal-Craft's alkylation, Diels-Alder reaction, asymmetric hydrogenation [17-20], Heck and Suzuki coupling reactions [21-23]. In addition to this, the special properties of the ionic liquids have influenced the rate of chemical reactions such as elimination reactions where, the rate of the reaction in ionic liquids was observed to be faster than those carried out in conventional organic solvents [24]. Notably, multifunctional group dicationic ionic liquids have been reported to have a greater range of physical properties than traditional and singly charged ionic liquids. They are often more thermally stable, less volatility and are more flexible in tuning their physicochemical virtues [25,26]. Herein, we report an efficient synthesis of various 1,5-benzothiazepines using dicationic liquids as a catalyst and as well as solvent.

EXPERIMENTAL

General procedure: A mixture of *o*-aminothiophenol (1.2 mmol)/*o*-phenylenediamine (1 mmol), chalcone (1.0 mmol) and IL-C (0.2 mmol, 0.1 g per mmol of chalcone) was stirred at 80 °C for 80 min under nitrogen atmosphere. After completion of the reaction, which was monitored by TLC, the reaction mixture was diluted with water (10 mL) and extracted with diethyl ether (3 × 25 mL). The combined organic layer was separated and dried over anhydrous magnesium sulphate. The solvent was evaporated under reduced pressure and the residue was purified by crystallization in ethanol to afford the pure solid 1,5-benzothiazepines. The water present in the aqueous layer was subjected for distillation and the left over residue contains the pure ionic liquid, which could be recycled.

2-(4-Phenyl-4,5-dihydro-3*H*-benzo[b][1,4]diazepin-2-yl)phenol: Light yellow solid; m.p.: 112-115 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 15.28 (s, OH), 7.42-7.43 (m, 2H), 7.27-7.37 (m, 6H), 7.12 (td, *J* = 1.5 Hz, *J* = 8.3 Hz, 1H), 6.99-7.05 (m, 2H), 6.85 (dd, *J* = 1.3 Hz, *J* = 7.8 Hz, 1H), 6.72-6.79 (m, 1H), 5.21 (dd, *J* = 3.1 Hz, *J* = 8.0 Hz, 1H), 3.84 (bs, NH), 3.33 (dd, *J* = 3.7 Hz, *J* = 13.6 Hz, 1H), 3.06 (dd, *J* = 8.6 Hz, *J* = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.32, 162.59, 144.26, 139.04, 135.23, 132.84, 128.99, 128.34, 128.29, 128.05, 127.42, 125.88, 121.48, 120.72, 119.07, 118.30, 118.0, 69.99, 36.52.

2,4-Diphenyl-2,3-dihydrobenzo[b][1,4]thiazepine (1) (Table-1, Entry 1): Yellow solid; m.p.100-102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01-8.06 (m, 3H), 7.30-7.52 (m, 11H), 4.98 (dd, *J* = 4.8 Hz, *J* = 12.7 Hz, 1H), 3.31 (dd, *J* = 4.7 Hz, *J* = 12.9 Hz, 1H), 3.07 (t, *J* = 12.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.67, 152.42, 144.84, 137.65, 135.04, 128.81, 128.74, 128.60, 128.48, 128.42, 128.32, 127.82, 127.29, 126.00, 121.84, 60.47, 37.63.

2-(2-Phenyl-2,3-dihydrobenzo[b][1,4]thiazepin-4yl)-phenol (2) (Table-1, Entry 2): Yellow Crystal (recrystalized from ethanol); m.p.: 149-151 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.49 (bs, OH), 7.65 (dd, *J* = 1.7 Hz, *J* = 8.0 Hz, 1H), 7.50 (dd, *J* = 1.7 Hz, *J* = 8.5 Hz, 1H), 7.49 (dt, *J* = 1.1 Hz, *J* = 8.0 Hz, 1H), 7.39-7.43 (m, 1H), 7.31-7.34 (m, 6H), 7.22 (dt, *J* = 1.3 Hz, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 6.68-6.92 (m, 1H), 5.06 (dd, *J* = 4.7 Hz, *J* = 12.6 Hz, 1H), 3.41 (dd, *J* = 4.7 Hz, *J* = 13.3 Hz, 1H), 3.09 (t, *J* = 13.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.13, 162.78, 148.83, 143.68, 135.21, 133.65, 129.95, 128.89, 128.36, 128.07, 126.41, 126.04, 125.66, 124.44, 118.68, 118.59, 118.29, 60.05, 36.89; IR (ATR): 3055, 1596, 1445, 1194, 725, 737 cm^{-1}.

2-[2-(4-Methoxyphenyl)-2,3-dihydrobenzo[b][1,4]-thiazepin-4-yl]phenol (3) (Table-1, Entry 3): Yellow solid; m.p.: 163-165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.52 (bs, OH), 7.58 (dd, *J* = 1.6 Hz, *J* = 7.7 Hz, 1H), 7.58 (dd, *J* = 1.4 Hz, *J* = 7.9 Hz, 1H), 7.48 (dt, *J* = 1.6 Hz, *J* = 8.4 Hz, 1H), 7.38-7.43 (m, 1H), 7.19-7.32 (m, 4H), 7.07 (dd, *J* = 1.2 Hz, *J* = 8.6 Hz, 1H), 6.84-6.92 (m, 3H), 5.04 (dd, *J* = 5.0 Hz, *J* = 2.1 Hz, 1H), 3.80 (s, 3H), 3.38 (dd, *J* = 5.0 Hz, *J* = 12.7 Hz, 1H), 3.05 (t, *J* = 12.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.12, 162.31, 159.31, 135.19, 133.59, 129.86, 128.41, 127.20, 126.34, 125.62, 125.48, 124.42, 118.65, 118.55, 114.15, 59.67, 55.35, 37.07.

2-[2-(3,4-Dimethoxyphenyl)-2,3-dihydrobenzo[b][1,4]-thiazepin-4-yl]phenol (4) (Table-1, Entry 4): Yellow solid; m.p.: 161-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.52 (bs, OH), 7.65 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.40 (t, *J* = 8.5 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.21 (dt, *J* = 1.3 Hz, *J* = 7.8 Hz, 2H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.78 - 6.90 (m, 3H), 5.05 (dd, *J* = 4.9 Hz, *J* = 11.7 Hz, 1H), 3.87 (s, 3H), 3.77 (s, 3H), 3.38 (dd, *J* = 5.0 Hz, *J* = 12.9 Hz, 1H), 3.08 (t, *J* = 12.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.20, 162.74, 149.04, 148.82, 136.81, 135.05, 133.62, 131.59, 130.87, 129.97, 128.58, 126.28, 125.58, 124.68, 118.61, 118.13, 115.20, 110.97, 109.45, 60.17, 55.94, 55.77, 36.99; IR (ATR):2920, 1565, 1419, 1266, 651 cm^{-1}; HRMS (ESI): calculated for $C_{23}H_{21}NO_3SH$ $[M+H]^+$ 392.1276, found 392.1295; CHN analysis: calculated for $C_{23}H_{21}NO_3S$: C: 70.56; H: 5.41; N: 3.58; O: 12.26; S: 8.19. Found: C: 70.42; H: 5.22; N: 3.44.

2-[2-(3,4,5-Trimethoxyphenyl)-2,3-dihydrobenzo[b]-[1,4]thiazepin-4-yl]phenol (5) (Table-1, Entry 5): Yellow crystal; m.p.: 160-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.51 (bs, OH), 7.66 (d, *J* = 8.2 Hz, 1H), 7.47-7.52 (m, 2H), 7.38-7.42 (m, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 7.21 (dt, *J* = 1.4 Hz, *J* = 8.4 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 1H), 6.87 (t, *J* = 8.2 Hz, 1H), 6.54 (s, 2H), 5.02 (dd, *J* = 4.7 Hz, *J* = 11.3 Hz, 1H), 3.83 (s, 3H), 3.77 (s, 6H), 3.38 (dd, *J* = 4.7 Hz, *J* = 12.9 Hz, 1H), 3.08 (t, *J* = 12.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.21, 162.72, 153.27, 148.89, 138.80, 134.99, 133.67, 130.11, 128.62, 126.29, 125.63, 124.67, 118.63, 118.61, 118.47, 103.30, 103.28, 60.84, 60.66, 56.02, 36.90; IR (ATR): 3001, 2926, 1589, 1455, 1243, 760 cm^{-1}; HRMS (ESI): calculated for $C_{24}H_{23}NO_4SH$ $[M+H]^+$ 422.1381, found 422.1391; CHN analysis: calculated for $C_{24}H_{23}NO_4S$: C: 68.39; H: 5.50; N: 3.32; O: 15.18; S: 7.61. Found: C: 68.50; H: 5.64; N: 3.18.

2-[2-(Benzo[d][1,3]dioxol-5-yl)-2,3-dihydrobenzo-[b][1,4]thiazepin-4-yl]phenol (6) (Table-1, Entry 6): Light yellow solid; m.p.: 135-138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.47 (bs, OH), 7.65 (dd, *J* = 1.3 Hz, *J* = 7.7 Hz, 1H), 7.58 (dd, *J* = 1.3 Hz, *J* = 7.9 Hz, 1H), 7.48 (dt, *J* = 1.3 Hz, *J* = 8.4 Hz, 1H), 7.38-7.41 (m, 1H), 7.31 (dd, *J* = 1.2 Hz, *J* = 8.0 Hz, 1H), 7.22 (dt, *J* = 1.4 Hz, *J* = 8.4 Hz, 1H), 7.07 (dd, *J* = 1.0 Hz, *J* = 8.3 Hz, 1H), 6.82-6.91 (m, 1H), 6.82 (d, *J* = 1.3 Hz, 1H), 6.72-6.78 (m, 2H), 5.96 (s, 2H), 5.0 (dd, *J* = 4.7 Hz, *J* = 12.2 Hz, 1H), 3.37 (dd, *J* = 5.0 Hz, *J* = 13.3 Hz, 1H), 3.02 (t, *J* = 13.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.95, 162.85, 148.76, 148.09, 147.42, 137.95, 135.25, 133.74, 130.03, 128.40, 126.54, 125.77, 119.33, 118.77, 118.69, 101.34, 60.05, 37.20.

2-(2-*p*-Tolyl-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)phenol (7) (Table-1, Entry 7): Yellow solid; m.p.: 152-154 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.44 (bs, OH), 7.51-758 (m, 2H), 7.42 (dt, *J* = 1.6 Hz, *J* = 9.2 Hz, 1H), 7.34 (dt, *J* = 1.8 Hz, *J* = 9.5 Hz, 1H), 7.22-7.25 (m, 1H), 7.09-7.14 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.0 (d, *J* = 7.9 Hz, 1H), 6.81-6.86 (m, 1H), 4.95 (dd, *J* = 4.6 Hz, *J* = 12.43 Hz, 1H), 3.29 (dd, *J* = 4.6 Hz, *J* = 12.4 Hz, 1H), 3.0 (t, *J* = 12.4 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.20, 162.73, 148.86, 141.00, 137.95, 135.30, 133.71, 129.60, 128.39, 125.97, 124.53, 118.73, 118.59, 59.95, 36.96, 21.16.

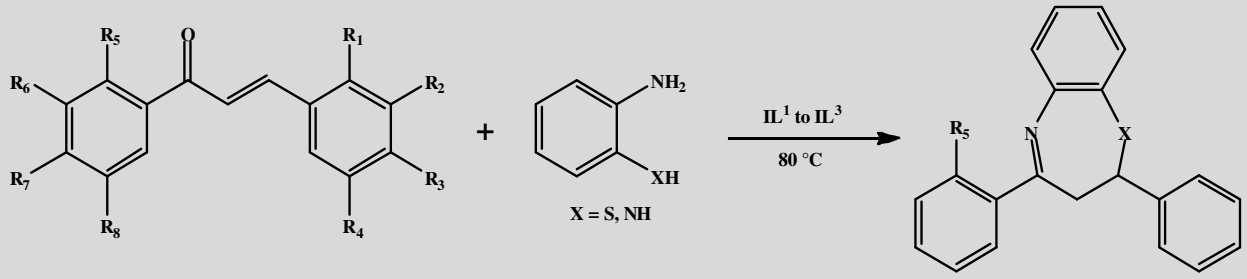
2-[2-(4-Chlorophenyl)-2,3-dihydrobenzo[b][1,4]-thiazepin-4-yl]phenol (8) (Table-1, Entry 8): Yellow solid; m.p.: 160-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.42 (bs, OH), 7.63 (dd, *J* = 1.9 Hz, *J* = 8.1 Hz, 1H), 7.55 (dd, *J* = 1.7 Hz, *J* = 8.6 Hz, 1H), 7.5 (dt, *J* = 1.7 Hz, *J* = 9.0 Hz, 1H), 7.40-7.44 (m, 1H), 7.29-7.33 (m, 4H), 7.20-7.24 (m, 2H), 7.08 (d, *J* = 7.6 Hz, 1H), 6.89-6.30 (m, 1H), 5.02 (dd, *J* = 4.9 Hz, *J* = 12.2 Hz, 1H), 3.38 (dd, *J* = 4.7 Hz, *J* = 13.0 Hz, 1H), 3.04 (t, *J* = 12.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.93, 162.95, 142.18, 135.09, 133.83, 130.16, 129.11, 128.42, 127.53, 126.69, 125.72, 123.44, 118.75, 118.63, 59.29, 36.89.

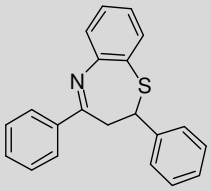
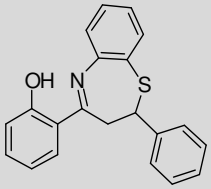
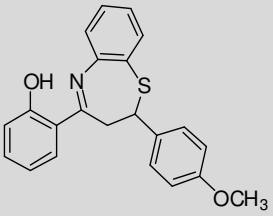
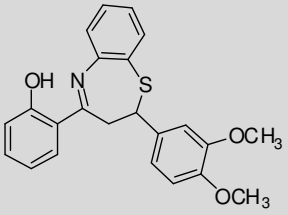
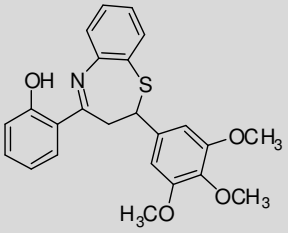
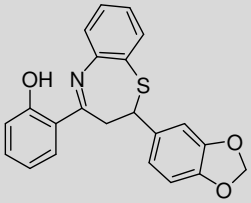
2-[2-(4-Fluorophenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl]phenol (9) (Table-1, Entry 9): Yellow solid; m.p.: 150-152 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.45 (bs, OH), 7.66 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.51 (dt, *J* =

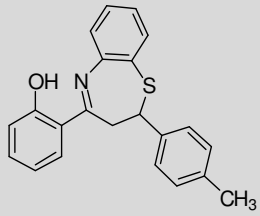
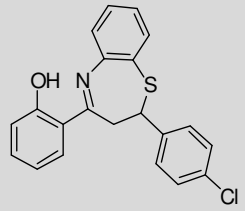
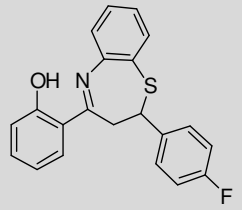
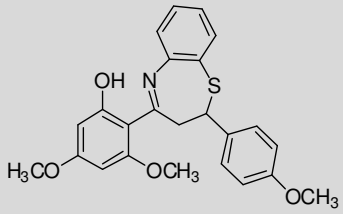
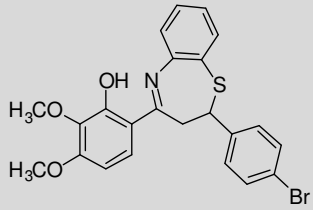
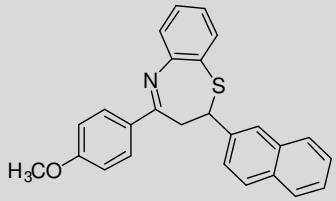
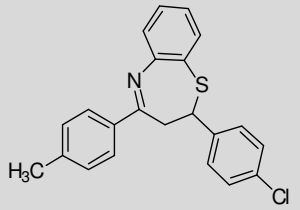
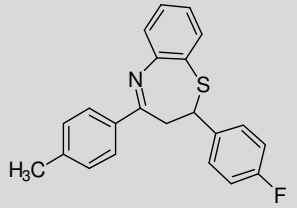
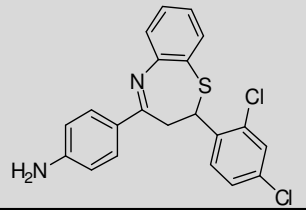
1.3 Hz, *J* = 7.8 Hz, 1H), 7.42 (dt, *J* = 1.3 Hz, *J* = 8.0 Hz, 1H), 7.29-7.38 (m, 4H), 7.09 (d, *J* = 7.8 Hz, 1H), 7.02 (t, *J* = 8.3 Hz, 2H), 6.92 (t, *J* = 7.5 Hz, 1H), 5.05 (dd, *J* = 4.4 Hz, *J* = 12.0 Hz, 1H), 3.41 (dd, *J* = 4.7 Hz, *J* = 13.0 Hz, 1H), 3.05 (t, *J* = 12.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ172.94, 163.13, 149.00, 134.72, 133.71, 130.14, 128.36, 127.98, 126.06, 124.42, 118.81, 115.75, 59.33, 36.91.

3,5-Dimethoxy-2-[2-(4-methoxyphenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl]phenol (10) (Table-1, Entry 10): Yellow solid; m.p.: 168-170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 16.82 (bs, OH), 7.64 (d, *J* = 8.2 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.16-7.31 (m, 4H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.17 (d, *J* = 1.9 Hz, 1H), 5.96 (d, *J* = 1.9 Hz, 1H), 5.20 (dd, *J* = 4.4 Hz, *J* = 12.9 Hz, 1H), 3.89 (s,

TABLE-1



Compd. No.	Structure	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Yield (%)
1		H	H	H	H	H	H	H	H	52
2		H	H	H	H	OH	H	H	H	92
3		H	H	OMe	H	OH	H	H	H	91
4		H	OMe	OMe	H	OH	H	H	H	83
5		H	OMe	OMe	OMe	OH	H	H	H	80
6		H	O-CH_2-O		H	OH	H	H	H	75

7		H	H	Me	H	OH	H	H	H	87
8		H	H	Cl	H	OH	H	H	H	85
9		H	H	F	H	OH	H	H	H	90
10		H	H	OMe	H	OH	H	OMe	OMe	87
11		H	H	Br	H	OH	OMe	OMe	H	78
12		H	Ph		H	H	H	OMe	H	82
13		H	H	Cl	H	H	H	Me	H	73
14		H	H	F	H	H	H	Me	H	75
15		Cl	H	Cl	H	H	H	NH_2	H	70

3H), 3.87 (s, 3H), 3.79 (s, 3H), 3.62 (dd, *J* = 4.7 Hz, *J* = 12.3 Hz, 1H), 2.89 (t, *J* = 12.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ172.14, 168.42, 164.23, 161.65, 158.90, 147.28, 135.29, 129.79, 127.12, 126.02, 125.63, 114.15, 103.71, 94.72, 90.55, 59.13, 55.66, 55.54, 55.39, 41.90; HRMS (ESI): calculated for $C_{24}H_{23}NO_4SH$ $[M+H]^+$ 422.1381, found 422.1973.

6-[2-(4-Bromophenyl)-2,3-dihydrobenzo[b][1,4]-thiazepin-4-yl]-2,3-dimethoxyphenol (11) (Table-1, Entry 11): Yellow solid; m.p.: 156-157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 14.40 (bs, OH), 7.60 (dd, *J* = 1.1 Hz, *J* = 7.6 Hz, 1H), 7.48 (dd, *J* = 1.3 Hz, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.18-7.30 (m, 5H), 6.50 (d, *J* = 8.9 Hz, 1H), 4.97 (dd, *J* = 4.9 Hz, *J* = 12.5 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.31 (dd, *J* = 4.7 Hz, *J* = 13.1 Hz, 1H), 3.02 (t, *J* = 12.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.34, 157.60, 156.62, 148.70, 142.56, 137.19, 135.05, 131.98, 131.96, 130.17, 127.80, 126.29, 125.67, 124.09, 123.97, 121.78, 113.44, 102.52, 60.60, 59.16, 56.04, 36.64; IR (ATR): 2927, 1605, 1556, 1449, 1289, 1076, 783, 702 cm^{-1}; HRMS (ESI): calculated for $C_{23}H_{20}BrNO_3SH$ $[M+H]^+$ 470.0350, found 470.0454; CHN analysis: calculated for $C_{23}H_{20}BrNO_3S$: C: 58.73; H: 4.29; Br: 16.99; N: 2.98; S: 6.82. Found: C: 58.81; H: 4.35; N: 2.84.

4-(4-Methoxyphenyl)-2-(naphthalen-2-yl)-2,3-dihydro-benzo[b][1,4]thiazepine (12) (Table-1, Entry 12): Yellow crystals (recrystalized from 20 % ethylacetate in *n*-hexane); m.p. 128-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.8 Hz, 2H), 7.76-7.89 (m, 3H), 7.67 (s, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.42-7.51 (m, 4H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.14 (t, *J* = 8.2 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 5.13 (dd, *J* = 5.0 Hz, *J* = 12.4 Hz, 1H), 3.88 (s, 3H), 3.34 (dd, *J* = 4.9 Hz, *J* = 12.7 Hz, 1H), 3.18 (t, *J* = 12.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.24, 162.21, 152.77, 129.88, 129.29, 128.94, 128.04, 127.78, 126.49, 126.17, 125.13, 124.29, 114.19, 60.66, 55.57, 37.23; IR (ATR):3051, 2929, 1592, 1235, 751 cm^{-1}; HRMS (ESI): calculated for $C_{26}H_{21}NOSH$ $[M+H]^+$ 396.1377, found 396.1473.

2-(4-Chlorophenyl)-4-*p*-tolyl-2,3-dihydrobenzo[b][1,4]-thiazepine (13) (Table-1, Entry 13): Light yellow solid; m.p.: 119-121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.1 Hz, 2H), 7.58 (d, *J* = 7.2 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.22-7.30 (m, 7H), 7.13 (t, *J* = 8.1 Hz, 1H), 4.93 (dd, *J* = 4.0 Hz, *J* = 12.5 Hz, 1H), 3.27 (dd, *J* = 4.0 Hz, *J* = 13.2 Hz, 1H), 3.0 (t, *J* = 12.6 Hz, 1H), 2.43 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.53, 152.55, 142.63, 141.60, 135.0, 134.98, 133.43, 129.89, 129.53, 128.90, 127.45, 127.39, 125.37, 122.39, 59.65, 37.36, 21.47; IR (ATR): 2919, 1600, 1565, 1452, 1246, 749 cm^{-1}; HRMS (ESI): calculated for $C_{22}H_{18}ClNSH$ $[M+H]^+$ 364.0921, found 364.0914; CHN analysis: calculated for $C_{22}H_{18}ClNS$: C: 72.61; H: 4.99; Cl: 9.74; N: 3.85; S : 8.81. Found: C: 72.73; H: 4.86: N, 3.97.

2-(4-Fluorophenyl)-4-*p*-tolyl-2,3-dihydrobenzo[b][1,4]-thiazepine (14) (Table-1, Entry 14): Light yellow solid; m.p.: 118-119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 7.8 Hz, 2H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.24-7.34 (m, 5H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.98 (t, *J* = 8.5 Hz, 2H), 4.95 (dd, *J* = 4.5 Hz, *J* = 12.3 Hz, 1H), 3.26 (dd, *J* = 3.9 Hz, *J* = 12.3 Hz, 1H), 3.0 (t, *J* = 13.0 Hz, 1H), 2.43 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.60, 163.36, 160.95, 152.55, 141.60, 140.16, 134.97, 129.82, 129.50, 127.75, 127.38, 125.37, 125.16, 122.53, 115.66, 115.45, 59.68, 37.67, 21.48; IR (ATR): 2891, 1600, 1580, 1505, 1450, 1212, 744 cm^{-1}; HRMS (ESI): calculated for $C_{22}H_{18}FNSH$ $[M+H]^+$ 348.1217, found 348.1232; CHN analysis: calculated for $C_{22}H_{18}FNS$: C: 76.05; H: 5.22; F: 5.47; N: 4.03; S: 9.23. Found: C: 76.17; H: 5.13; N: 4.14.

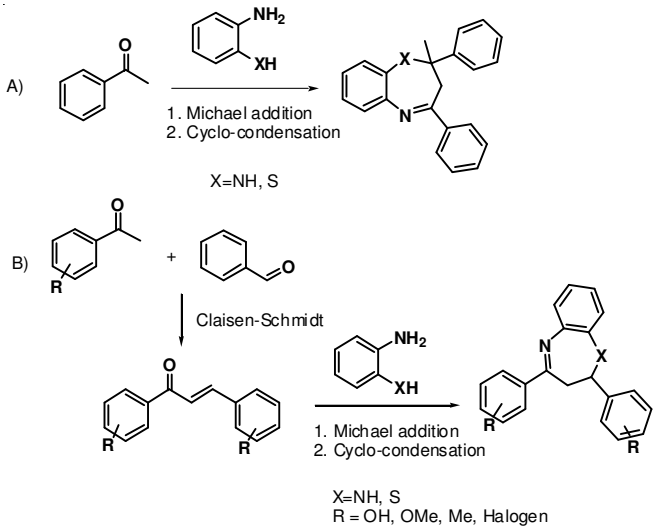
4-[2-(2,4-Dichlorophenyl)-2,3-dihydrobenzo[b][1,4]-thiazepin-4-yl]aniline (15) (Table-1, Entry 15): Pale yellow solid; m.p.: 179-181°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.5 Hz, 2H), 7.59-7.67 (m, 2H), 7.45 (dt, *J* = 1.9 Hz, *J* = 8.9 Hz, 1H), 7.38 (d, *J* = 1.9 Hz, 1H), 7.28 (s, 1H), 7.20 (dd, *J* = 1.5 Hz, *J* = 8.5 Hz, 1H), 7.10 (dt, *J* = 1.5 Hz, *J* = 8.1 Hz, 1H), 6.74 (d, *J* = 8.8 Hz, 2H), 5.43 (dd, *J* = 4.4 Hz, *J* = 12.6 Hz, 1H), 4.02 (bs, NH_2), 3.27 (dd, *J* = 4.8 Hz, *J* = 13.0 Hz, 1H), 2.78 (t, *J* = 13.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.61, 153.09, 149.51, 140.15, 134.94, 131.83, 129.96, 129.27, 129.05, 128.97, 127.71, 127.41, 125.50, 124.78, 122.20, 114.59, 55.32, 35.72; IR (ATR):3315, 3060, 1626, 1550, 1450, 1240, 735 cm^{-1}; HRMS (ESI): calculated for$C_{21}H_{16}Cl_2N_2SH$ $[M+H]^+$ 399.0484, found 399.0524; CHN analysis: calculated for $C_{21}H_{16}Cl_2N_2S$: C: 63.16; H: 4.04; Cl: 17.76; N: 7.01; S: 8.03. Found: C: 63.23; H: 4.25; N: 7.28.

3-(4-Methoxyphenyl)-2-(naphthalen-2-ylmethyl)-2H-benzo[b][1,4]thiazine (III): Golden yellow crystal; m.p. 157-158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.3 Hz, 2H), 7.74-7.83 (m, 3H), 7.57 (t, *J* = 8.3 Hz, 2H), 7.39-7.47 (m, 3H), 7.28-7.33 (m, 2H), 7.17-7.21 (m, 1H), 6.93 (d, *J* = 8.3 Hz, 2H), 4.26 (dd, *J* = 4.9 Hz, *J* = 9.3 Hz, 1H), 3.83 (s, 3H), 3.60 (dd, *J* = 4.6 Hz, *J* = 13.6 Hz, 1H), 2.83 (dd, *J* = 10.0 Hz, *J* = 13.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.80, 158.33, 143.07, 129.73, 129.49, 129.24, 128.93, 128.28, 127.99, 127.68, 126.61, 126.52, 126.06, 125.61, 119.84, 55.42, 37.21, 35.79; IR (ATR):3053, 2935, 1561, 1507, 1249, 751 cm^{-1}; HRMS (ESI): calculated for $C_{26}H_{21}NOSH$ $[M+H]^+$ 396.1377, found 396.1982.

3-(2-Aminophenylthio)-1,3-diphenylpropan-1-one: Colourless crystal (recrystalized from ethanol); m.p. 107-108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.3 Hz, 2H), 7.51-7.55 (m, 1H), 7.42 (t, *J* = 8.8 Hz, 1H), 7.12-7.26 (m, 5H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.66 (d, *J* = 8.3 Hz, 1H), 6.52 (t, *J* = 7.8 Hz, 1H), 4.74 (t, *J* = 6.7 Hz, 1H), 4.43 (bs, NH_2), 3.64 (dd, *J* = 7.3 Hz, *J* = 17.5 Hz, 1H), 3.56 (dd, *J* = 7.0 Hz, *J* = 17.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.15, 149.47, 141.61, 137.66, 136.73, 133.23, 130.63, 129.29, 128.36, 128.06, 127.61, 127.26, 117.98, 115.69, 114.81, 47.07, 44.03; IR (ATR): 3449, 3352, 1679, 1600, 1477, 744 cm^{-1}; HRMS (ESI): calculated for $C_{21}H_{19}NOSH$ $[M+H]^+$ 334.1221, found 334.1356.

RESULTS AND DISCUSSION

The synthesis of 1,5-benzothiazepines and 1,5-benzodiazepines from ketones and chalcones are outlined in **Scheme-I**. The precursor chalcone is prepared *via* Claisen-Schmidt reaction of various benzaldehydes and acetophenones [27]. In second step, the chalcone will react with *o*-phenylenediamine or *o*-aminothiophenol through Michael addition followed by cyclo-



Scheme-I: Synthesis of 1,5-benzodiazepines and 1,5-benzothiazepines from ketone (A) and chalcone (B)

condensation to give the desired 1,5-benzodiazepines and 1,5-benzothiazepines, respectively.

Here we would like to explore the efficiency of three dicationicimidazolium ionic liquids for the synthesis of various 1,5-benzothiazepines (Fig. 1) [28]. To investigate the effect of acidity of the media on these syntheses, the influence of various counter ions on the catalytic properties of ionic liquids were tested. Among these dicationic ionic liquids, IL-A with two bromides as counter ion expected to be less acidic than triflamide IL-B and with triflate IL-C respectively. The main aim of this investigation was to explore the efficiency of ionic liquids as promoter as well as media for the synthesis of 1,5-benzothiazepines. However, in order to generalize the method, the reaction of various ketones and chalcone with *o*-phenylenediamine has also been carried out.

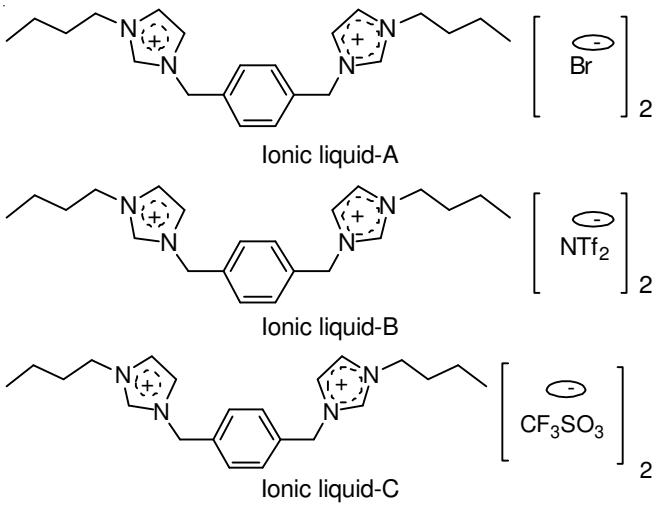


Fig. 1. Structures of different dicationic liquids

To optimize the reaction conditions, we commenced the reaction of *o*-aminothiophenol and *o*-phenylenediamine with 2′-hydroxychalcone as a model substrate in three ionic liquids IL-A, IL-B and IL-C. All the ionic liquids were found to be best in equimolar quantity with respect to *o*-phenylenediamine and the chalcone whereas, in the case of *o*-aminothiophenol, excess amount of the reagent was needed for the reaction to occur [29]. All the ionic liquids proved to promote the synthesis of 1,5-benzothiazepine selectively and the yields observed to be good to excellent compared with the reaction of the chalcone with *o*-phenylenediamine which resulted the lower yields (Fig. 2). Presumably, this low yield is due to the lower reactivity of *o*-phenylenediamine compare to *o*-aminothiophenol. However, the counter ion was observed to influence the reaction time as well as yield of the reaction. Notably, the effect of bromide, triflamide and triflate counter ions were found to be more effective with the reaction time and yield differently (Fig. 2). This observation could be explained by effect of the counter ions for the acidity of ionic liquids [30]. Amongst all the ionic liquids, the ionic liquid IL-C was observed to be the most efficient reaction media for the reaction of *o*-aminothiophenol/*o*-phenylenediamine with chalcone in terms of reaction time and yield of desired product (Fig. 2). Based on the above optimized conditions, the IL-C was chosen as the reaction media to explore its efficiency for the synthesis of various 1,5-benzothiazapines from different chalcones. The results of these reactions are shown in Table-1. In all the reactions, the ionic liquid IL-C seems to act not only as the solvent but also as a promoter and the reactions were accomplished in relatively short reaction times compared to those reported in conventional medium. The yields obtained for all the products was observed to be relatively good in ranging between 75 to 90 % yields. The reusability of the catalyst has also been studied for three cycles (Fig. 3).

As expected, the reaction between chalcone (**I**) with *o*-aminothiophenol in IL-C produced 1,5-benzothiazepine (II).

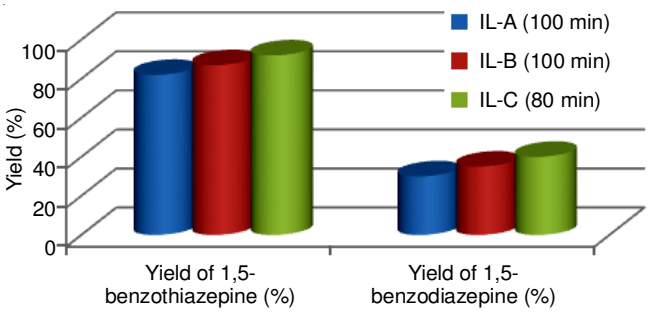


Fig. 2. Screening of the ionic liquids IL-A, IL-B and IL-C for the reaction between 2′-hydroxychalcone and *o*-aminothiophenol/*o*-phenylenediamine

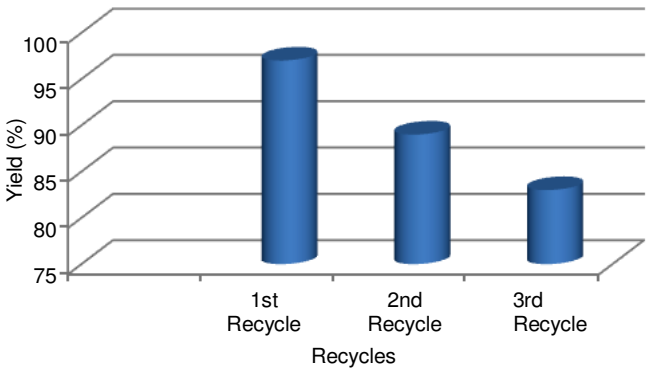


Fig. 3. Ionic liquid IL-C recycling for the reaction between *o*-aminothiophenol and 2′-hydroxychalcone

Formation of compound **II** was observed in ^{1}H NMR data (crude reaction mixture). In order to obtain pure 1,5-benzothiazepine (**II**), the crude mixture was passed through a basified silica column chromatography. Surprisingly, a six membered ring thiazine (**III**) was obtained as the product from ring contraction of the seven membered ring thiazepine II (**Scheme-II**). The ^{1}H NMR profile of three aliphatic protons for compounds **II** and **III** is shown in Fig. 4.

This ring rearrangement caused an up field shift in all the signals belonging to aliphatic protons of the thiazepine ring. In addition, due to this ring contraction, the splitting profile of these protons was also affected. In compound **II**, a triplet at 3.17 ppm, doublet of doublet at 3.34 ppm, and another doublet of doublet at 5.12 ppm were observed while in compound **III** three sets of doublet of doublet at 2.82, 3.05 and 4.25 ppm were observed (Fig. 4). Interestingly, in ^{13}C NMR spectrum, the aliphatic carbon of compound **II** appeared at δ 60.66 ppm while aliphatic carbon of compound **III** was observed at 35.78 ppm. This significant up field shift may be attributed to the distance of this carbon from imine group in six membered ring. Finally, compounds **II** and **III** were recrystallized from ethyl acetate. The crystal structure of compounds **II** and **III** are shown in Figs. 5 and 6.

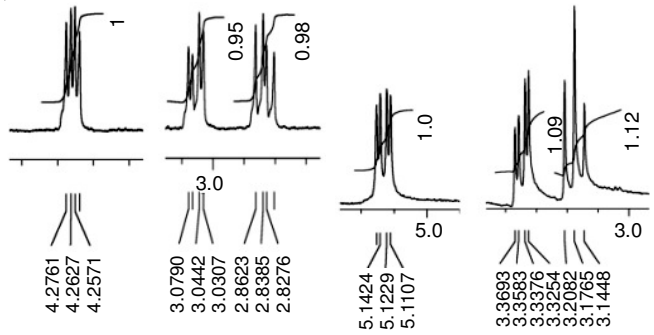


Fig. 4. Comparison of ^{1}H NMR spin-spin coupling between CH and CH_2 of the compounds **II** and **III**

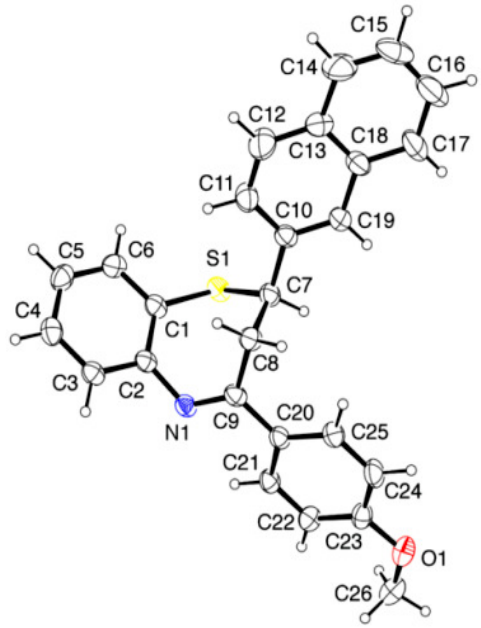
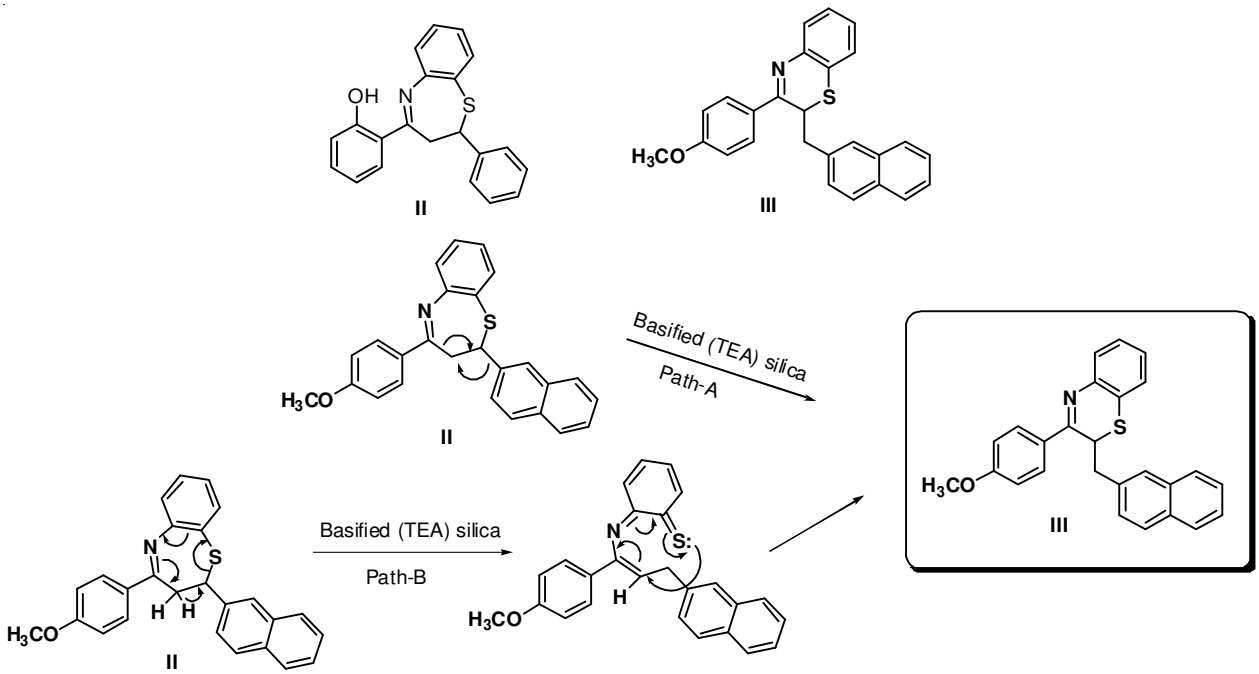


Fig. 5. X-ray crystal structure of 4-(4-methoxyphenyl)-2-(naphthalene-2-yl)-2,3-dihydrobenzo [*b*][1,4]thiazepine with thermal ellipsoids at 50 % probability. Atoms are labeled anonymously

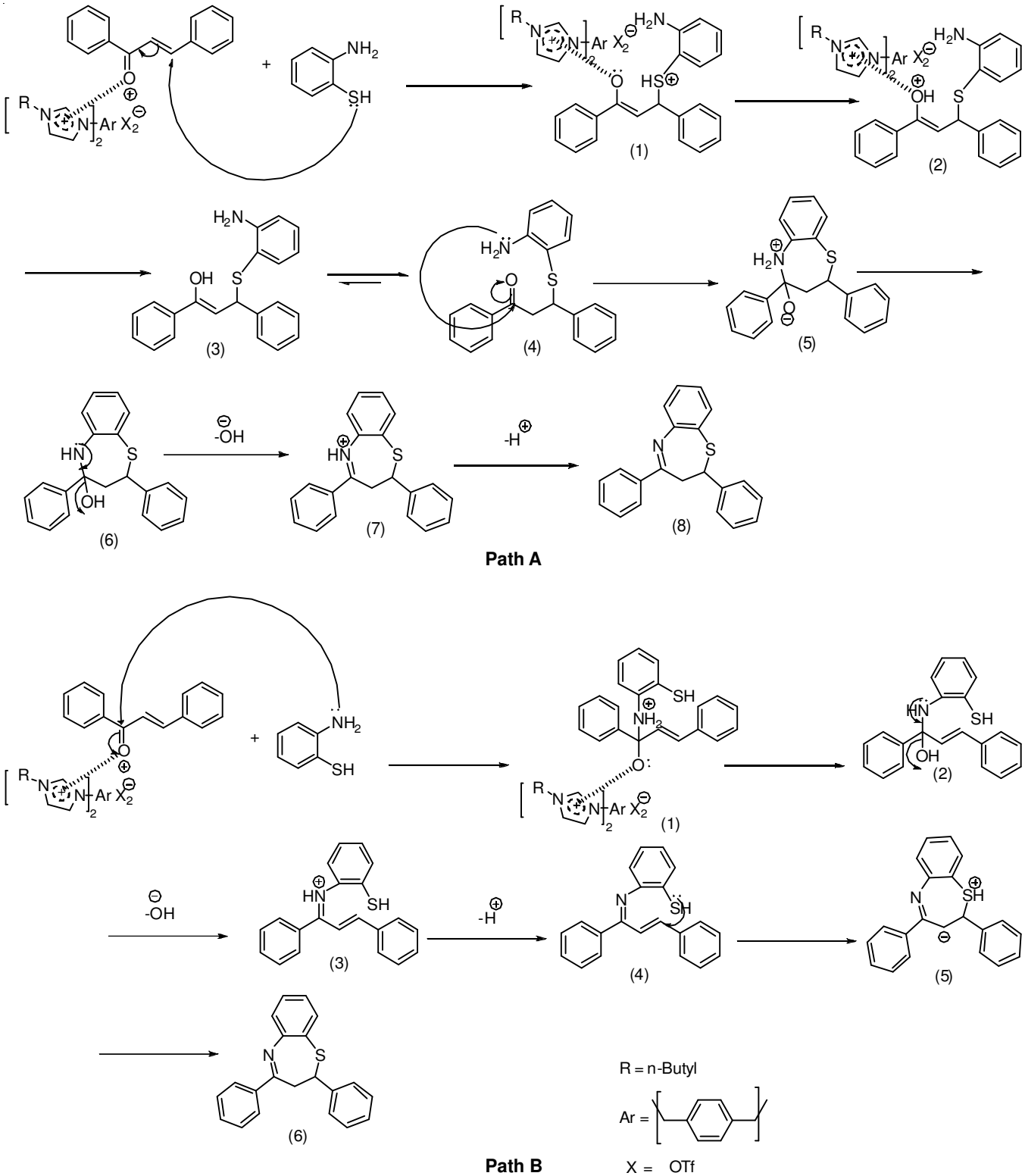
There are two possibilities for this transformation. The first possible mechanism is demonstrated in **Scheme-III** in which the compound **II** is converted to compound **III** through a naphthyl shift (Path-A). The second plausible mechanism for this transformation is shown in **Scheme-II** (Path-B) in which hydrogen shift followed by a ring opening and finally a ring closing.

To deduce the reaction mechanism, the intermediate of the reaction between *trans*-chalcone and *o*-aminothiophenol was isolated and characterized by ^{1}H and ^{13}C NMR spectroscopy. The NMR data clearly indicated that amongst the two possible intermediates (**Scheme-II** path A and path B), the preferred path is A due to the presence of three key aliphatic



Scheme-II: Conversion of thiazepine II to thiazine III through napthyl shift (Path-A) and hydrogen shift (Path-B)

protons in the ^{1}H NMR spectrum; *i.e.* at δ 3.56 (dd, *J* = 6.9 Hz, *J* = 17.6 Hz, 1H; CO-$\underline{CH_2}$-CH-S), δ 3.64 (dd, *J* = 7.3 Hz, *J* = 17.5 Hz, 1H; CO-$\underline{CH_2}$-CH-S), δ 4.74 (t, *J* = 6.7 Hz, 1H; CO-CH_2-$\underline{CH}$-S) and a carbonyl group in ^{13}C NMR spectrum at δ 197.15 which is in agreement with the reported data for a Michael adduct [31]. The IR spectra of this compound indicated the presence of NH_2 at 3352 cm^{-1}. This intermediate was recrystallized from ethanol and the structure was confirmed by X-ray crystallography (Fig. 7) [32]. The addition at the carbonyl carbon was expected to be faster since the complexation of the ionic liquid to oxygen makes the carbonyl more electrophilic. However, the bulkiness of ionic liquid could reduce this side to be more hindered. The softer fourth position, which presumably more exposed then is subjected to the attack by sulfur and the reaction will proceed through a 1,4-Michael addition reaction (**Scheme-III**).



Scheme-III: Proposed mechanism for the synthesis of 1,5-benzothiazepines in IL-C

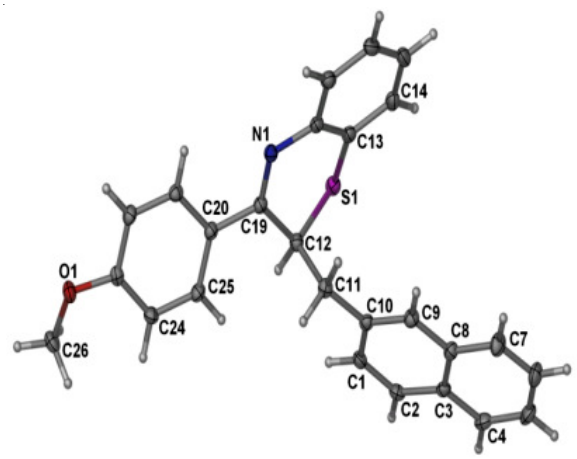


Fig. 6. X-ray crystal structure of 3-(4-methoxyphenyl-2-(naphthalene-2-ylmethyl)-2-hydrobenzo[*b*][1,4]thiazine with thermal ellipsoids at 50 % probability. Atoms are labeled anonymously

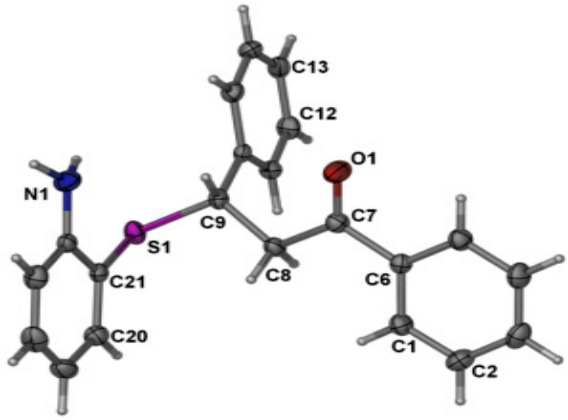


Fig. 7. X-ray crystal structure of the intermediate (4), path A, 3-(2-amino-phenylthio)-1,3-diphenylpropan-1-one with thermal ellipsoids at 50 % probability. Atoms are labeled anonymously

Conclusion

A new and environmental friendly method is developed for the synthesis of 1,5-benzothiazapines. The same reaction in three dicationic liquids is demonstrated and also checked the recyclability upto three cycles. The substrate scope for this reaction has also been investigated and the yields obtained were reasonably good to excellent.

ACKNOWLEDGEMENTS

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