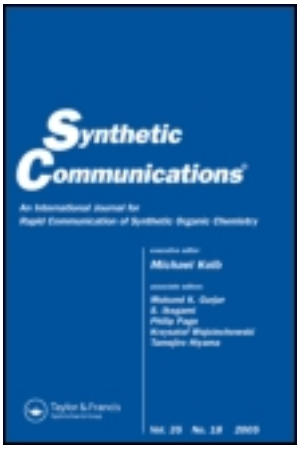

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Version of record first published: 02 May 2011.

To cite this article: Renuka Jain, Tripti Yadav, Manoj Kumar & Ashok K. Yadav (2011): Facile Ionic Liquid-Mediated Protocol for the Regioselective Synthesis of 1,5-Benzothiazepines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 41:13, 1889-1900

To link to this article: http://dx.doi.org/10.1080/00397911.2010.493626

Synthetic Communications®, 41: 1889–1900, 2011

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2010.493626

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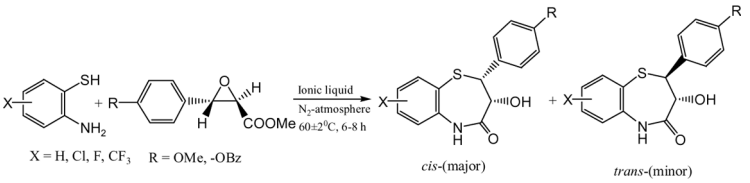
FACILE IONIC LIQUID–MEDIATED PROTOCOL FOR THE REGIOSELECTIVE SYNTHESIS OF 1,5-BENZOTHIAZEPINES

Renuka Jain, Tripti Yadav, Manoj Kumar, and Ashok K. Yadav

Department of Chemistry, University of Rajasthan, Jaipur, India

GRAPHICAL ABSTRACT



Abstract *An efficient one-step ionic liquid–mediated green protocol for the regioselective synthesis of* (+)/(±)-cis-*2-(4-methoxy/benzyloxyphenyl)-3-hydroxy-2,3-dihydro-1,5-benzothiazepin-4-*[5H]-*ones has been developed from the reaction between substituted 2-aminobenzenethiol and methyl-*(±)-trans-*3-(4-methoxy/benzyloxy phenyl)glycidate, under nitrogen atmosphere, at 60 ± 2 °C. The reaction has been performed in ionic liquids (viz, 1-butyl-3-methylimidazolium bromide/hexafluorophosphate), and the yields of the 1,5-benzothiazepine derivatives were found to be excellent. The* cis-*stereoisomer was obtained as the major product along with a* trans-*isomer as minor product.*

Keywords Benzothiazepines; glycidate; green chemistry; ionic liquids; regioselectivity

INTRODUCTION

1,5-Benzothiazepines constitute an important class of privileged scaffolds as a result of their immense chemotherapeutic applications, such as antibacterial,[1] anticancer,[2] antihypertensive,[3] antifeedant,[4] analgesic,[5] anticonvulsant,[6] coronary vasodilatory,[7] antidepressant,[8] central nervous system stimulant,[9] calcium channel blocker,[10] and platelate aggregation,[11] activities. Some notable pharmacologically important patented 1,5-benzothiazepin-4-ones include diltiazem,[12] thiazesim,[13] and clentiazem.[14] Owing to their remarkable pharmacological activities, several approaches have been reported for the synthesis of 1,5-benzothiazepines such as the reactions between 2-aminothiophenol(s) with α,β-unsaturated ketones[15] or ω-bromoacetophenone and aromatic aldehyde[16] or chalcone in the presence of

Received August 22, 2009.

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SiO_2[17] or chalcone analogs of dehydroacetic acid,[18] α,β-unsaturated ketones with *bis*(2-nitrophenyl)disulfide in presence of $TiClO_4$/Sm,[19] 2-aminophenyldisulfide with itaconic anhydride and dimethylitacone,[20] photochemical reaction of 2-phenylbenzothiazole with ethoxyacetylene/ethoxy propyne,[21] and the microwave-activated reaction between 3-(4′-fluoro-2′-methylbenzoyl)-2-propenoic acid with 2-aminothiolphenol.[22]

Most of these methods have some drawbacks, such as long reaction time, high temperature, poor yields, and use of volatile organic compounds and environmentally hazardous solvents. Inspired by the biological profile of 1,5-benzothiazepines, the applications of ionic liquids as ecofriendly solvent/catalytic system, and our interest in developing efficient green methodology,[20] we herein report, for the first time, a convenient regioselective one-step synthesis of *cis*-1,5-benzothiazepines in ionic liquids, namely 1-butyl-3-methylimidazolium bromide [BMIM]Br and 1-butyl-3-methylimidazolium hexafluorophosphate [BMIM]PF_6.

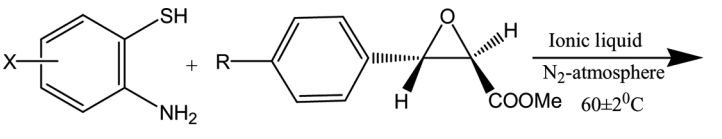
RESULTS AND DISCUSSION

In our strategy, we have carried out the reaction between substituted 2-aminobenzenethiols (viz., 2-aminobenzenethiol, 4/5/6-chloro-2-amino-benzenethiol, 6-fluoro-2-aminobenzenethiol, and 4-trifluoromethyl-2-aminobenzenethiol) with methyl-(±)-*trans*-3-(4-methoxyo/benzyloxy phenyl) glycidate in an ionic liquid (viz., [BMIM]Br and [BMIM]PF_6). The reaction has been performed under a nitrogen environment at $60 \pm 2\,^{\circ}C$. The products obtained were (+)-*cis*-(2*S*,3*S*)-2,3-dihydro-3-hydroxy-2-(4′-methoxyphenyl)-1,5-benzo-thiazepin-4-[5H]-one **3a**, (+)-*cis*-(2*S*,3*S*)-7-chloro-2,3-dihydro-3-hydroxy-2-(4′-methoxyphenyl)-1,5-benzothiazepin-4-[5H]-one **3b**, (+)-*cis*-(2*S*,3*S*)-8-chloro-2,3-dihydro-3-hydroxy-2-(4′-methoxyphenyl)-1,5-benzothiazepin-4-[5H]-one **3c**, (+)-*cis*-(2*S*,3*S*)-9-chloro-2,3-dihydro-3-hydroxy-2-(4′-methoxyphenyl)-1,5-benzothiazepin-4-[5H]-one **3d**, (±)-*cis*-(2S,3S)-9-fluoro-2,3-dihydro-3-hydroxy-2-(4′-methoxyphenyl)-1,5-benzothiazepin-4-[5*H*]-one **3e**, (±)-*cis*-(2*S*,3*S*)-7-trifluoromethyl-2,3-dihydro-3-hydroxy-2-(4′-methoxyphenyl)-1,5-benzothiazepin-4-[5H]-one **3f**, (±)-*cis*-(2*S*,3*S*)-2-(4′-benzyloxyphenyl)-2,3-dihydro-3-hydroxy-1,5-benzothiazepin-4-[5H]-one **3g**, (±)-*cis*-(2*S*,3*S*)-2-(4′-benzyloxy phenyl) 8-chloro-2,3-dihydro-3-hydroxy-1,5-benzothiazepin-4-[5*H*]-one **3i,** and (±)-*cis*-(2*S*,3*S*)-2-(4′-benzyloxyphenyl)-7-trifluoro-2,3-dihydro-3-hydroxy-1,5-benzo-thiazepin-4-[5*H*]-one **3j**, respectively, as major products. The corresponding *trans*-isomers **4a-j** were isolated as minor products in each case.

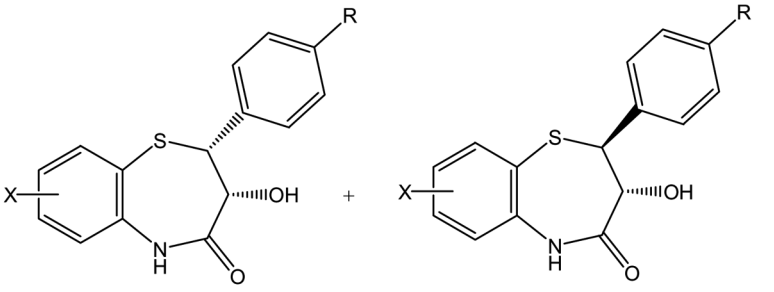
The progress of the reaction was monitored by thin-layer chromatography (TLC; Merck silica gel $^{60}F_{254}$ aluminium sheets) in petroleum ether–ethyl acetate (4:1), and it reached completion in 6–8 h. The separation of *cis*- and *trans*-isomers was accomplished in petroleum ether–ethyl acetate (4:1) on a column of silica gel G (60–120 mesh), and the yields of the products are presented (Scheme 1, Table 1).

The stereochemistry (i.e., *cis*- and *trans*-) of compounds **3a–j** and **4a–j** was deduced from the ^{1}H NMR vicinal compling constant between C_2^- and C_3^- methine protons, which showed $^2J_{HH} = 6.4$–7.2 Hz and $^2J_{HH} = 8.3$–10.2 Hz for *cis*- and *trans*-isomers, respectively.

The observation of data (Table 1) reveals that the *cis*-**3a–j** were obtained in 76–90% yield in [BBIM]Br and in 82–95% yield in [BBIM]PF_6. The better yield in



1 **2a,b**



cis -**3a-j** (major) *trans*-**4a-j** (minor)

Compound	3a,4a	3b,4b	3c,4c	3d 4d	3e,4e	3f,4f	3g,4g	3h,4h	3i,4i	3j,4j
X	H	7-Cl	8-Cl	9-Cl	9-F	7-CF_3	H	7-Cl	8-Cl	7-Cl
R	OMe	OMe	OMe	OMe	OMe	OMe	OBz	OBz	OBz	OBz

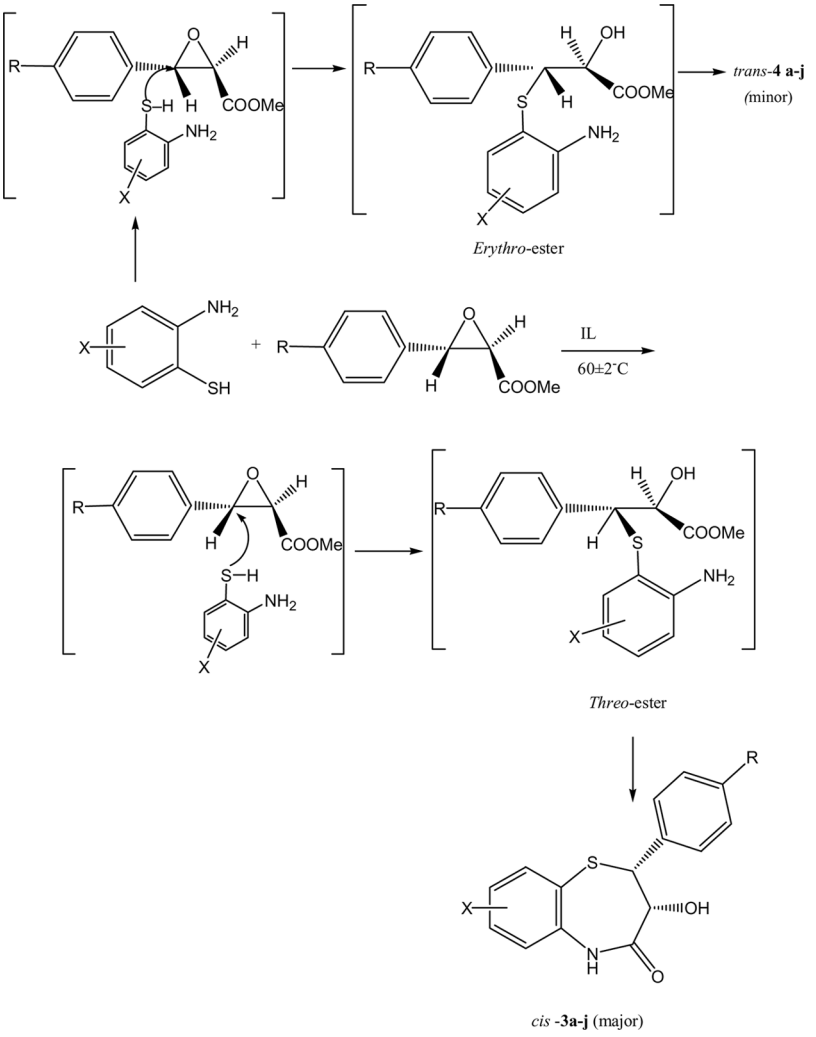
Scheme 1. Synthesis of 1,5-benzothiazepine derivatives.

the latter ionic liquid is perhaps a result of the change in lipophilicity/hydrophilicity of ionic liquid resulting from a change in anion as [BBIM]BF_4 is miscible in water, whereas [BBIM]PF_6 is immiscible in water.

In our study, we were unable to isolate *threo*- and *erythro*-esters as has been done by Hashiyama et al.[24] These authors studied the oxirane ring opening with 2-/4-nitrophenol/2-aminophenol and obtained the corresponding *threo*- and *erythro*-esters in benzene, dioxan, Bu^tOH, hexamethyl phosphoramide (HMPA), and CH_3CN. The effects of various catalyst, such as $ZnCl_2$, BF_3-Et_2O, SnX_2, and SnX_4, on yields of *threo*- and erythro esters have been investigated. In our method, the ring opening of methyl-(±)-*trans*-(4-methoxy)/4-benzyloxy phenyl) glycidate with substituted 2-aminothiophenol in [BBIM]Br/PF_6 gave directly *cis*-**3a–j** as major products along with *trans*-**4a–j** as minor products. This observation suggests that in the ionic liquid, the oxirane ring opens stereoselectively, followed by subsequent cyclization. Also, the time to complete the reaction in our case is 6–8 h, far less than reported earlier:[24] 18–48 h.

Effect of Substituent on the Benzene Ring of *trans*-Phenylglycidate 2

A careful look at the data of Table 1 reveals that with the glycidate **2b** the overall yields of **3a–j** and **4a–j** and also the stereoselectivity for the *cis*-isomer is better



Scheme 2. Plausible mechanism of the reaction process.

than with glycidate **2a**. This is probably because of the better electron-donating ability of **2b** (due to benzyloxy substituent), thereby resulting in increased carbocationic character of the benzylic carbon in the transition state. This observation is in agreement with an earlier report.[24]

Effect of Substituents on Thiolphenols

An observation of Table 1 suggests that the total yields of compounds **3** and **4** and the *cis*-/*trans*-ratio obtained were dependent upon the electron-withdrawing effect of the substituents attached to 2-aminothiophenols; the total yields of compounds **3** and **4** in both ionic liquids follow the order 7-CF_3 > 9-F/9-Cl > 8-Cl > 7-Cl > H and 7-CF_3 > 8-Cl > 7-Cl > H when the reaction was carried out with the

Table 1. Yield of 1,5-benzothiozepine derivatives **3** and **4**

			[BMIM]Br		[BMIM]PF_6	
Entry	X	R	Yield (%)[a]/Time (h)	*cis*/*trans*	Yield (%)[a]/Time (h)	*cis*/*trans*
1	H	OMe	72/8.0	76/24	78/7.5	82/18
2	7-Cl	OMe	80/7.5	82/18	85/7.0	88/12
3	8-Cl	OMe	82/7.5	84/16	86/7.0	90/10
4	9-Cl	OMe	84/7.0	86/14	88/6.5	92/8
5	9-F	OMe	84/6.5	86/14	90/6.5	92/8
6	7-CF_3	OMe	86/6.5	90/10	94/6.0	95/5
7	H	OBz	76/7.5	82/18	80/7.5	84/16
8	7-Cl	OBz	80/7.0	85/15	85/7.0	86/14
9	8-Cl	OBz	82/7.0	86/14	88/6.5	90/10
10	7-CF_3	OBz	88/6.0	90/10	94/6.0	94/6

[a]Total yield of *cis* and *trans* isomers (compounds **3** and **4**).

Table 2. Recyclability data for products

		Yield (%)/Time (h)	
Products	Cycle	[BMIM]Br	[BMIM]PF_6
3a + **4a**	0	72/8.0	78/7.5
3a + **4a**	1	70/8.0	75/7.5
3a + **4a**	2	68/8.0	72/7.5
3g + **4g**	0	76/7.5	80/7.5
3g + **4g**	1	72/7.5	78/7.5
3g + **4g**	2	70/7.5	75/7.5

corresponding substituted 2-aminothiophenol and glycidate **2a** and **2b**, respectively. Furthermore, reaction between the 6-chloro/6-fluoro-2-aminothiophenol (entries 4 and 5 of Table 1) and glycidate **2a/2b** gave better yields and stereoselectivity in comparison to the reaction between 4-chloro/5-chloro-2-aminothiophenol (entries 2 and 3 of Table 1) and glycidate **2a/2b**, thereby indicating that no neighboring group participation was involved in the reaction.

We have also investigated the recyclability of the ionic liquids for the overall products (*cis* + *trans*), and the results are presented in Table 2. These data clearly suggest that the ionic liquids can be reused with significant success and thus offer an attractive alternative methodology for the regioselective synthesis of 1,5-benzothiazepines.

CONCLUSION

In conclusion, we have developed a regioselective one-pot synthesis of 1,5-benzothiazepines at $60 \pm 2\,^{\circ}C$ in environmentally friendly conditions in ionic liquids. The simple experimental procedure, absence of catalyst, and the recyclability of reaction media makes this procedure attractive for scale up.

EXPERIMENTAL

Melting points of all the synthesized compounds were determined in open capillary tubes and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu Fourier transform (FT)–IR spectrometer using KBr pellets. ^{1}H NMR spectra were recorded on a Jeol AL 300-MHz NMR spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard (chemical shift in δ ppm). ^{13}C NMR spectra were recorded on a Jeol AL 75.47-MHz NMR spectrometer in $CDCl_3$ using TMS as an internal standard. The purity of each compound was checked by TLC using silica-gel $^{60}F_{254}$ aluminium sheets as adsorbent and visualization was accomplished by iodine/ultraviolet light. Ionic liquids were prepared by a reported method.[25] 2-Aminobenzenethiol, 2-amino-4-chlorobenzenethiol, and 2-amino-4-trifluoromethylbenzenethiols were purchased from Sigma-Aldrich Co. Inc. Other halogen substituted-2-aminobenzenethiols were synthesized according to the reported method.[26] Methyl-(±)-*trans*-3-(4-methoxyphenyl)glycidate is commercially available and purchased from Sigma-Aldrich Chemical Co. Inc., whereas methyl-(±)-*trans*-3-(4-benzyloxyphenyl) glycidate was synthesized by the reaction between 4-benzyloxybenzaldehyde and methyl chloroacetate in dioxane according to the reported method.[27]

General Procedure for the Synthesis of 2,3-Dihydro-3-hydroxy-2-(4′-methoxy/benzyloxyphenyl)-1,5-benzothiazepin-4-(5H)-one (3 and 4)

Substituted 2-aminobenzenethiol (0.05 mol), methyl-(±)-*trans*-3-(4-methoxyl/benzyloxyphenyl) glycidate (0.05 mol), and ionic liquid (5 mL) were taken in a round-bottomed flask to carry out the reaction under a nitrogen atmosphere. The contents of the flask were stirred magnetically at $60 \pm 2\,^{\circ}C$ for 6–8 h. The progress of the reaction was monitored by TLC plates (Merck silica-gel $^{60}F_{254}$ aluminium sheets) in petroleum ether–ethyl acetate (4:1), and visualization was accomplished in iodine chamber/ultraviolet light. Upon completion of the reaction, water was added to it and the organic mass was extracted with ethyl acetate (3×10 mL). The combined organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure (10 mm of Hg) to afford compounds **3** and **4**. The organic mixture was separated on a silica-gel column (60–120 mesh, 12'') by eluting with petroleum ether–ethyl acetate (4:1). Compound **3** (i.e., *cis*-isomer) was obtained first, followed by compound **4** (i.e., *trans*-isomer). The ionic liquids were regenerated by keeping then at $80 \pm 2\,^{\circ}C$ (5 mm of Hg) and were reused for another cycle. The characteristic data of the synthesized compounds are given.

Selected Data

(+)-*cis*-(2*S*,3*S*)-2,3-Dihydro-3-hydroxy-2-(4′-methoxyphenyl)-1,5-benzothiazepin-4-[5*H*]-one 3a. White solid, mp 200–202 °C; $[\alpha]_D^{22} + 116.6°$ (c 0.50 DMF); IR (KBr, cm^{-1}) *v*: 3350, 3200, 3100, 1680, 1510, 1475; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.76 (s, 3H, $-OCH_3$), 4.29 (dd, $J = 6.6$ Hz and 6.4 Hz, 1H, C_3-H), 4.74 (d, $J = 6.4$ Hz, 1H, C_2-H), 5.05 (d, $J = 6.6$ Hz, 1H, -OH), 6.87–7.62 (m, 8H, Ar-H), 10.31 (s, 1H,

-NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 172.50, 160.25, 147.30, 136.10, 132.60, 132.04, 129.90, 128.60, 128.20, 126.40, 114.30, 70.40, 57.93, 55.50. Anal. calcd. for $C_{16}H_{15}NO_3S$: C, 63.75; H, 5.01; N, 4.64. Found: C, 63.90; H, 5.22, N, 4.52%.

(−)-*trans*-(2*S*,3*R*) Isomer 4a. Solid 196–198 °C; $[\alpha]_D^{22} - 84.2°$ (c 1.0 DMF); IR (KBr, cm^{-1}) *v*: 3500, 3160, 3030, 1690, 1515, 1475; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.72 (s, 3H, -OCH_3), 4.07 (dd, $J = 10.2$ Hz and 8.3 Hz, 1H, C_3-H), 4.35 (d, $J = 10.2$ Hz, 1H, C_2-H), 5.33 (d, $J = 8.3$ Hz 1H, -OH), 6.83–7.56 (m, 8H, Ar-H), 10.21 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 173.20, 160.25, 147.45, 136.10, 132.45, 132.04, 129.80, 128.65, 128.20, 126.40, 114.25, 70.60, 57.93, 55.40. Anal. calcd. for $C_{16}H_{15}NO_3S$: C, 63.75; H, 5.01; N, 4.64. Found: C, 63.85; H, 5.28; N, 4.51%.

(+)-*cis*-(2*S*,3*S*)-7-Chloro-2,3-dihydro-3-hydroxy-2-(4′-methoxyphenyl)-1,5-benzothiazepin-4-[5*H*]-one 3b. Yellowish solid, mp 225–258 °C; $[\alpha]_D^{22} + 63.7°$ (c 0.31 DMF); IR (KBr, cm^{-1}) *v*: 3350, 3170, 3100, 1680; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3H, -OCH_3), 4.32 (dd, $J = 6.6$ Hz and 6.4 Hz, 1H, C_3-H), 4.88 (b d, $J = 6.6$ Hz, 1H, -OH), 5.09 (d, $J = 6.4$ Hz, 1H, C_2-H), 6.80–7.60 (m, 7H, Ar-H), 10.25 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 173.20, 160.30, 148.40, 137.40, 132.60, 132.40, 129.90, 128.90, 128.60, 126.50, 114.35, 72.40, 58.40, 55.50. Anal. calcd. for $C_{16}H_{14}ClNO_3S$: C, 57.20; H, 4.20; N, 4.17. Found: C, 57.42; H, 4.02; N, 4.35%. (–)-*cis*-(2*R*, 3*R*) Isomer **3b**: $[\alpha]_D^{22} - 62.5°$ (c 0.29 DMF), and other data are identical with those of the (+)-*cis*-(2*S*,3*S*) isomer.

(±)-*trans*-(2*R*,3*S*) Isomer 4b. Yellowish solid, mp 204–206 °C; IR (KBr, cm^{-1}) *v*: 3480, 3190, 3090, 1685; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3H, -OCH_3), 4.05 (dd, $J = 10.2$ Hz and 8.3 Hz, 1H, C_3-H), 4.74 (d, $J = 10.2$ Hz, 1H, C_2-H), 5.29 (d, $J = 8.3$ Hz, 1H, -OH), 6.78–7.55 (m, 7H, Ar-H), 10.15 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 173.40, 160.20, 148.50, 137.45, 132.50, 132.30, 129.85, 128.90, 128.60, 126.50, 114.30, 72.45, 58.30, 55.50. Anal. calcd. for $C_{16}H_{14}ClNO_3S$: C, 57.20; H, 4.20; N, 4.17. Found: C, 57.35; H, 4.01; N, 4.40.

(+)-*cis*-(2*S*,3*S*)-8-Chloro-2,3-dihydro-3-hydroxy-2-(4′-methoxyphenyl)-1,5-benzothiazepin-4-[5*H*]-one 3c. Yellowish solid, mp 232–234 °C; $[\alpha]_D^{20} + 91.1°$ (c 1.02 DMF); IR (KBr, cm^{-1}) *v*: 3350, 3180, 3100, 1680; EIMS *m/z* 335; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3H, -OCH_3), 4.37 (dd, $J = 6.6$ Hz and 6.4 Hz, 1H, C_3-H), 4.90 (b d, $J = 6.6$ Hz, 1H, -OH), 5.10 (d, $J = 6.4$ Hz, 1H, C_2-H), 6.80–7.58 (m, 7H, Ar-H), 10.21 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 173.20, 160.30, 148.40, 140.62, 138.50, 134.40, 132.60, 129.90, 128.60, 126.50, 114.35, 72.40, 58.40, 55.50. Anal. calcd. for $C_{16}H_{14}ClNO_3S$: C, 57.20; H, 4.20; N, 4.17%. Found: C, 57.42; H, 4.36; N, 4.05. (–)-*cis* (2*R*,3*R*) Isomer (**3c**): $[\alpha]_D^{20} - 92°$ (c 1.06 DMF), and other data are identical with those of the (+)-*cis*-(2*S*, 3*S*) isomer **3c**.

(±)-*trans*-(2*R*,3*S*) Isomer 4c. Yellowish solid, mp 184–185 °C; IR (KBr, cm^{-1}) *v*: 3490, 3190, 3090, 1685; EIMS m/z 335; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3H, -OCH_3), 4.10 (dd, $J = 10.2$ Hz and 8.3 Hz, 1H, C_3-H), 4.60 (d, $J = 10.2$ Hz, 1H, C_2-H), 5.33 (d, $J = 8.3$ Hz, 1H, -OH), 6.78–7.86 (m, 7H, Ar-H), 10.11 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 173.40, 160.20, 148.50, 140.62, 138.40, 134.50, 132.50,

129.90, 128.60, 126.50, 114.30, 72.40, 58.30, 55.50. Anal. calcd. for $C_{16}H_{14}ClNO_3S$: C, 57.20; H, 4.20; N, 4.17. Found: C, 57.30; H, 4.32; N, 4.02%.

(+)-*cis*-(2*S*,3*S*)-9-Chloro-2,3-dihydro-3-hydroxy-2-(4′-methoxyphenyl)-1,5-benzothiazepin-4-[5*H*]-one 3d. Yellowish solid, mp 188–190 °C; $[\alpha]_D^{20}$ 0° (c 0.27 DMF); IR (KBr, cm^{-1}) *v*: 3350, 3160, 3100, 1680, 1630; ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3H, -OCH_3), 4.32 (dd, $J = 6.6$ Hz and 6.4 Hz, 1H, C_3-H), 4.88 (b d, $J = 6.6$ Hz, 1H, -OH), 5.09 (d, $J = 6.4$ Hz, 1H, C_2-H), 6.80–7.62 (m, 7H, Ar-H), 10.21 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 173.20, 160.30, 148.30, 138.40, 132.50, 132.20, 129.80, 128.60, 128.20, 126.60, 114.30, 72.40, 58.40, 55.50. Anal. calcd. for $C_{16}H_{14}ClNO_3S$: C, 57.20; H, 4.20; N, 4.17. Found: C, 57.04; H, 3.96; N, 4.38%.

(–)-*cis*-(2*R*,3*R*) Isomer 3d. $[\alpha]_D^{22}$ 0° (c 0.27 DMF), and other data are identical with those of (+)-*cis*-(2*S*,3*S*) isomer **3d**.

(±)-*trans*-(2*R*,3*S*) Isomer 4d. Yellowish solid, mp 196–198 °C; IR (KBr, cm^{-1}) *v*: 3480, 3170, 3110, 1685, 1640; ^1H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3H, -OCH_3), 4.07 (dd, $J = 10.2$ Hz and 8.3 Hz, 1H, C_3-H), 4.70 (b d, $J = 10.2$ Hz, 1H, C_2-H), 5.30 (d, $J = 8.3$ Hz, 1H, -OH), 6.75–7.62 (m, 7H, Ar-H), 10.15 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 173.30, 160.75, 148.45, 138.30, 132.60, 132.20, 129.85, 128.70, 128.20, 126.60, 114.30, 72.50, 58.35, 55.50. Anal. calcd. for $C_{16}H_{14}ClNO_3S$: C, 57.20; H, 4.20; N, 4.17. Found: C, 57.45; H, 3.98; N, 4.35%.

(±)-*cis*-(2*S*,3*S*)-9-Fluoro-2,3-dihydro-3-hydroxy-2-(4′-methoxyphenyl)-1,5-benzothiazepin-4-[5*H*]-one 3e. White solid, mp 218–220 °C; IR (KBr, cm^{-1}) *v*: 3380, 3230, 3100, 1680, 1610; ^1H NMR (300 MHz, $CDCl_3$) δ 3.31 (s, 3H, -OCH_3), 4.32 (t, $J = 7.0$ Hz, 1H, C_3-H), 4.70 (d, $J = 7.0$ Hz, 1H, -OH), 4.78 (d, $J = 7.0$ Hz, 1H, C_2-H), 6.85–7.85 (m, 7H, Ar-H), 10.31 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 173.30, 160.40, 148.50, 146.40, 132.20, 129.80, 129.30, 128.60, 128.20, 126.90, 114.20, 72.50, 58.45, 55.40. Anal. calcd. for $C_{16}H_{14}FNO_3S$: C, 60.15; H, 4.42; N, 4.38. Found: C, 60.42; H, 4.10; N, 4.62%.

(±)-*trans*-(2*R*,3*S*) Isomer 4e. White solid, mp 226–228 °C; IR (KBr, cm^{-1}) *v*: 3500, 3260, 1685, 1640; ^1H NMR (300 MHz, $CDCl_3$) δ 3.31 (s, 3H, -OCH_3), 4.05 (dd, $J = 10.2$ Hz and 8.3 Hz, 1H, C_3-H), 4.65 (d, $J = 10.2$ Hz, 1H, C_2-H), 5.10 (d, $J = 8.3$ Hz, 1H, -OH), 6.70–7.75 (m, 7H, Ar-H), 10.21 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 173.40, 160.30, 148.55, 146.25, 132.20, 129.90, 129.30, 128.60, 128.25, 126.90, 124.30, 72.55, 58.50, 55.40. Anal. calcd. for $C_{16}H_{14}FNO_3S$: C, 60.15; H, 4.42; N, 4.38. Found: C, 60.45; H, 4.20; N, 4.58%.

(±)-*cis*-(2*S*,3*S*)-7-Trifluoromethyl-2,3-dihydro-3-hydroxy-2-(4′-methoxyphenyl)-1,5-benzothiazepin-4-[5*H*]-one 3f. White solid, mp 244–246 °C; IR (KBr, cm^{-1}) *v*: 3400, 3250, 1680, 1590; ^1H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 3H, -OCH_3), 4.35 (dd, $J = 6.6$ Hz and 6.4 Hz, 1H, C_3-H), 4.90 (b d, $J = 6.6$ Hz, 1H, -OH), 5.12 (d, $J = 6.4$ Hz, 1H, C_2-H), 6.85–7.70 (m, 7H, Ar-H), 10.31 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 174.50, 162.40, 147.25, 142.60, 138.40, 132.80, 132.60, 129.90, 128.80, 126.40, 114.20, 78.40, 72.60, 58.30, 55.40. Anal. calcd. for $C_{17}H_{14}F_3NO_3S$: C, 55.26; H, 3.82; N, 3.79. Found: C, 55.05; H, 3.98; N, 4.10%.

(±)-*trans*-(2*R*,3*S*) Isomer 4f. White solid, mp 255–257 °C; IR (KBr, cm^{-1}) *v*: 3480, 3260, 1690, 1640; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (s, 3H, -OCH_3), 4.08 (dd, $J = 10.8$ Hz and 8.3 Hz, 1H, C_3-H), 4.76 (d, $J = 10.2$ Hz, 1H, C_2-H), 5.35 (d, $J = 8.3$ Hz, 1H, -OH), 6.80–7.85 (m, 7H, Ar-H), 10.25 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 174.60, 162.50, 147.20, 142.55, 138.50, 132.95, 132.55, 129.90, 128.80, 126.50, 114.20, 78.40, 72.60, 58.20, 55.50. Anal. calcd. for $C_{17}H_{14}F_3NO_3S$: C, 55.26; H, 3.82; N, 3.79. Found: C, 55.10; H, 3.85; N, 4.05%.

(±)-*cis*-(2*S*,3*S*)-2-(4′-Benzyloxyphenyl)-2,3-dihydro-3-hydroxy-1,5-benzothiazepin-4-[5*H*]-one 3g. White solid, mp 145–146 °C; IR (KBr, cm^{-1}) *v*: 3400, 3250, 1680, 1240; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31 (b t, $J = 7.2$ Hz 1H, C_3-H), 4.88 (b d, $J = 7.2$ Hz, 1H, -OH), 4.92 (d, $J = 7.2$ Hz, 1H, C_2-H), 5.05 (s, 2H, -OCH_2 -OBz), 6.98–7.70 (m, 13H, Ar-H), 10.31 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 173.50, 167.50, 165.35, 145.30, 142.40, 138.70, 136.60, 136.20, 132.60, 132.40, 131.50, 129.90, 128.50, 126.20, 118.30, 70.40, 67.50, 58.40. Anal. calcd. for $C_{23}H_{19}NO_4S$: C, 68.11; H, 4.72; N, 3.45. Found: C, 68.45; H, 4.42; N, 3.60%.

(±)-*trans*-(2*S*,3*R*) Isomer 4g. White solid, mp 158–160 °C; IR (KBr, cm^{-1}) *v*: 3480, 3300, 1690, 1260; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (dd, $J = 10.2$ Hz and 8.3 Hz, 1H, C_3-H), 4.75 (d, $J = 10.2$ Hz, 1H, C_2-H), 5.05 (s, 2H, -OCH_2, OBz), 5.28 (d, $J = 8.3$ Hz, 1H, -OH), 6.90–7.80 (m, 13H, Ar-H), 10.21 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 173.60, 167.40, 165.40, 147.35, 142.40, 138.65, 136.50, 136.20, 132.60, 132.20, 131.60, 130.40, 129.80, 128.60, 126.25, 118.30, 70.40, 67.50, 58.50. Anal. calcd. for $C_{23}H_{19}NO_4S$: C, 68.11; H, 4.72; N, 3.45. Found: C, 68.35; H, 4.55; N, 3.58%.

(±)-*cis*-(2*S*,3*S*)-2-(4′-Benzyloxyphenyl)-7-chloro-2,3-dihydro-3-hydroxy-1,5-benzothiazepin-4-[5*H*]-one 3h. Yellowish solid, mp 172–174 °C; IR (KBr, cm^{-1}) *v*: 3420, 3260, 1685, 1250; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35 (b t, $J = 7.2$ Hz 1H, C_3-H), 4.92 (d, $J = 7.2$ Hz, 1H, C_2-H), 5.08 (s, 2H, -OCH_2, OBz), 5.12 (d, $J = 7.2$ Hz, 1H, -OH), 6.95–7.80 (m, 13H, Ar-H), 10.35 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 174.20, 167.80, 165.40, 148.30, 140.30, 137.40, 136.40, 132.80, 132.60, 130.60, 130.20, 129.80, 128.40, 126.30, 124.30, 118.40, 72.50, 68.40, 58.30. Anal. calcd. for $C_{23}H_{18}ClNO_4S$: C, 62.77; H, 4.12; N, 3.18. Found: C, 62.92; H, 3.90; N, 3.40%.

(±)-*trans*-(2*S*,3*R*) Isomer 4h. Yellowish solid, mp 186–188 °C; IR (KBr, cm^{-1}) *v*: 3500, 3320, 1690, 1240; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08 (d d, $J = 10.2$ Hz and 8.3 Hz, 1H, C_3-H), 4.70 (d, $J = 10.2$ Hz, 1H, C_2-H), 5.10 (s, 2H, -OCH_2 -OBz), 5.28 (d, $J = 8.2$ Hz, 1H, -OH), 6.90–7.85 (m, 13H, Ar-H), 10.31 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 174.40, 167.75, 165.50, 148.25, 140.40, 137.35, 136.40, 132.85, 132.55, 130.25, 129.70, 128.40, 126.25, 124.50, 118.40, 72.50, 68.40, 58.30. Anal. calcd. for $C_{23}H_{18}ClNO_4S$: C, 62.77; H, 4.12; N, 3.18. Found: C, 62.82; H, 3.95; N, 3.24%.

(±)-*cis*-(2*S*,3*S*)-2-(4′-Benzyloxyphenyl)-8-chloro-2,3-dihydro-3-hydroxy-1,5-benzothiazepin-4-[5*H*]-one 3i. Yellowish solid, mp 176–178 °C; IR (KBr, cm^{-1}) *v*: 3420, 3250, 1680, 1240; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.32 (b t, $J = 7.2$ Hz

1H, C_3-H), 4.90 (d, $J = 7.2$ Hz, 1H, C_2-H), 5.10 (s, 2H, -OCH_2 -OBz) 5.15 (d, $J = 7.2$ Hz, 1H, -OH) 6.92–7.85 (m, 13H, Ar-H), 10.31 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 174.20, 167.80, 165.40, 148.20, 140.30, 137.40, 136.30, 132.70, 132.40, 130.50, 130.20, 129.80, 128.40, 126.40, 124.60, 118.40, 72.60, 68.40, 58.30. Anal. calcd. for $C_{23}H_{18}ClNO_4S$: C, 62.77; H, 4.12; N, 3.18. Found: C, 62.90; H, 4.30; N, 3.05%.

(±)-*trans*-(2*S*,3*R*) Isomer 4i. Yellowish solid, mp 188–189 °C; IR (KBr, cm^{-1}) *v*: 3540, 3320, 1690, 1250; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (dd, $J = 10.2$ Hz and 8.3 Hz, 1H, C_3-H), 4.72 (d, $J = 10.2$ Hz, 1H, C_2-H), 5.12 (s, 2H, -OCH_2 -OBz), 5.32 (d, $J = 8.2$ Hz, 1H, -OH), 6.90–7.85 (m, 13H, Ar-H), 10.25 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 174.40, 167.90, 165.40, 148.25, 140.30, 137.35, 136.45, 132.60, 132.40, 130.45, 130.25, 129.80, 128.50, 126.40, 124.50, 118.50, 72.50, 68.45, 58.30. Anal. calcd. for $C_{23}H_{18}ClNO_4S$: C, 62.77; H, 4.12; N, 3.18. Found: C, 62.80; H, 4.23; N, 3.12%.

(±)-*cis*-(2*S*,3*S*)-2-(4′-Benzyloxyphenyl)-7-trifluoromethyl-2,3-dihydro-3-hydroxy-1,5-benzothiazepin-4-[5*H*]-one 3j. White solid, mp 195–196 °C; IR (KBr, cm^{-1}) *v*: 3450, 3280, 1690, 1260; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.35 (b t, $J = 7.2$ Hz 1H, C_3-H), 4.95 (d, $J = 7.2$ Hz, 1H, C_2-H), 5.10 (s, 2H, -OCH_2 -OBz), 5.20 (d, $J = 7.2$ Hz, 1H, -OH) 6.80–7.95 (m, 13H, Ar-H), 10.38 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 174.60, 168.20, 165.60, 148.20, 142.60, 138.60, 137.40, 136.70, 134.80, 132.90, 132.60, 131.60, 130.20, 129.65, 128.80, 126.70, 78.50, 72.50, 68.40, 58.30. Anal. calcd. for $C_{24}H_{18}F_3NO_4S$: C, 60.86; H, 3.83; N, 2.95. Found: C, 60.52; H, 3.60; N, 3.18%.

(±)-trans-(2*S*,3*R*) Isomer 4j. White solid, mp 202–204 °C; IR (KBr, cm^{-1}) *v*: 3510, 3350, 1695, 1280; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (dd, $J = 10.2$ Hz and 8.3 Hz, 1H, C_3-H), 4.75 (d, $J = 10.2$ Hz, 1H, C_2-H), 5.08 (s, 2H, -OCH_2 -OBz), 5.28 (d, $J = 8.2$ Hz, 1H, -OH), 6.90–7.98 (m, 13H, Ar-H), 10.31 (s, 1H, -NH); ^{13}C NMR ($CDCl_3$, 75.47 MHz) δ 174.75, 168.30, 165.55, 148.30, 142.65, 138.60, 137.40, 136.75, 134.70, 132.95, 132.25, 131.60, 130.25, 129.70, 128.90, 126.75, 78.50, 72.60, 68.50, 58.40. Anal. calcd. for $C_{24}H_{18}F_3NO_4S$: C, 60.86; H, 3.83; N, 2.95. Found: C, 60.60; H, 3.72; N, 3.15%.

ACKNOWLEDGMENTS

We thank the head of the Department of Chemistry, University of Rajasthan, Jaipur, for providing laboratory facilities. We are also grateful to Central Drug Research Institute (CDRI), Lucknow, for some analytical data. Financial assistance from the University Grants Commission, New Delhi, is thankfully acknowledged.

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