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A NEW SULFA-HETEROCYCLIC COMPOUNDS CONTAINING AZIRIDINE MOIETY, 3-BENZYL-2-THIA-1,3-DIAZABICYCLO[3.1.0]-HEXANE 2,2-DIOXIDE AND ITS REACTION WITH NUCLEOPHILES

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Dedicated to the memory of Pr. Chabbi Yacine (1955-2008)

Abstract – New sulfa-heterocyclic containing aziridine moiety derivatives such as 3-benzyl-2-thia-1,3-diazabicyclo[3.1.0]hexane 2,2-dioxide has been obtained starting from 2-benzyl-4-chloromethyl-1,2,5-thiadiazolidine 1,1-dioxide in alkaline conditions. The aziridine moiety was opened by various nucleophiles to give vicinal diamines which used as an intermediate in the preparation of other bicyclic compounds with orthogonal protections such as 2,5-dibenzyl-1,2,5-thiadiazolo[2,3-*a*]pyrazine 1,1-dioxide in good yield.

INTRODUCTION

Heterocyclic compounds containing aziridine moiety constitute an important class of compounds, which have found use in organic and medicinal chemistry. The presence of aziridine motif into heterocyclic structure can leads to interesting new chemical and/or pharmacological potentialities. Some of these compounds showed immunomodulatory proprieties. For example, Imexon **I**[1] is active against various transplanted syngeneic tumors in rodents[2] and transplanted human tumors.[3]

Dauban *et al*[4] described a bicyclic fused aziridines **II** starting from olefinic sulfamates undergo copper-catalyzed aziridination in the presence of iodosylbenzene. The latter were opened by various nucleophiles to give the corresponding substituted cyclic sulfamates.

The versatility of aziridines as precursors to amine derivatives drives the development of preparative methods for this unique class of heterocycles.[5] They are useful and versatile synthetic intermediates, as relief ring-strain provides a driving force for efficient ring opening or ring expansion reactions.[6] The importance of aziridines[7] is also well recognized in asymmetric synthesis, where the need for chiral

auxiliaries and ligands continuously increasing. In our previous work,[8] we have reported the synthesis and the reactivity of cyclosulfamides. In this report, we extended our studies in the reactivity of this heterocycles by intramolecular aziridination. We present a new and easy method to access at the new aziridine fused with cyclosulfamide with benzyl protection. Aziridines fused with cyclosulfamide such as 3-benzyl-2-thia-1,3-diazabicyclo[3.1.0]hexane 2,2-dioxide **III** constitutes an original intermediate in synthesis of heterocycles. It can be considered as a sulfonyl equivalent of aziridine fused with cyclourea **I** and an analogue of cyclosulfamate **II Figure 1**.

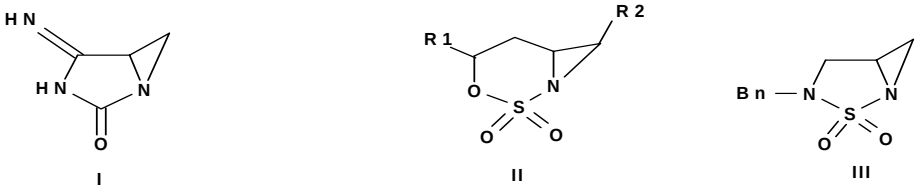


Figure 1

We describe also the efficient and high yielding ring opening of **III** with nucleophiles such as ethoxide and amines. With nitrogen nucleophiles such as primary amine, aziridines yield vicinal secondary diamines which react with 1,2-dibromoalkane to give 2,5-dibenzylhexahydro-2*H*-[1,2,5]thiadiazolo [2,3-*a*]pyrazine 1,1-dioxide **7**. The structure of cyclosulfamide **7** correspond to an analogue of 2,7-dialkylhexahydroimidazo[1,5-*a*]pyrazin-3-one **IV** known for anti-inflammatory, coronary dilator and C.N.S depressant activities[9] and an 2,7-dibenzylhexahydropyrazino[1.2-c]pyrimidin-6-one **V** tested for antifilarial activity.[10]

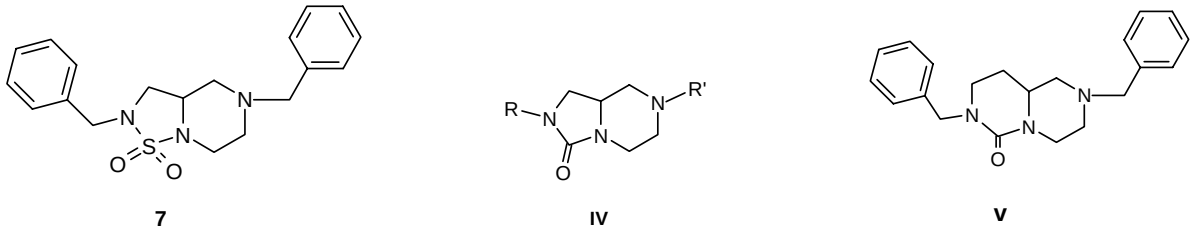
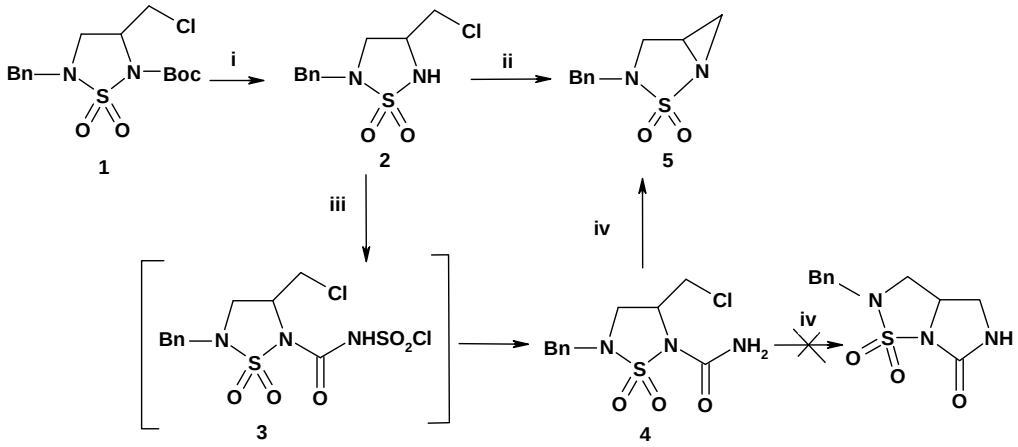


Figure 2

RESULTS AND DISCUSSION

The starting racemic N^2-Boc-N^5-benzyl-3-chloromethyl-1,2,5-thiadiazolidine **1** has been previously described by our group.[8a-b] As outlined in Scheme 1, the heterocycles **2**, **3**, **4** and **5** were synthesized after differents steps. Starting from **1**, regioselective cleavage of the *tertio*-butyloxycarbonyl (Boc) protection under trifluoroacetic acid gives compound **2**. The deprotected heterocycle **2** was obtained in 95% yield and found to be able to be stored for several weeks at room temperature without notable decomposition. Compound **2** was then engaged in a direct intramolecular aziridination in alkaline medium (triethylamine, K_2CO_3, Cs_2CO_3) and afforded bicyclic aziridine **5** in quantitative yield. No other products could be

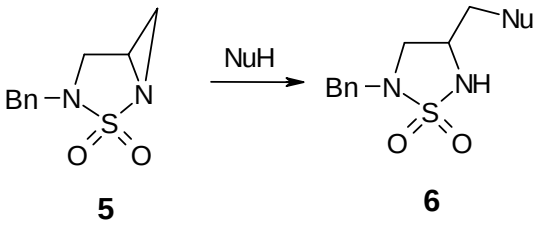
detected by TLC analysis of the crude reaction mixture. In perspective to access fused-bicyclic cyclosulfamide and cyclourea *via* intermediate **3**, the addition reaction of **2** with chlorosulfonyl isocyanate (CSI) was carried out to give compound **4**. The intermediate, chlorosulfonyl derivative **3**, could not be isolated because of its instability in standard conditions. Treatment of **4** with triethylamine (TEA) in dichloromethane or K_2CO_3 in acetonitrile afforded aziridine **5**, comparatively with treatment of **2** in the same conditions (Scheme 1). The one-pot procedure appeared to be efficient than two-step procedure involving isolation of the intermediate **4**. ^{1}H NMR spectral properties were in accordance with that of aziridine structure. The two protons of the aziridine ring methylene group were non equivalent. The small couplings (~2.8 Hz) have been observed for geminal protons and the smaller coupling to the methylene group.



Scheme 1. *Reagents and conditions*: (i) TFA, CH_2Cl_2, 0 °C and rt, (95%); (ii) Et_3N, CH_2Cl_2, or K_2CO_3, MeCN, rt, (95%) (iii) CSI, CH_2Cl_2, 0 °C and rt, (75%); (iv) Et_3N, CH_2Cl_2, rt, (85%).

We next focalised our attention to the study of the electrophilic reactivity of these new types of heterocyclic structures particularly with respect to any possible regioselectivity of ring opening. Nucleophilic attack on **5** would be expected to occur at the methylene group of the aziridine ring to give 5-membered ring **6**. Reaction of **5** with sodium ethoxide in absolute ethanol gave only the contracted product **6a** (**Scheme 2**) which was proven to have five-membred system by NMR proton analysis. If the reaction is effected with amines in aprotic medium, the nucleophilic opening of the aziridine ring leading to the formation of vicinal diamines **6b-6d** derivatives in good yield.

The choice of benzylamine as the amine nucleophile has special significance because the products are vicinal diamines which have varied applications in organic synthesis and generated the same benzyl protection. A nucleophilic attack on the methylene carbon of aziridine led to the formation of 5-membered; the nucleophilic attack of the aziridine carbon adjacent to the cyclosulfamide moiety would have resulted in the formation of 6-membered ring which was not detected in crude mixtures by TLC and ^{1}HNMR analysis.



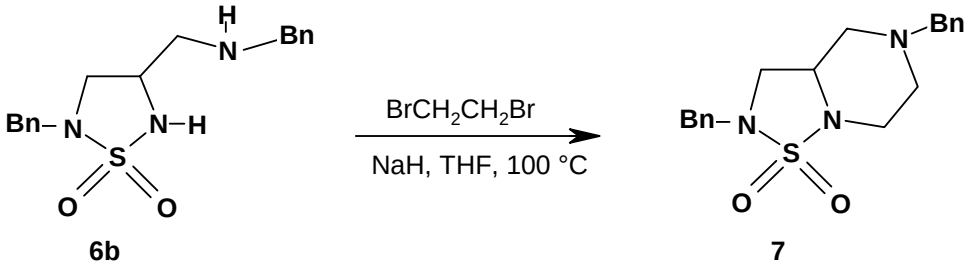
5 **6**

Entry	Nu	Regents and Conditions	Yield %
6a	EtO	EtOH/EtONa, reflux	90
6b	BnNH	$BnNH_2$, Et_3N, THF, reflux	85
6c		 , MeCN, reflux	55
6d		 , Et_3N, THF, reflux	58

Scheme 2

The regioselective aziridine ring-opening reaction then afforded the opportunity to introduce a second nucleophile which can be reacted with different nucleophiles by condensation and substitution reactions. Also, in these compounds, the sulfonyl group SO_2 increases the acidity of the adjacent NH and allows an expedient intermolecular cyclization.[10]

On the other hand, the derivative **6b** was reacted with a 1,2-dibromoethane in alkaline conditions and in aprotic medium occur an orthogonally protected benzylpiperazine **7** fused with cyclic sulfamide as solid in 69% yield (Scheme 3).



6b **7**

Scheme 3

EXPERIMENTAL

All commercial chemicals and solvents were used without further purification. All reactions were carried out under inert argon atmosphere. Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. Microanalysis were performed in analyse center of Vernaison (Lyon France). ^{1}H-and ^{13}C NMR spectra were recorded in a 250 MHz Brücker spectrometer. Chemical shifts are reported in δ units (ppm). All coupling constants *J* are reported in Hertz. Multiplicity is indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and combination of theses signals. Electron ionisation mass spectra (30 eV) were recorded in positive or negative mode on a Water MicroMass ZQ. High-resolution mass spectra were measured on a Jeol SX102 mass spectrometer and recorded in FAB positive mode. All reactions were monitored by TLC on silica Merck 60 F_{254} precoated aluminium plates and were developed by spraying with ninhydrin solution. Columns chromatographies were performed on Merck silica gel (230-400 mesh).

The synthesis of the racemic 2-Boc-5-Bn-3-chloromethyl-1,2,5-thiadiazolidine 1,1-dioxyde **1** has been previously reported.[8a]

2-Benzyl-4-(chloromethyl)-1,2,5-thiadiazolidine 1,1-dioxide 2. To a stirred solution of racemic **1** (1.09 g, 3 mmol) in dry CH_2Cl_2 (3.6 mL) was added dropwise to l 3.6 mL of TFA/CH_2Cl_2 (50:50) solution in ice bath. The mixture was stirred until TLC analysis indicated the disappearance of the starting material. The solvent was removed in vacuum and then by coevaporation four times with Et_2O. The crude residue was purified on silica gel (CH_2Cl_2). Compound **2** was obtained as a white powder in 95% yield after recrystallization from hexanes/AcOEt (9:1)

R_f = 0.30 (CH_2Cl_2), (mp 64 °C), IR (KBr, ν cm^{-1}): 3263 (NH), 1319 and 1172 (SO_2); ^{1}H NMR ($CDCl_3$): δ 3.18 (m, 1H, CH), 3.40-3.70 (m, 3H, CH_2 + CH), 3.90 (m, 1H, HC_{asy}), 4.18 and 4.30 (AB, 2H, ^2J = 13.70 Hz, CH_2Ph), 4.90 (br s, 1H, NH), 7.35 (m, 5H, H-Ar); ^{13}C NMR ($CDCl_3$) δ 44.70, 50.62, 56.32, 59.90, 125.32, 127.54, 128.45, 140.15; MS ESI$^+$ 30eV *m/z*: 283 ([M+Na]$^+$, 100%), 285 ([M+Na]$^+$+2 40%). M = 260/262.

Anal. Calcd for $C_{10}H_{13}N_2O_2SCl$: C, 46.06; H, 5.03; N, 10.74. Found: C, 46.12; H, 5.01; N, 10.71.

5-Benzyl-3-(chloromethyl)-1,2,5-thiadiazolidine-2-carboxamide 1,1-dioxide 4.

To a stirred solution of chlorosulfonyl isoyanate (0.84 mL, 0.9 mmol) in dry CH_2Cl_2 at 0 °C under argon, was added (0.25 g, 0.9 mmol) a solution of **2** in the same solvent. The mixture was stirred at rt for 2 h. The reaction mixture was diluted with 50 mL of CH_2Cl_2, washed with 0.1 N HCl and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was purified on silica gel (CH_2Cl_2) to afford **4** as a white solid in 75% yield; R_f = 0.25 (CH_2Cl_2), (mp 106-107 °C), IR (KBr, ν cm^{-1}): 3363.6 (NH_2), 1681 (CO), 1319 and 1164 (SO_2); ^{1}H NMR ($CDCl_3$): δ 3.30 (dd, 1H, *J* = 4.10 and 6.50 Hz, CH), 3.45 (dd, 1H, *J* = 3.10 and 7.40 Hz, CH), 3.60 (m, 1H, CH), 3.90 (dd, 1H, *J* = 3.50 and 7.20 Hz, CH), 4.15 and 4.30 (AB, 2H, ^2J = 13.80 Hz, CH_2Ph), 4.45 (m, 1H, HC_{asy}), 5.6 (br s, 2H, NH_2), 7.40 (m, 5H, Harom); ^{13}C NMR ($CDCl_3$) δ 44.80, 50.70, 56.20, 59.90, 125. 45, 127.50, 128.72, 140.15, 157.85; MS ESI$^+$ 30eV *m/z*: 326.09 ([M+Na]$^+$, 100%), 328 ([M+Na]$^+$+2, 40%), 285 (([M+Na]$^+$ +2)–NHCO, 10%), 283 ([M+Na]$^+$–NHCO, 23%). M = 303/305.

Anal. Calcd for $C_{11}H_{14}N_3O_3SCl$: C, 43.49; H, 4.65; N, 13.83. Found: C, 43.17; H, 4.70; N, 13.87.

3-Benzyl-2-thia-1,3-diazabicyclo[3.1.0]hexane 2,2-dioxide 5. A solution of **2** (0.54 g, 2 mmol) and K_2CO_3 (0.55 g, 4 mmol) in MeCN (20 mL) was stirred at rt for 2 h. The reaction was monitored with TLC (UV and ninhydrine). The mixture was filtered and concentrated in vacuo. Aziridine **5** was obtained in 98% yield as white solid without purification; R_f = 0.66 (CH_2Cl_2), (mp 98 °C), IR (KBr, ν cm^{-1}): 1326

and 1168 (SO_2); ^{1}H NMR ($CDCl_3$): δ 2.40 (dd, 1H, *J* = 1.40 and 3.60 Hz, CH), 2.65 (dd, 1H, *J* = 1.30 and 2.70 Hz, CH), 3.12 (m, 1H, HC_{asy}), 3.31 (dd, 1H, *J* = 3.90 and 6.10 Hz, CH), 3.44 (dd, 1H, *J* = 10 and 3.90 Hz, CH), 3.90 and 4.48 (AB, 2H, ^2J = 13.80 Hz, CH_2Ph), 7.40 (m, 5H, Harom); ^{13}C NMR ($CDCl_3$) δ 40.60, 47.40, 51.30, 62.80, 125.45, 126.80, 128.70, 141.56, 157.8; MS ESI$^+$ 30eV *m/z*: 247 $[M+Na]^+$, 100%). M = 224.

Anal. Calcd for $C_{10}H_{12}N_2O_2S$: C, 53.55; H, 5.39; N, 12.49. Found: C, 53.62; H, 5.34; N, 12.47.

Nucleophylic opening of aziridine

2-Benzyl-4-(ethoxymethyl)-1,2,5-thiadiazolidine 1,1-dioxide 6a.

Sodium (0.06 g, 2 mmol) was put into 10 mL of absolute EtOH and the solution was stirred for 30 min to build *in situ* the sodium ethoxide. After this step, (0.1 g, 0.4 mmol) of **5** was added into solution as a powder and the reaction mixture being refluxed for 3 h. The solvent was removed and the residue diluted with 100 mL of CH_2Cl_2, acidified with 0.1 N HCl and washed with water. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The crude residue was purified on silica gel column ($CHCl_3$) to afford the product **6a** as oil.

Yield = 90%; R_f = 0.34 (CH_2Cl_2); oil; ^{1}H NMR ($CDCl_3$): δ 1.23 (t, 3H, *J* = 6.90 Hz, CH_3), 3.30 (m, 5H , $2CH_2$+HC_{asy}), 3.50 (m, 1H, CH), 3.73 (m, 1H, CH), 4.10 and 4.62 (AB, 2H, ^2J = 13.90Hz; CH_2Ph), 7.25 (m, 5H, Harom) ; ^{13}C NMR ($CDCl_3$) δ 18.30, 51.12, 52.10, 58.20, 64.20, 65.10, 125.20, 127.30, 128.50, 141.60; MS ESI$^+$ 30eV *m/z*: 538.92 ($[2M-H]^-$, 10%), 563.05 ([2M+Na], 25%), 293,15 ($[M+Na]^+$, 100%), 271 ($[M+H]^+$, 60%), 268,96 ($[M-H]^-$, 10%). M = 270.

Anal. Calcd for $C_{12}H_{18}N_2O_3S$: C, 53.31; H, 6.71; N, 10.36. Found: C, 53.29; H, 6.74; N, 10.38.

***N*-Benzyl-*N*-[(5-benzyl-1,1-dioxido-1,2,5-thiadiazolidin-3-yl)methyl]amine 6b.**

To a solution of **5** (0.1 g, 0.40 mmol) and benzylamine in anhydrous THF (10 mL) was added dropwise triethylamine (0.06 mL, 0.44 mmol) in the same solvent and the mixture was refluxed for 3 h. The reaction was monitored by TLC (ninhydrine and UV). The solvent was removed and the residue was diluted with 100 mL of CH_2Cl_2 acidified with 1N HCl and washed with water. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure on a rotary evaporator. The residue was purified by chromatography on silica gel (CH_2Cl_2) to give **6b** as white solid in 85% yield; R_f = 0.43, (CH_2Cl_2/MeOH, 98:2), (mp 128-129 °C); ^{1}H NMR ($CDCl_3$): δ 2.8 (br s, 1H, NH), 3.10 (dm, 1H, *J* = 8.40 Hz, CH), 3.40 (m, 3H, 2CH+C*H), 3.62 (m, 3H, CH+CH_2Ph); 3.80 and 4.87 (AB, 2H, ^2J = 13.7 Hz, CH_2Ph), 4.80 (br s, 1H, NH), 7.45 (m, 10H, Harom); ^{13}C NMR ($CDCl_3$) δ 48.42, 49.51, 50.25, 53.11, 61.88, 125.42, 126.12, 126.43, 128.23, 128.68, 128.85, 139.74, 142.49. MS ESI$^+$ 30eV *m/z*: 354.04 ($[M+Na]^+$, 30%), 331.96 ($[M+H]^+$, 100%), 330.34 ($[M-H]^-$, 10%). M = 331.

Anal. Calcd for $C_{17}H_{21}N_3O_2S$:C, 61.61; H, 6.39; N, 12.68. Found: C, 61.67; H, 6.37; N, 12.63.

4-[(5-Benzyl-1,1-dioxido-1,2,5-thiadiazolidin-3-yl)methyl]morpholine 6c.

To a solution of **5** (0.03 g, 0.10 mmol) MeCN (10 mL) and morpholine (8.70 g, 100 mmol) was added dropwise in the same solvent and the mixture was refluxed for 3 h. The reaction was monitored by TLC. The solvent was removed and the residue was diluted with 100 mL of CH_2Cl_2 acidified with 1N HCl and washed with water. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure on a rotary evaporator. The residue was purified by chromatography on silica gel ($CHCl_3$) to give **6c** as an oil in 55% yield; R_f = 0.37 (CH_2Cl_2/MeOH, 98:2); ^{1}H NMR ($CDCl_3$): δ 2.30 (m, 2H, CH_2), 2.62 (m, 4H, $2CH_2$), 3.20 (m, 2H, CH_2), 3.70 (m, 6H, $2CH_2O$+HC_{asy}+CHPh), 4.55 (AB, 1H, ^{2}J=13.20Hz, CHPh), 7.37 (m, 5H, Harom); ^{13}C NMR ($CDCl_3$) δ 51.28, 59.00, 59.30, 59.70, 60.00, 62.40, 125.20, 127.30, 128.50, 141.45. MS ESI$^+$ 30 eV *m/z*: 334.10 ([M+Na], 40%), 311.90 ([M+H]$^+$, 100%). M = 311.
Anal. Calcd for $C_{14}H_{21}N_3O_3S$:C, 54.00; H, 6.80; N, 13.50. Found: C, 54.06; H, 6.77; N, 13.53.

4-[(5-Benzyl-1,1-dioxido-1,2,5-thiadiazolidine-3-yl]piperidine 6d.

To a solution of **5** (0.11 g, 0.49 mmol) and piperidine (0.045 g, 0.52 mmol) in anhydrous THF (10 mL) was added drop wise triethylamine (0.07 mL, 0.53 mmol) in the same solvent and the mixture was refluxed for 3 h. The reaction was monitored by TLC (ninydrine and UV). The solvent was removed and the residue was diluted with 100 mL of CH_2Cl_2 acidified with 1N HCl and washed with water. The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure on a rotary evaporator. The residue was purified by chromatography on silica gel ($CHCl_3$) to give **6d** as pal white solid in 70% yield, R_f = 0.30 (CH_2Cl_2/MeOH:98/2), (mp 71-72 °C) ; ^{1}H NMR ($CDCl_3$): δ 1.50 (m, 6H. 3 CH_2), 2.40 (m, 3H, CH_2+CH), 2.55 (m, 3H, CH_2+CH), 2.90 and 3.25 (ABX, 2H, *J* = 2.60, 3.10 and 6.90 Hz, CH_2), 3.76 (m,1H, HC_{asy}), 3.90 and 4.30 (AB, 2H, ^2J =13.40, CH_2Ph), 7.40 (m, 5H, Harom); MS ESI$^+$ 30eV *m/z* : 310 ([M+H]$^+$, 100%. M = 309.
Anal. Calcd for $C_{15}H_{23}N_3O_2S$: C, 58.22; H, 7.49; N, 13.58. Found: C, 58.18; H, 7.41; N, 13.53.

2,5-Dibenzylhexahydro-2*H*-[1,2,5]thiadiazolo[2,3-*a*]pyrazine 1,1-dioxide 7.

6b (0.04 g, 0.12 mmol) and 1,2-dibromoethane (0.24 mmol, 0.045 g) of in dry THF (5 mL) were added slowly to a stirred solution of NaH (0.0086 g, 0.36 mmol) in the same solvent (5 mL) at 0 °C. After complete addition, the reaction mixture was heated at 80 °C for 2 h. The reaction was monitored by TLC (ninhydrine and UV). Upon cooling to rt, the reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel ($CHCl_3$) to give **7** as white solid in 69 % yield; R_f = 0.38 (CH_2Cl_2); (mp 146-147 °C); ^{1}H NMR ($CDCl_3$): δ 2.50 (m, 1H, CH), 2.60

(t, 1H, *J* = 2.20 Hz, CH), 2.92 (dd, 1H, *J* = 2.20 and 10.30 Hz, CH), 3.30 (s, 2H, CH_2Ph), 3.31-3.57 (m, 4H, 2CH+CH_2), 3.60 (AB, 1H, ^2J = 13.30 Hz, CHPh), 3.90 (dm, 1H, *J* = 11.90 Hz, CH), 4.15 (dt, 1H, *J* = 2.10 and 9.60 Hz, CH), 4.88 (AB, 1H, ^2J = 13.30 Hz, CHPh), 7-7.30 (m, 10H, Harom); ^{13}C NMR ($CDCl_3$): δ 41.98, 42.82, 50.02, 53.01, 56.38, 66.78, 125.42, 127.39, 128.85, 128.94, 128.56, 139.60, 142.23. MS ESI$^+$ 30eV *m/z*: 380.04 ($[M+Na]^+$; 10%); 358.15 ($[M+H]^+$,100%). M = 357.

Anal. Calcd for $C_{19}H_{23}N_3O_2S$: C, 63.86; H, 6.44; N, 11.76. Found: C, 63.88; H, 6.41; N, 11.80.

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