Diastereoselective Synthesis of Novel Pyrrolidine or Pyrrolizine-Fused Benzo-δ-sultams via 1,3-Dipolar Cycloadditions

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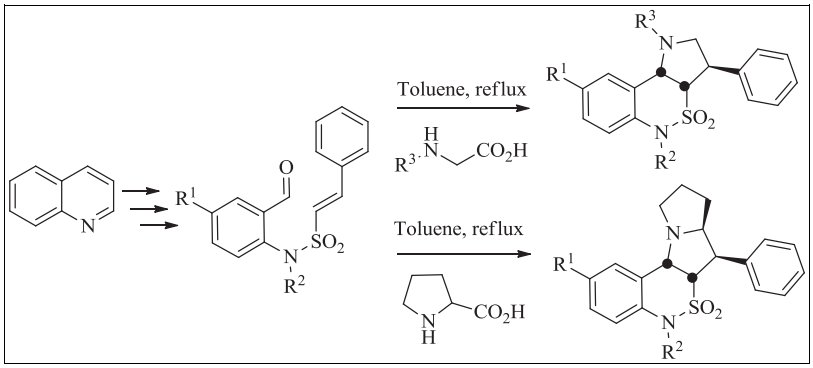

The synthesis of novel pyrrolidine or pyrrolizine-fused benzosultams is described. A number of (*E*)-*N*-(2-formylphenyl)-*N*-alkyl-2-phenylethenesulfonamides derivatives were synthesized and subjected to intramolecular [3 + 2] cycloaddition with azomethine ylides derived *in situ* from the reaction with sarcosine, phenylglycine, and *L*-proline.

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INTRODUCTION

Cycloaddition is one of the most efficient and reliable synthetic transformations for the rapid, predictable, and reliable assembly of molecular complexity. Among these processes, for example, 1,3-dipolar cycloaddition of azomethine ylides [1] has been developed for construction of pyrrolidines [2] or pyrrolizidines [3]. These scaffolds are specifically important for the creation of diverse chemical libraries of drug-like molecules for biological screening [4]. Construction of five-membered pyrrolidines and pyrrolizine rings via simple synthetic methods affords an important class of substances with highly pronounced biological activities [5].

Sulfonamides have a rich chemical and biological history and are an important class of compounds in drug discovery due to their extensive chemical and biological activities [6]. Significant interest has been directed toward cyclic sulfonamides, also known as sultams. Although not found in nature, these compounds demonstrate a wide spectrum of activities [7]. Figure 1 depicts some sultam derivatives such as COX-2 inhibitor ampiroxicam [8], benzodithiazine dioxides (anti-HIV-1) [9], the antiepileptic agent sulthiame [10], carbonic anhydrase inhibitor [11], and MMP-2 inhibitor (Fig. 1) [12]. As chemically important materials, sultams have been utilized as efficient chiral auxiliaries and reagents [13].

Sultams have traditionally been synthesized via cyclization protocols such as the Pictet–Spengler [6a], and Friedel–Crafts [14], dianion alkylation [15], cyclization of aminosulfonyl chlorides [16], [3 + 2] cycloadditions [17], Diels–Alder [18], Heck [19], and other reactions [20]. Recently, a number of transition metal catalyzed approaches to sultams have been reported, including the use of Pd [21], Au [22], Cu [23], and Rh [24].

Synthesis of heterocyclic compounds containing the benzo-δ-sultam and five-membered pyrrolidine or pyrrolizine motifs in a molecule seemed to be interesting due to their individual widespread known biological activities and uses. As a part of our own interest in cycloaddition reactions [25], herein, we describe the synthesis of novel pyrrolidine or pyrrolizidine-fused benzo-δ-sultams. A number of (*E*)-*N*-(2-formylphenyl)-*N*-methyl-2-phenylethenesulfonamides were synthesized and subjected to intramolecular [3 + 2] cycloaddition with azomethine ylides derived *in situ* from the reaction with sarcosine or *L*-proline. To the best of our knowledge, no report on similar systems where the dipolarophile is tethered to the dipole moiety by a sulfonamide linkage is present in literature.

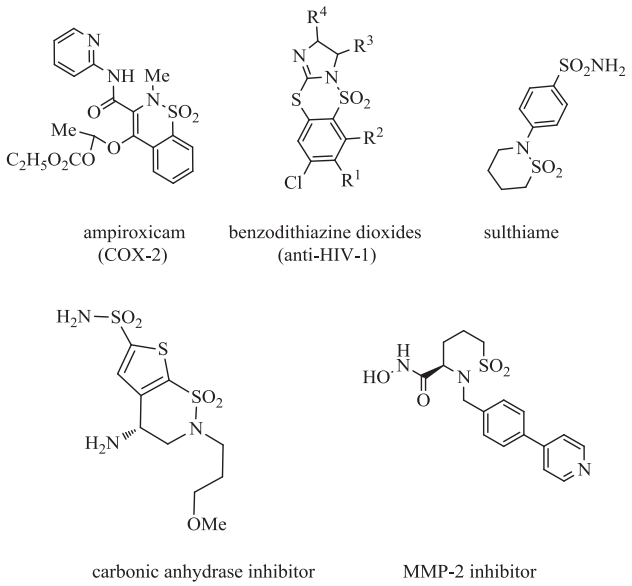


Figure 1. Biologically active six-membered sultams.

RESULTS AND DISCUSSION

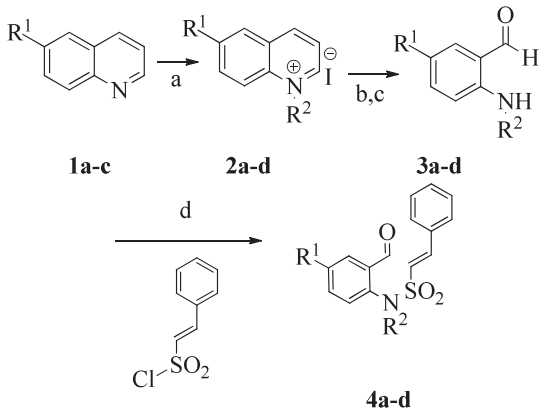
The (*E*)-2-phenylethenesulfonyl chloride was prepared according to the previously reported procedure [26]. *N*-Alkyl-2-aminobenzaldehydes **3a–d** were prepared using a reported method starting from quinolines **1a–c** in three steps [27]. Subsequent treatment of (*E*)-2-phenylethenesulfonyl chloride with **3a–d** in the presence of pyridine in CH_2Cl_2 for 48 h afforded **4a–d** in 48% to 61% (Table 1). The structures of **4a–d** were confirmed from analytical data. For example, the presence of two doublet at δ 6.73 and 7.40 with $J = 15.4$ Hz for SO_2CHC and PhCHC along with a singlet at δ 10.49 in the ^{1}H NMR spectrum of **4a** is consistent with the (*E*)-configuration of the olefin protons and the presence of an aldehyde group, respectively.

Sulfonamides **4a–d** were then treated with sarcosine or phenylglycine in boiling toluene (Scheme 1). After completion of the reactions (12 h), pyrollidines **5a–g** were obtained by filtration and recrystallization from EtOH (Table 2). All analytical data including ^{1}H, ^{13}C NMR, and MS were consistent with the proposed structures. For example, the ^{1}H NMR spectrum of pyrrolidine **5a** exhibited characteristic signals at δ 2.37 (s, 3H, MeN), 3.41 (s, 3H, $MeNSO_2$), 3.71 (d, 1H, $J = 8.8$ Hz, ArCHN), and 4.13–4.15 (m, 2H, $CHSO_2$, CHPh).

In the next step, **4a–c** were reacted with *L*-proline in boiling toluene over 12 h. Pyrrolizines **5h–j** were obtained when the crude products were subjected to preparative thin-layer chromatography on silica gel (Table 3). All analytical data including ^{1}H, ^{13}C NMR, and MS were consistent with the proposed structures. For example, the ^{1}H NMR spectrum of pyrrolizine **5i** exhibited signals at δ δ 2.41 (s, 3H, MePh), 3.31 (s, 3H, MeN), 3.94 (1H, dd, $J = 10.8$, 8.5 Hz, CHPh), 4.50 (dd, $J = 10.8$, 8.4 Hz, 1H, $CHSO_2$), and 4.56 (d, $J = 8.4$ Hz, 1H, PhCHN).

Table 1

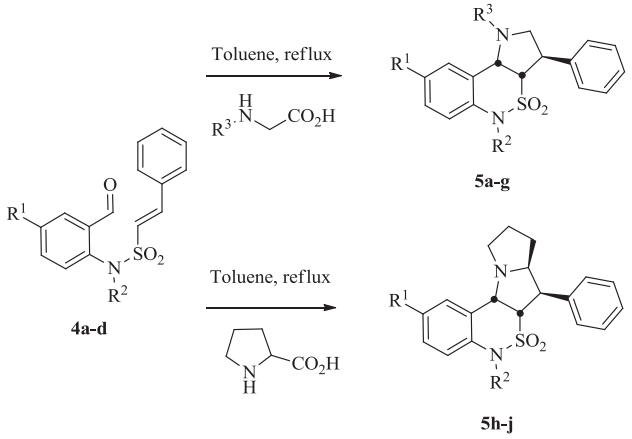
Results obtained for the synthesis of **4a–c**.



R^1	R2	Product (%)
-H	-Me	4a (48)
4-Me	-Me	4b (50)
4-OMe	-Me	4c (55)
-H	-Et	4d (55)

Reagents and conditions: (a) MeI or EtI, 1,4-dioxane, reflux, 1 h; (b) KOH, H_2O/CH_2Cl_2 (1:1); (c) H_2O_2 (35%), 48 h; (d) pyridine, dry CH_2Cl_2, 48 h.

Scheme 1. Synthesis of pyrrolidine and pyrrolizidine-fused benzosultones.



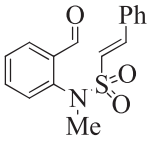
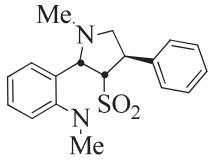
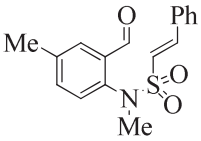
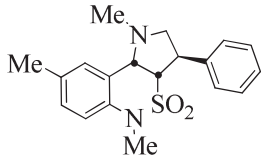
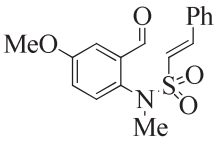
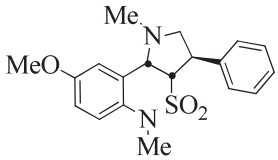
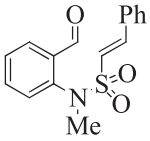
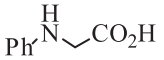
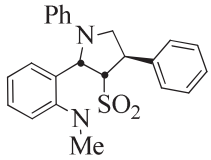
Unambiguous evidence for the proposed structure of **5i** was finally obtained by single-crystal X-ray-diffraction analysis (Fig. 2) [28].

In contrast to pyrrolidines **5a–c** and **5f**, which were formed in good yields, **5d**, **5e**, and **5g** were obtained in rather lower yields. Although obtaining these derivatives in lower yields were not anticipated [29], such observation is in accord with the lesser activity of phenylglycine in comparison with that of sarcosine.

The dipolar cycloaddition of an azomethine ylide generated from sarcozine or *L*-proline and an aldehyde with a dipolarophile could lead to a mixture of stereoisomers. Because the *trans* stereochemistry of the alkene dipolarophile has been maintained in the pyrrolidine and pyrrolizidine rings (Scheme 1), the cycloadditions have proceeded in a concerted manner with both carbon–carbon s-bonds being

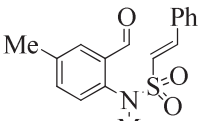
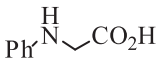
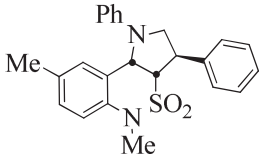
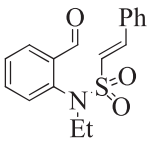
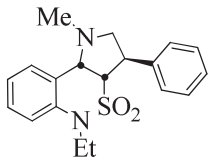
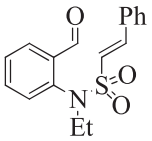
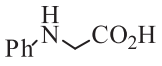
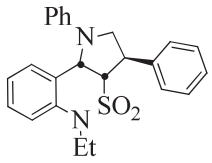
Table 2

Results obtained for the formation of pyrollidines **5a–h**.

Entry	Sulfonamide	Amino acid	Product (yield, %)	Product structure
1	 **4a**		**5a** (80)	
2	 **4b**		**5b** (69)	
3	 **4c**		**5c** (75)	
4	 **4a**		**5d** (51)	

(*Continued*)

Table 2 *(Continued)*

Entry	Sulfonamide	Amino acid	Product (yield, %)	Product structure
5	 **4b**		**5e** (56)	
6	 **4d**		**5f** (61)	
7	 **4d**		**5g** (49)	

formed at the same time, although not necessarily to the same extent. On the other hand, the stereochemistry of the resultant pyrrolidines **5a–g** and pyrrolizidines **5h–j** at the annelation bonds emerges from the geometry of the azomethine ylides. Hence, either the *E*- or Z- and S- or W- azomethine ylides [30] could have been implicated in the formation of **5a–g** and **5h–j**, respectively (Scheme 2). It seems justified that the *cis–trans* and *trans–trans* annelated products are expected to be formed via endo-*E*-syn transition state **I** and **I** or exo-*E*-anti transition state **II** and **II** (Scheme 2), respectively, if aromatic α,β-unsaturated aldehydes are used in the cycloaddition step [31]. The endo-*E*-syn transition state leading to the *cis–trans* annulated cycloadducts must have been more favorable than the exo-*E*-anti transition state due to an sp^2-geminal effect based on the phenomenon of 1,3-allylic strain [32].

In conclusion, novel pyrrolidine and pyrrolizidine-fused benzosultams were synthesized via condensation of (*E*)-2-phenylethenesulfonyl chloride with 2-(methylamino) benzaldehyde derivatives followed by intramolecular [3 + 2] cycloaddition of the azomethine ylides derived *in situ* from the reaction with sarcosine, phenylglycine, or *L*-proline. These new structures broaden the benzosultam scaffolds that are accessible through intramolecular cycloaddition, and many of them may represent interesting pharmacophores. An important aspect of the aforementioned reported syntheses is that the dipolarophile is tethered to the dipole moiety by a sulfonamide linkage.

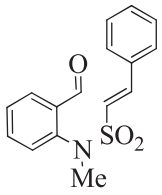
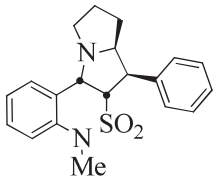
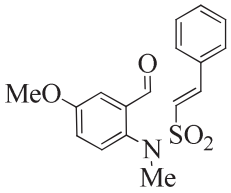
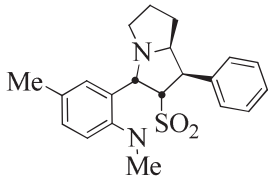
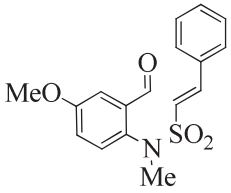
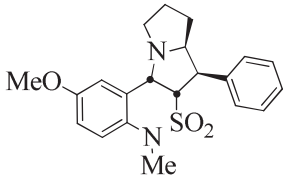
EXPERIMENTAL

All commercially available chemicals and reagents were purchased from Merck Chemical Company and used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Bomem B100 series spectrophotometer, in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-500-AVANCE spectrometer at 500 (^1H) and 125 MHz (^{13}C) using $CDCl_3$ and D_2O as solvents and with the residual solvent signal as internal reference ($CDCl_3$, 7.24 and 77.0 ppm), respectively. Mass spectra of the products were obtained with an HP (Agilent technologies) 5937 Mass Selective Detector. analyses were carried out by a CHN-Rapid Heraeus elemental analyzer (Wellesley, MA).

General procedure for the preparation of 4a–d. To a stirred solution containing 5-substituted *N*-alkylaminbenzaldehyde **3a–c** (10 mmol) and pyridine (15 mmol), dry CH_2Cl_2 (15 mL) was added dropwise to a solution of (*E*)-2-phenylethenesulfonyl chloride (12 mmol) in dry CH_2Cl_2 (15 mL). The mixture was stirred at 25°C for 48 h. The organic solution was then washed with water (30 mL) and saturated sodium sulfite solution (30 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude residue was purified by column

Table 3

Results obtained for the formation of pyrrolizines **5h–j**.

Entry	Sulfonamide	Product (yield, %)	Product structure
1	 **4a**	**5h** (59)	
2		**5i** (60)	
3		**5j** (60)	

chromatography on silica gel (230–400 mesh; Merck), using hexane–EtOAc (5:1, 3:1, and 1:1) as eluent to give the sultam derivatives **4a–d**.

***(E)*-*N*-(2-Formylphenyl)-*N*-methyl-2-phenylethenesulfonamide (4a)**. Yellow solid; yield: 48%; mp 120–122°C; IR (KBr) 2920 (CHO), 2840 (CHO), 1680 (CO), 1330 (NSO_2), 1140 (NSO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.55 (s, 3H, NMe), 6.73 (1H, d, *J* 15.4 Hz, SO_2CH), 7.31 (1H, d, *J* 8.1 Hz, Ar), 7.40 (1H, d, *J* 15.4 Hz, PhC*H*), 7.43–7.49 (7H, m, Ar), 7.51 (1H, d, *J* 7.5 Hz, Ar), 10.49 (1H, s, C*H*O); ^{13}C NMR (125 MHz, $CDCl_3$): δ 38.8, 126.7, 127.1, 128.4, 128.5, 128.8, 129.2, 130.2, 130.8, 131.3, 134.4, 134.8, 144.5 (C-Ar), 189.9 (CO); ms: *m/z* (%) 301 (8) [M^+], 265 (51), 167 (68), 148 (100), 91(72). *Anal*. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.63; H, 5.01; N, 4.66.

***(E)*-*N*-(2-Formyl-4-methylphenyl)-*N*-methyl-2-phenylethenesulfonamide (4b)**. Gray solid; yield: 50%, mp 125–126°C; 2845 (CHO), 2742 (CHO), 1689 (CO), 1336 (NSO_2), 1140 (NSO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.45 (3H, s, Me), 3.36 (3H, s, NMe), 6.77 (1H, d, *J* 15.5 Hz, SO_2CH), 7.24 (1H, d, *J* 8.1 Hz, Ar), 7.43–7.49 (5H, m, Ar), 7.51–7.53 (2H, m, Ar), 7.84 (1H, d, *J* 1.8 Hz, Ar), 10.48 (1H, s, C*H*O); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.4, 39.3, 121.2, 127.1, 128.8, 129.6, 129.9, 131.7, 132.8, 134.9, 135.7, 139.3, 141.4, 144.7 (*C*-Ar), 190.6 (*C*O); ms: *m/z* (%) 315 (2) [M^+], 279 (9), 167 (24), 148 (100), 91(37). *Anal*. Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44. Found: C, 64.51; H, 5.45; N, 4.50.

***(E)*-*N*-(2-Formyl-4-methoxyphenyl)-*N*-methyl-2-phenylethenesulfonamide (4c)**. White solid; yield: 61%; mp 113–115°C; IR (KBr) 2871 (CHO), 2764 (CHO), 1681 (CO), 1331 (NSO_2), 1139 (NSO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.36 (3H, s, NMe), 3.90 (3H, s, OMe), 6.77 (1H, d, *J* 15.5 Hz, SO_2CH), 7.15 (1H, dd, *J* 8.8, 3.1 Hz, Ar), 7.26 (1H, d, *J* 8.8 Hz, Ar), 7.42–7.52 (7H, m, Ar), 10.47 (1H, s, C*H*O) ^{13}C NMR (125 MHz, $CDCl_3$): δ 39.5, 56.2, 111.6, 121.0, 122.2, 128.4, 128.8, 129.7, 131.7, 132.7, 136.2, 136.8, 144.8, 159.7, 190.4 (*C*O); ms: *m/z* (%) 331 (3) [M^+], 279 (12), 164 (100), 149 (87), 57 (28). *Anal*. Calcd for $C_{17}H_{17}NO_4S$: C, 61.61; H, 5.17; N, 4.23. Found: C, 61.72; H, 5.17; N, 4.16.

***(E)*-*N*-Ethyl-*N*-(2-formylphenyl)-2-phenylethenesulfonamide (4d)**. White solid; yield: 55%; mp 142–144°C; IR (KBr) 3035, 2922, 2873, 1681 (CO), 1339 (NSO_2), 1149 (NSO_2) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): 1.08 (t, *J* = 7.3 Hz, CH_3CH_2N), 3.8 (q, *J* = 7.3 Hz, CH_3CH_2N), 6.68 (d, *J* = 15.5 Hz, 1H, SO_2CH), 7.18–7.86 (m, 10H, Ar), 10.41 (s, 1H, C*H*O); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 48.5, 121.9, 128.2, 128.3, 128.8, 128.9, 129.2, 131.2, 132.3, 134.0, 136.2, 141.2, 143.5, 190.2 (*C*O); ms: *m/z* (%) 316 (11) [M^+], 148 (100), 130 (80), 103 (22), 77 (33).

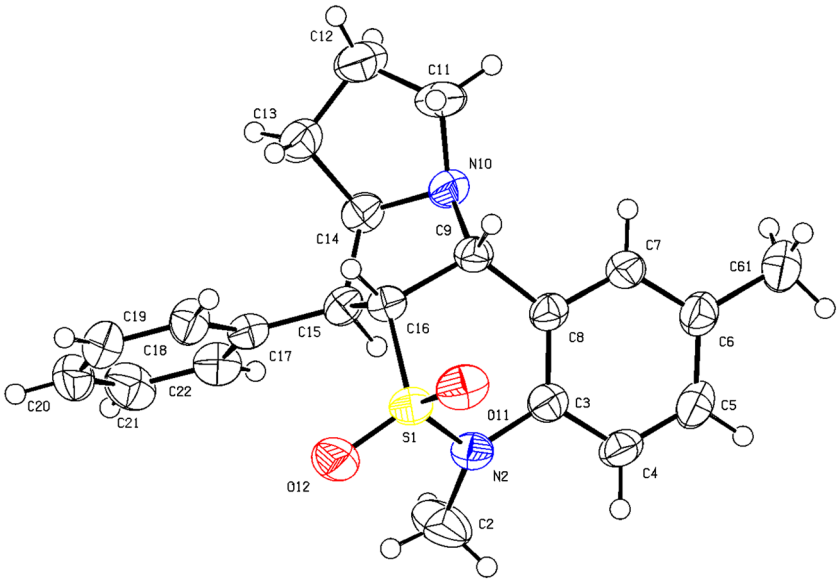
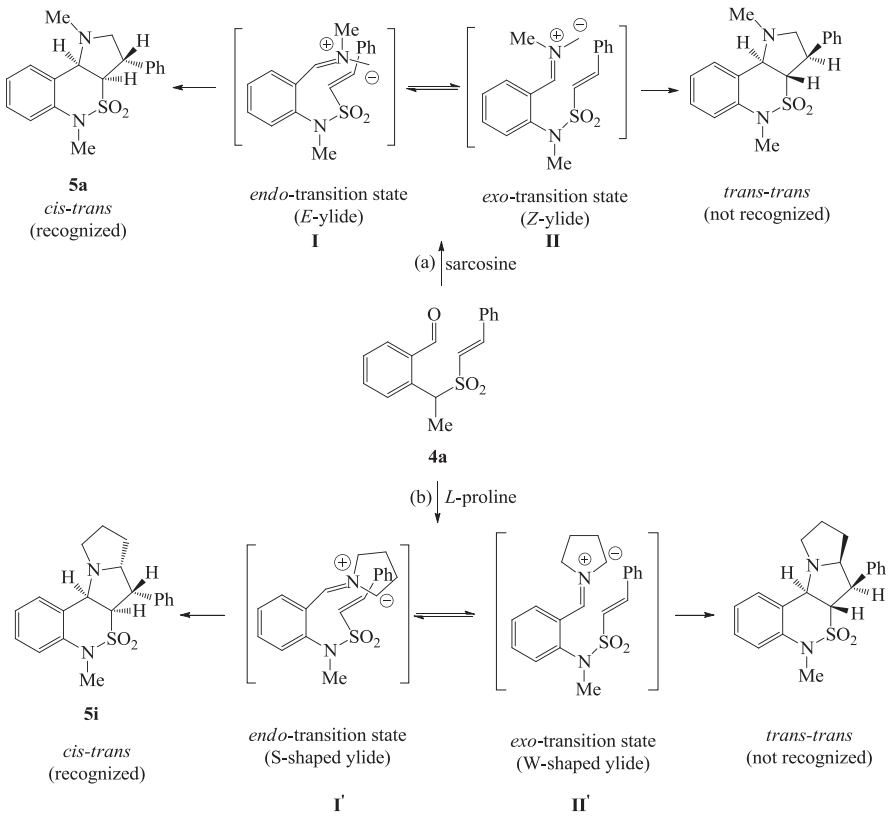


Figure 2. ORTEP diagram of **5i**.

Scheme 2. Transition state model evoked to account for reaction diastereoselectivities.



General procedure for the for the preparation of 5a–g. A mixture of sarcosine or phenylglycine (1.0 mmol), 2-formylphenyl (*E*)-*N*-(2-formylphenyl)-*N*-alkyl-2-phenylethenesulfonamides (1.0 mmol) in dry toluene (30 mL) containing molecular sieves (500 mg, 4 Å) was heated at reflux with stirring for 12 h. The solvent was then removed under reduced pressure, and the residue was recrystallized from EtOH to give **5a–g**.

***1,5-Dimethyl-3-phenyl-1,2,3,3a,5,9b-hexahydrobenzo[c]*pyrrolo [2,3-*e*][1,2]thiazine-4,4-dione (5a)**. White solid; yield: 80%; mp 182–184°C. IR (KBr): 1313 ($-SO_2$), 1126 ($-SO_2$) cm^{-1};

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.37 (s, 3H, MeN), 2.55–2.59 (m, 1H, CHN), 3.41 (s, 3H, $MeNSO_2$), 3.54–3.58 (m, 1H, CHN), 3.71(d, J = 8.8 Hz, 1H, ArCHN), 4.13–4.21 (m, 2H, $CHSO_2$, CHPh), 7.17–7.40 (m, 9H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 33.0, 39.8, 47.3, 63.7, 70.3, 71.4, 120.3, 125.1, 127.6, 127.8, 128.4, 129.2, 130.2, 131.1, 140.1, 143.0; ms: *m/z* (%) 328 (2) [M^+], 220 (62), 144 (100), 133 (97), 117 (42).

***1,5-8-Trimethyl-3-phenyl-1,2,3,3a,5,9b-hexahydrobenzo[c]*pyrrolo[2,3-*e*][1,2]thiazine-4,4-dione (5b)**. White solid; yield: 69%; mp: 165–167°C; IR (KBr) 1293 (−SO_2), 1128 (−SO_2) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.30 (s, 3H, MeN), 2.40 (s, 3H, MePh), 2.54–2.58 (m, 1H, CHN), 3.39 (s, 3H, $MeNSO_2$), 3.55–3.58 (m, 1H, CHN), 3.65 (d, J = 8.5 Hz, 1H, ArCHN), 4.13–4.17 (m, 2H, $CHSO_2$, CHPh), 7.06–7.44 (m, 8H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.3, 33.5, 39.9, 47.3, 63.7, 70.5, 71.4, 120.6, 127.5, 127.7, 128.4, 129.2, 130.7, 131.8, 134.9, 140.2, 140.4; ms: *m/z* (%) 342 (1) [M^+], 277 (7), 234 (61), 158 (100), 144 (62).

***8-Methoxy-1,5-dimethyl-3-phenyl-1,2,3,3a,5,9b-hexahydrobenzo[c]*pyrrolo[2,3-*e*][1,2]thiazine-4,4-dione (5c)**. White solid; yield: 75%; mp: 181–183°C; IR (KBr) 1308 (−SO_2), 1128 (−SO_2) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.32 (s, 3H, MeN), 2.53–2.57 (m, 1H, CHN), 3.40 (s, 3H, $MeNSO_2$), 3.55–3.59 (m, 1H, CHN), 3.64 (d, J = 8.4 Hz, 1H, ArCHN), 3.85 (s, 3H, $MeNSO_2$), 4.11–4.18 (m, 2H, $CHSO_2$, CHPh), 6.83–7.42 (m, 8H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 35.1, 39.9, 47.4, 56.0, 63.8, 70.8, 71.4, 114.3, 117.6, 123.0, 127.7, 128.4, 129.2, 129.61, 136.1, 140.3, 157.3; ms: *m/z* (%) 358 (3) [M^+], 250 (41), 174 (100), 160 (44), 133 (88).

***5-Methyl-1,3-diphenyl-1,2,3,3a,5,9b-hexahydrobenzo[c]*pyrrolo[2,3-*e*][1,2]thiazine (5d)**. White solid; yield: 51%; mp: 236–238°C; IR (KBr) 1316 (−SO_2), 1133 (−SO_2) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.30 (s, 3H, MeN), 3.51–3.5 (m, 1H, CHN), 3.95–4.11 (2H, m, CHN, CHPh), 4.47–4.55 (dd, J = 8.5, 9.7 Hz, 1H, $CHSO_2$), 5.45 (1H, d, J = 8.5, ArCHN), 6.63–7.37 (14H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.1, 45.2, 55.9, 61.0, 68.5, 112.3, 118.1, 118.3, 125.3, 127.6, 127.7, 127.9, 128.9, 129.0, 129.4, 129.5, 137.0, 138.9, 146.7; ms: *m/z* (%) 388 (5) [M^+], 195 (93), 144 (100), 130(26).

***5,8-Dimethyl-1,3-diphenyl-1,2,3,3a,5,9b-hexahydrobenzo[c]*pyrrolo[2,3-*e*][1,2]thiazine-4,4-dioxide (5e)**. White solid; yield: 56%; mp: 229–231°C; IR (KBr) 1320 (−SO_2), 1133 (−SO_2) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.33 (s, 3H, MePh), 3.32 (s, 3H, $MeNSO_2$), 3.54–3.55 (m, 1H, CHN), 3.93–3.98 (m, 1H, CHN), 4.09–4.12 (m, 1H, CHPh), 4.53 (dd, J = 8.6, 11.6 Hz, 1H, $CHSO_2$), 5.45 (d, J = 8.6 Hz, 1H, CHAr), 6.67–7.43 (m, 13H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.6, 30.8, 45.7, 56.4, 61.6, 68.9, 112.6, 118.3, 119.0, 128.1, 128.3, 128.5, 129.4, 129.9, 130.3, 136.8, 137.5, 147.5; ms: *m/z* (%) 404 (4) [M^+], 149 (41), 81 (60), 69 (100), 57 (94).

***5-Ethyl-1-methyl-3-phenyl-1,2,3,3a,5,9b-hexahydrobenzo[c]*pyrrolo[2,3-*e*][1,2] thiazine-4,4-dioxide (5f)**. White solid; yield: 61%; mp: 134–136°C; IR (KBr) 1314 (−SO_2), 1128 (−SO_2) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41 (t, 3H, J = 7.1 Hz, MeCN), 2.26 (s, 3H, MeN), 2.54–2.58 (m, 1H, CHN), 3.53–3.56 (m, 1H, CHN), 3.66 (d, 1H, J = 9.0 Hz, ArCHN), 3.90–3.93 (m, 1H, CHPh), 4.02–4.18 (m, 3H, CH_2NSO_2, $CHSO_2$), 7.23–7.44 (m, 9H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.8, 39.7, 44.3, 47.4, 63.8, 70.6, 72.4, 123.4, 125.7, 127.7, 128.3, 129.2, 129.3, 130, 131.4, 140.5, 142.0; ms: *m/z* (%) 342 (4) [M^+], 234 (28), 158 (93), 144 (97), 133 (100).

***5-Ethyl-1,3-diphenyl-1,2,3,3a,5,9b-hexahydrobenzo[c]*pyrrolo[2,3-*e*][1,2]thiazine-4,4-dioxide (5g)**. White solid; yield: 49%; mp: 229–231°C; IR (KBr) 1319 (−SO_2), 1133 (−SO_2) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.41 (t, J = 7.1 Hz, 3H, MeCN), 3.55–3.57 (m, 1H, CHN), 3.85–3.99 (m, 1H, CHN), 4.00–4.10 (m, 3H, $MeCH_2N$, CHPh), 4.55 (dd, J = 8.6, 11.5 Hz, 1H, $CHSO_2$), 5.45 (d, J = 8.6 Hz, 1H, ArCHN), 6.67–7.43 (m, 14H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): 21.6, 30.8, 45.7, 56.4, 61.6, 68.9, 112.6, 118.3, 119.0, 122.0, 128.1, 128.3, 128.5, 129.4, 129.9, 130.3,136.0 136.8, 137.5, 147.7; ms: *m/z* (%) 404 (3) [M^+], 167 (32), 149 (100), 130 (50), 57 (92).

General procedure for the preparation of 5h–j. A mixture of proline (1.0 mmol) and 2-formylphenyl (*E*)-*N*-(2-formylphenyl)-*N*-alkyl-2-phenylethenesulfonamides (1.0 mmol) in dry toluene (30 mL) containing molecular sieves (500 mg, 4 Å) was heated at reflux with stirring for 12 h. The solvent was then removed under reduced pressure, and the residue was subjected to plate chromatography using hexane-EtOAc (3:1) to give **5h–j**.

***5-Methyl-7-phenyl-5,7,7a,8,9,10-hexahydrobenzo[3,4][1,2]thiazino[6,5-b]*pyrrolizin-11-ium-6-olate 6-oxide (5h)**. White solid; yield: 59%; mp: 200–202°C; IR (KBr) *v* 1314 (−SO_2); 1127 (−SO_2) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22–1.24 (1H, m, C*H*CH_2CH_2N), 1.38–1.41 (1H, m, C*H*$_2CH_2CH_2N$), 1.76–1.78 (1H, m, CH_2CHCH_2N), 1.88–1.91 (1H,m, CH_2CHCH_2N), 2.88–2.90 (1H, m, CHN), 3.33 (3H, s, MeN), 3.43–3.45 (1H, m, CHN), 3.91 (1H, m, NCHCPh), 4.03 (1H, dd, J = 10.9, 8.5 Hz, CHPh), 4.50 (1H, dd, J = 10.9, 8.3 Hz, $CHSO_2$), 4.59 (1H, d, J = 8.3 Hz, ArCHN), 7.05–7.68 (9H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) 26.1, 29.1, 31.7, 49.4, 56.8, 61.9, 67.8, 69.1, 118.0, 118.2, 124.9, 127.4, 128.1, 129.0, 129.2, 129.5, 137.6, 140.0; ms: *m/z* (%) 354 (1) [M^+], 290 (30), 247(41), 220 (92), 144(100).

***2,5-Dimethyl-7-phenyl-5,7,7a,8,9,10-hexahydrobenzo[3,4][1,2]thiazino[6,5-b]*pyrrolizin-11-ium-6-olate 6-oxide (5i)**. White solid; yield: 60%; mp: 225–227°C; IR (KBr) 1306 (−SO_2); 1133 (−SO_2) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22–1.24 (1H, C*H*CH_2CH_2N), 1.38–1.41 (1H, m, C*H*CH_2CH_2N), 1.76–1.78 (1H, m, CH_2CHCH_2N), 1.88–1.91 (1H, m, CH_2CHCH_2N), 2.41 (3H, s, Me-Ph), 2.88–2.90 (1H, m, CHN), 3.31 (3H, s, MeN), 3.44–3.46 (1H, m, CHN), 3.92–3.93 (1H, m, CHN), 4.03 (1H, dd, J = 10.8, 8.5 Hz, CHPh), 4.50 (1H, dd, J = 10.8, 8.4 Hz, $CHSO_2$), 4.56 (1H, d, J = 8.4 Hz, ArCHN), 6.96–7.4 (8H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.40, 26.2, 29.1, 32.1, 49.40, 56.92, 61.2, 67.9, 69.9, 118.3, 127.4, 128.1, 128.9, 129.8, 129.9, 134.7, 137.2, 137.7, 149.8; ms: *m/z* (%) 368 (1.5) [M^+), 234 (41), 158 (100), 149 (65), 69 (96).

***2-Methoxy-5-methyl-7-phenyl-5,7,7a,8,9,10-hexahydrobenzo[3,4][1,2]thiazino[6,5-b]*pyrrolizin-11-ium-6-olate 6-oxide (5j)**. White solid; yield: 60%; mp: 241–243°C; IR (KBr), 1306 (−SO_2); 1133 (−SO_2) cm^{-1}; (500 MHz, $CDCl_3$) δ 1.18–1.22 (m, 1H, C*H*CH_2CH_2N), 1.36–1.40 (m, 1H, C*H*CH_2CH_2N), 1.74–1.77 (m, 1H, CH_2CHCH_2N), 1.86–1.90 (m, 1H, CH_2CHCH_2N), 1.94–1.98 (m, 1H, CH_2CHCH_2N), 2.84–2.87 (m, 1H, CHN), 3.41 (s, 3H, MeN), 3.87 (s, 3H, OMe), 3.92–3.98 (m, 2H, CHN), 4.48–4.52 (m, 2H, $CHSO_2$, ArCHN), 6.88–7.37 (m, 8H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.2, 29.9, 32.7, 49.4, 56.0, 56.8, 62.6, 67.8, 69.1, 114.2, 114.8, 120.4, 127.4, 128.0, 129.0, 132.5, 132.9, 137.7, 157.5; ms: *m/z* (%) 384 (2) [M^+]), 320 (40), 250 (86), 174 (100), 57 (94).

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