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Intramolecular sulfoxide electrophilic sulfenylation in 2- and 3-indoleanilides

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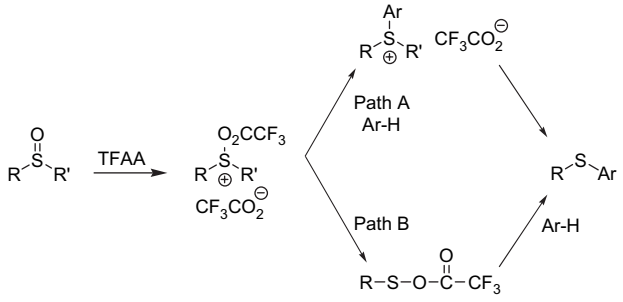
Abstract—When *N*-[2-(alkylsulfinyl)phenyl]-1*H*-indole-2-carboxamides with varying degrees of indolic and amidic N-alkylation are heated in an inert solvent or treated with trifluoroacetic anhydride; only compounds in which the amidic nitrogen is methylated cyclize to indolo[3,2-*b*]-1,5-benzothiazepinones (**9**, **10**). Successful cyclization is attributed to the ability of *N*-Me amides to readily adopt a conformation conducive to cyclization, which other derivatives are unable to achieve. The analogous 3-indoleanilide, *N*,*N*-dimethyl *N*-[2-(ethylsulfinyl)phenyl]-1*H*-indole-3-carboxamide (**17a**), undergoes SES/rearrangement to produce **10** upon heating in *p*-xylene. An intermediate 3*H*-indolinium spirocyclic species is proposed to account for this result.

1. Introduction

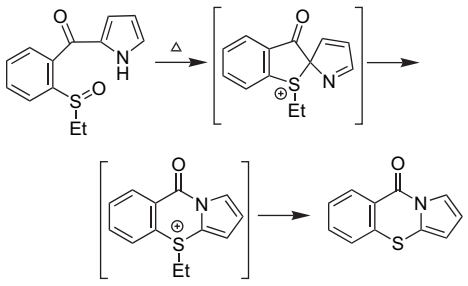
Sulfoxides are widely used as electrophilic sulfenylating agents. There are two general mechanistic pathways by which sulfoxides become sulfenylating agents and *both* are promoted by reagents and conditions typical for the Pummerer reaction.[1] Many reported 'anomalous' Pummerer reactions are electrophilic sulfenylation reactions, with the 'anomalous' pathway favored by the presence of a proximate nucleophilic group[2] or a non-acidic hydrogen atom on the carbon α to the sulfoxide.[3] This primary sulfenylation pathway involves formation of a sulfonium salt by reaction at the electrophilic sulfoxide sulfur in a species such as R_2S–$O_2CCF_3^+$ or R_2S–OH^+. The sulfonium salt subsequently undergoes dealkylation, either in situ or as a separate step, to form the sulfenylation product. There are numerous examples of electrophilic sulfenylations of aromatics[4] and heteroaromatics[5] utilizing this approach and similar reactions using sulfides and PIFA.[6]

The other pathway to sulfenylation involves a sulfenic acid derivative formed from S–C bond cleavage in the sulfoxide. Presumptive intermediates are a mixed anhydride of the sulfenic acid ($RSOCOCF_3$, RSOAc, etc.) or a protonated sulfenic acid ($RSOH_2^+$).[7] There are also many examples of electrophilic addition (with alkenes)[8,9] and electrophilic substitution (with arenes).[10] The two pathways are shown in Scheme 1.



Scheme 1. Sulfenylation pathway depends upon the timing of events.

We have exploited sulfonium ions generated in situ from sulfoxides (sulfoxide electrophilic sulfenylation—SES) followed by variations in the mode of dealkylation to prepare new *N*,*S*-heterocyclic systems: SES/displacement,[11] SES/ring enlargement,[12] and SES/rearrangement (Eq. 1).[13]



(1)

In the latter process the unexpected rearrangement was not the dominant pathway. We have sought to observe this

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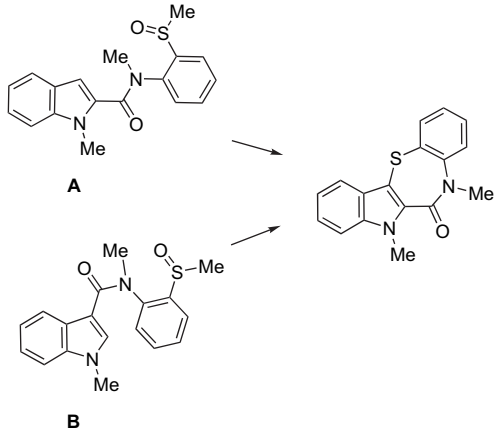
process in other systems, attempting to enhance the pathway and to determine if the process is a general phenomenon. In designing a system, the strong preference of indoles for electrophilic attack at C-3 even when that position is already substituted[14] was an important consideration. We now report that *both* 2- and 3-substituted indoles (**A**) and (**B**) produce the same product under SES conditions.



2. Results and discussion

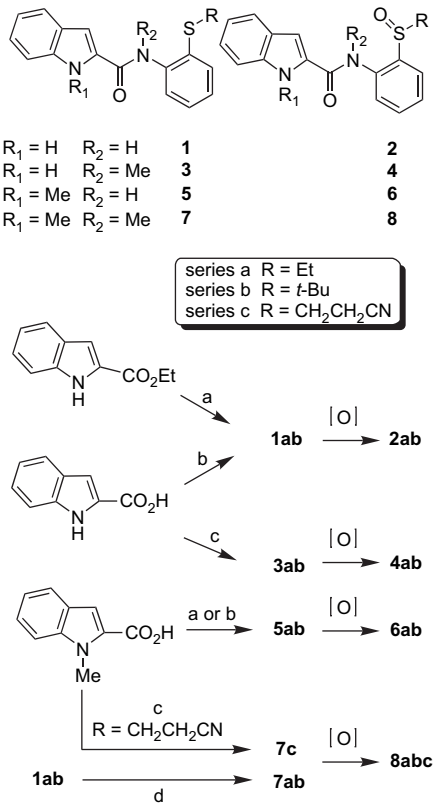
2.1. Indoleanilides substituted at C-2

Indoleanilides substituted at C-2 (**2**, **4**, **6**, **8**) were prepared using standard methodologies (Scheme 2). Indole-2-carboxylic acid chloride[15] and a 2-(alkylthio)aniline[16] produced sulfides **1a–c** in modest yields. Problems have been reported with reactions of indole carboxylic acids with thionyl chloride[17] and use of the unstable acid chloride (and consequent low yield of amide) could be avoided by trimethylaluminum-catalyzed condensation[18] of 2-(alkylthio)anilines and ethyl indole-2-carboxylate. For example, **1a** was obtained in 92% yield by this approach. Oxidations were accomplished using standard methodologies: $NaIO_4$ in CH_2Cl_2/MeOH/H_2O;[3a] Oxone® in THF/MeOH/H_2O;[19] or *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane.[20] Success of the oxidations was insensitive to the reagent used; the method selected was typically based on solubility of the starting sulfide in the oxidation medium.

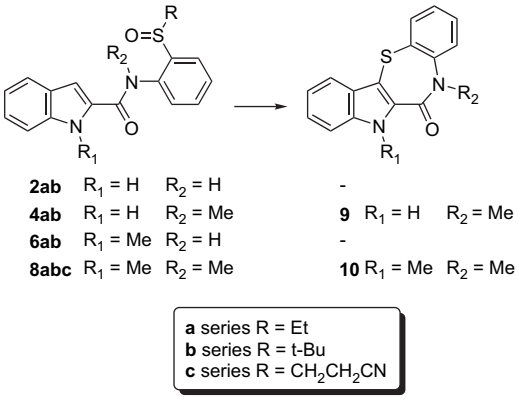
Monoalkylated compounds (**4ab**) bearing a methyl substituent on the amide nitrogen were prepared similarly, replacing the aniline component with an *N*-methyl-2-(alkylthio)aniline[21] followed by oxidation. Monoalkylated compounds bearing the methyl substituent on the indole (**6ab**) were prepared from alkylthioanilines and *N*-methylindole carboxylic acid followed by oxidation.

N,*N*′-Dimethylated compounds (**8ab**) were prepared by dialkylation of amides (**1ab**) by catalytic phase transfer methylation[22] followed by oxidation. Sulfide **1c** decomposed under phase transfer conditions (retro-Michael) so compound **8c** was prepared in low yield by reaction of 1-methyl-1*H*-indole-2-carboxylic acid chloride with 3-{[2-(methylamino)-phenyl]thio}propanenitrile followed by oxidation.

When the sulfoxides were subjected to cyclization conditions [either activation by electrophilic species (TFAA) or thermally (refluxing in chloroform or *p*-xylene)] clear patterns of reactivity emerged when the sulfoxides were cyclized (Scheme 3). Conditions for cyclization were either



Scheme 2. Synthesis of 2-indoleanilides. Reagents and conditions (compound number, % yield): (a) 2-ethylthioaniline, $AlMe_3$, toluene, reflux (**1b** 92%, **5a** 84%); (b) $SOCl_2$, Et_2O, 2-(alkylthio)aniline, rt (**1a**, 32%, **1b** 71%, **5b** 59%); (c) $SOCl_2$, Et_2O, *N*-methyl-2-(alkylthio)aniline, rt (**3a** 38%, **3b** 79%, **7c** 27%); (d) 50% NaOH, CH_3I, *n*-Bu_4NHSO_4, toluene (**7a** 82%, **7b** 79%).



Sulfoxide	Product, % yield (TFAA, Thermal)	Sulfoxide	Product, % yield (TFAA, Thermal)
2a	- (0, 0)	**6a**	- (0, 0)
2b	- (0, 0)	**6b**	- (0, 0)
4a	**9** (75, 56)	**8a**	**10** (90, 22)
4b	**9** (100, 58)	**8b**	**10** (100, 66)
		8c	**10** (50, 41)

Scheme 3. SES reactions of 2-indoleanilides.

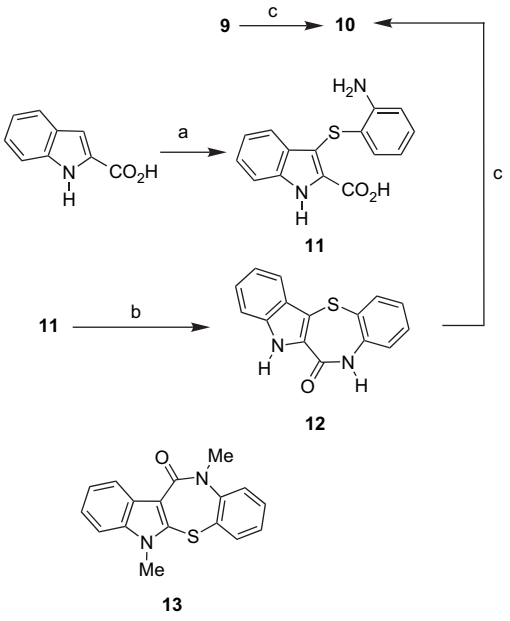
thermal (refluxing in chloroform or *p*-xylene) or electrophilic activation (TFAA). In successful reactions, *tert*-butyl sulfoxide derivatives cyclize thermally in refluxing chloroform whereas ethyl sulfoxide derivatives require higher temperatures (refluxing in *p*-xylene).[23] In addition, a substituent at the amidic nitrogen is essential for cyclization and the ^{1}H NMR spectrum (25 °C) of every sulfoxide that successfully cyclized is very poorly resolved. Poorly resolved spectra are generally indicative of conformational interconversion between two or more rotomers on the NMR time scale. Recording ^{1}H NMR spectra at 100 °C showed fewer, sharper peaks as expected for an increased rate of interconversion in a dynamic process.[24]

N,*N*-Disubstituted amides have higher energy, non-planar ground states compared to primary or secondary amides.[25] They often exhibit broadened ^{1}H NMR spectra due to the low C(O)–N rotational barrier to *cis*-/*trans*-amide interconversion. Disubstituted amides also exist predominately in the *cis*-form.[25b] In our compounds this means the amidic *N*-methyl substituted series is expected to exist primarily in a conformation, which places the sulfoxide and indole entities near one another and to possess conformational flexibility to easily obtain a geometry conducive to indole π electron–sulfoxide sulfur atom interaction for SES reaction.

Sulfoxides in the amidic N–H series (**2ab**, **6ab**) either produced decomposition products or were recovered unchanged. The failure of compounds containing amidic N–H to cyclize is attributable to factors preventing the sulfoxide sulfur atom and the indole π-system from assuming a favorable conformation for cyclization: a formidable energy barrier to interconversion of *cis*- and *trans*-amides, and a large energy difference between the *cis*- and *trans*-amides with the unfavorable (for cyclization) *trans*-isomer greatly preferred. These factors are supported by the sharp, well-resolved ^{1}H NMR spectra of **2ab** and **6ab** in contrast to the severely broadened ^{1}H NMR spectra of compounds in which the amidic nitrogen is methylated. Further restricting conformational flexibility of these compounds is a strong S=O···H–N intramolecular hydrogen bond as evidenced by IR[26] and ^{1}H NMR[27] spectra.

Compounds in which the amidic site is methylated (but still contain an indolic N–H) (**4ab**) cyclize both thermally and with TFAA activation to 10,11-dihydro-10-methyl-12*H*-indolo[3,2-*b*]-1,5-benzothiazepin-11-one (**9**). Dimethylated compounds **8abc** react to give 10,11-dihydro-10,12-dimethylindolo[3,2-*b*]-1,5-benzothiazepin-11-one (**10**). Due to competing side reactions, yields of **10** from 2-propanenitrile compounds were inferior to both ethyl and *tert*-butyl sulfoxides and were not pursued further.

As with product **9**, spectral data for **10** clearly shows that cyclization was effected, however, additional proof of structure was sought due to the possibility of migration of amide or sulfur groups either during the reaction or subsequent equilibration of products.[28,29] Resultant isomeric compounds would be expected to exhibit very similar spectral properties. Fortunately, rearrangement-scrambled product (**13**) is a known compound. The UV spectrum and melting point of our cyclization product differs considerably from that of **13** reported by Grandolini and co-workers[30] ruling out this alternative isomer. In addition, **10** was synthesized via an unambiguous route (Scheme 4) from **11**, prepared using methodology described by Atkinson et al.[31] Refluxing **11** in toluene using SiO_2 as catalyst[32] gave **12**, which upon catalytic phase transfer dimethylation gave a product chromatographically and spectroscopically identical to the cyclization product (**10**). This clearly establishes the sites of attachment of the sulfur and carbonyl groups on the indole ring of the SES product. Catalytic phase transfer methylation of **9** also produced **10** (76%) confirming the structure of that product as well.



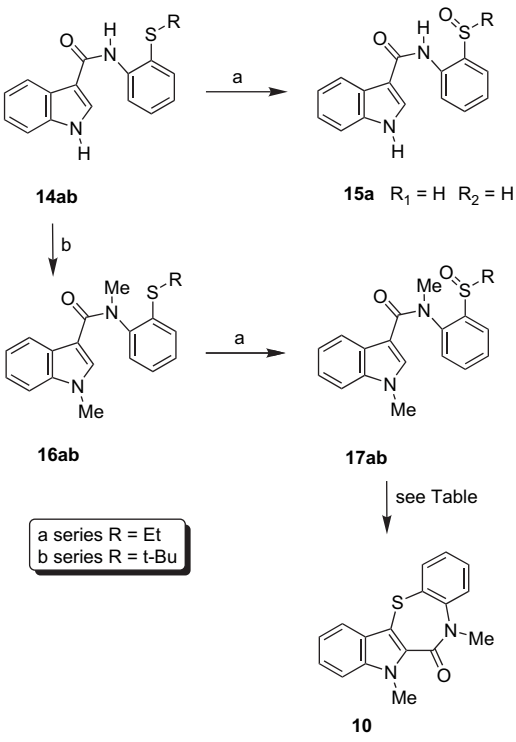
Scheme 4. Confirmation of structures of **9** and **10**. Reagents and conditions: (a) 2,2′-diaminodiphenyldisulfide, NaH, DMF (93%); (b) SiO_2, toluene, reflux (63%); (c) *n*-Bu_4NHSO_4, 50% NaOH, CH_3I, toluene, reflux [from **9** (76%), from **12** (89%)].

2.2. Indoleanilides substituted at C-3

Syntheses of 3-indoleanilide sulfoxides (**15a**, **17ab**) were similar to those for the 2-substituted analogues. Reproducibility problems were encountered with the reported[33] preparation of 3-indole carboxylic acid while preparing **14a**, so the *tert*-butyl analogue (**14b**) was prepared directly from indole and 2-(*tert*-butylthio)aniline in the presence of triphosgene and pyridine in 33% yield. Methylation and oxidation provided **17b**.

Cyclizations of sulfoxides **15a**, **17ab** were conducted under both thermal and TFAA activation. As shown in Scheme 5, results in this series were mixed. Like its 2-substituted indole counterpart, the compound with an amidic N–H (**15a**) did not cyclize under any conditions attempted. Compound **17a**, which had a broad ^{1}H NMR spectrum, gave a cyclized product in good yield under thermal conditions, but decomposed to an intractable tar under TFAA activation. The *tert*-butyl sulfoxide **17b**, although it too had the ^{1}H NMR and IR patterns of successfully cyclized sulfoxides, decomposed (under both thermal and TFAA activation).

The product obtained from heating **17a** under reflux for 15 h in *p*-xylene (67% yield after chromatography) proved



14ab 15a R_1 = H R_2 = H

16ab 17ab

10

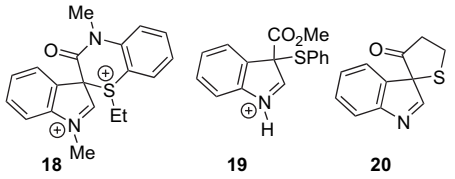
Sulfoxide	Product (% yield TFAA, thermal)	^{1}H NMR (rt)	$\upsilon_{S=O}$ (cm^{-1})
15a	- (0, 0)	sharp	1003
17a	**10** (0, 67%)	broad	1014
17b	- (0, 0)	broad	1030

Scheme 5. Preparation and SES reactions of 3-indoleanilides. Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, −10 °C (**15a** 96%, **17a** 72%, **17b** 49%); (b) *n*-Bu_4HSO_4, 50% NaOH, CH_3I, toluene, reflux (**16a** 90%, **16b** 73%).

to be identical to **10**, the cyclization product from the 2-substituted indole sulfoxide. Mechanistically, there are several possible explanations for this observation.

- Migration of the amide group from C-3 to C-2 of indole prior to cyclization (**17a**→**8a**→**10**). However, heating the sulfide **16a** (which cannot cyclize via SES) for 12 h in *p*-xylene showed no evidence of migration (95% recovery of unchanged starting material). There is literature precedence for acyl migration from C-3 to C-2 in indoles but typically strongly acidic conditions are required.[34]
- Initial formation of **13** by direct cyclization to C-2, followed by rearrangement to **10** upon prolonged heating in *p*-xylene, as we had observed previously in another indolic system.[28] However, authentic **13** (synthesized as reported by Grandolini and co-workers)[30] showed no sign of rearrangement to **10** after 22 h in refluxing *p*-xylene. Even an additional 24 h at reflux in 0.1% TFA in *p*-xylene solution resulted in 92% recovery of unchanged starting material.
- Initial formation of a 3*H*-spirocyclic intermediate (such as **18**) during SES, followed by *amide migration* to C-2 and loss of a proton to give **10**.

Formation of product **10** via amide migration is unprecedented. Several examples of ketone/S(II)-based spirocyclic intermediates have been proposed (for example, **19**[35] and **20**[36]). However, the products observed derive from preferential sulfur migration in the 3*H*-indolium species. 3*H*-Indolic S(IV)/ketone or amide spirocyclic intermediates have not been invoked previously, although Hartke and Wendebourg[5d] proposed 2*H*- and 3*H*-pyrrolium sulfonium dications as intermediates in the acid-promoted sigmatropic [1,5] rearrangement of 2-pyrrolylsulfonium salts to 3-pyrrolylsulfonium salts.



18 19 20

Formation of **10** via a spirocyclic intermediate requires migration of the amide group to occur in preference to an arylsulfonium group[37] (or arylsulfanyl group if sulfur dealkylation precedes migration; the timing of events and the form of the sulfur substituent are unknown). Both 3-acylindoles[34] and simple 3-alkylthio- and 3-arylthioindoles[38] undergo acid-catalyzed isomerization to their 2-substituted counterpart in thermodynamically controlled processes (under significantly more acidic conditions than used here). However, when both acyl and sulfur groups are present at indole C-2/C-3, the thermodynamically more stable product cannot be determined by inspection and, in this work, neither the product nor the alternative isomer is interconverted under the conditions of the reaction. Thus, the product that forms predominately could be a kinetic product derived by migration in a spirocyclic intermediate of the group having the greater migratory aptitude.

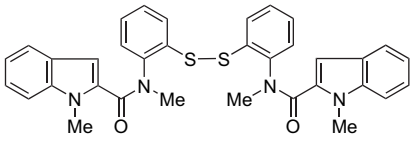
2.3. A comment on the sulfenic acid pathway for SES chemistry

Sulfenylation of nucleophilic nitrogen via a sulfenic acid generated from a sulfoxide is reported to occur under nearly the same conditions reported here ($(CCl_3CO)_2O$/pyridine or refluxing toluene/pyridine).[39] Glucosulfinylpropanenitriles[40] as well as *tert*-butyl alkyl sulfoxides,[41] upon mild heating in an inert solvent, generate transient sulfenic acids that have been trapped.

To explore the possibility that **10** may also form via a transient sulfenic acid, we conducted thermal reactions of **8b** in the presence of a sulfenic acid trapping agent. When **8b** was refluxed in chloroform in the presence of 2-mercaptobenzothiazole[42] (1 M equiv) cyclization product **10** was obtained in 32% yield (compared to 66% yield in the absence of the trapping agent). This result demonstrates the reaction does not require a sulfenic acid pathway. However, it does not allow elimination of this pathway entirely, even though the reduced yield may be due to the trapping agent interfering with sulfoxide activation in the SES pathway.

In some reactions of *tert*-butyl sulfoxides, small amounts of **21** and **22** were isolated in addition to cyclized product. These compounds are indicative of sulfenic acid formation,[43] but were never detected in reactions of ethyl sulfoxides. Yields of cyclized product from *tert*-butyl sulfoxides

were considerably lower when **21/22** were found in the crude reaction product. In earlier work, we isolated sulfonium salts from SES reactions.[6a] We believe sulfenic acids are *not* intermediates in SES sulfenylation reactions and, if formed, produce side reactions.



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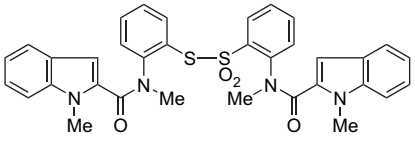

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The difference in the two sulfenylation reaction pathways (shown in Scheme 1) is in the timing of the departure of the R′ substituent on the sulfoxide. It must be able to leave easily for successful SES processes, but not so easily as to depart prematurely (resulting sulfenic acid formation); it is important to conduct reactions for 2-propanenitrile and *tert*-butyl sulfoxides below the threshold for sulfenic acid formation to obtain optimal yields of SES products.

3. Conclusions

Both 2- and 3-indoleanilides (**8abc** and **17a**) undergo cyclization to produce the same product-indolo[3,2-*b*]-1,5-benzothiazepin-11-one (**10**). For the 3-indoleanilides, the possibility of indole substituent migration before or after cyclization was eliminated and a 3*H*-indolinium spirocyclic intermediate, with preferential migration of the amide-containing moiety from C-3 to C-2, is proposed to rationalize the rearrangement. We also discovered that successful cyclization in this series requires the *absence* of an amidic hydrogen in the compounds. The lack of cyclization of compounds containing an amidic hydrogen is attributed to N–H···O=S hydrogen bonding, a low energy *trans*-amide conformation, and a formidable rotational barrier to the *cis*-amide conformation, all of which enforce a molecular geometry that precludes the sulfur atom from achieving an orientation conducive to interaction with indole π-electrons. By extrapolation, if cyclized compounds containing an amidic hydrogen are synthetic targets, one should consider introducing an easily removable amidic alkyl substituent (e.g., benzyl) into the SES substrate.

4. Experimental

4.1. General

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ solutions unless otherwise indicated. IR spectra were recorded in KBr pellets for solid samples and neat on NaCl plates for liquid samples. Mass spectra were recorded at 70 eV (EI) unless indicated otherwise.

4.2. *N*-[2-(Ethylthio)phenyl]-1*H*-indole-2-carboxamide (1a)

4.2.1. Method A. To a well-stirred solution of indole-2-carboxylic acid (10.0 g, 60 mmol) in Et_2O (194 mL) at 0 °C under a drying tube was added dropwise, $SOCl_2$ (9.6 mL, 140 mmol, 2.2 equiv) neat over 5 min. The mixture was allowed to warm to room temperature. After stirring an additional 2 h, volatiles were removed in vacuo leaving a yellow solid, which was redissolved in Et_2O (96 mL) and added to a well-stirred solution of 2-(ethylthio)aniline (2 equiv, 18.4 g, 0.12 mol) in Et_2O (96 mL) over 8 min at 0 °C. The resulting yellow slurry was stirred for 50 min at 0 °C and at room temperature for 30 min at which time the mixture was diluted with EtOAc (100 mL). The combined organics were washed with 5% aq HCl (3×150 mL), 5% aq $NaHCO_3$ (3×150 mL), H_2O (2×100 mL), dried (Na_2SO_4), and the solvent evaporated in vacuo to yield a wet orange solid. Column chromatography (1:1 $CHCl_3$/hexane) gave a yellow solid, **1a** (5.7 g, 32%). Analytically pure material could be obtained by recrystallization from acetone. Mp 153–155 °C; IR 3350, 3298, 1654 cm^{-1}; ^{1}H NMR (200 MHz) δ 10.09 (1H, d, J=0.6 Hz), 9.51 (1H, s), 8.60 (1H, dd, J=1, 6 Hz), 7.65 (1H, dd, J=0.6, 8 Hz), 7.53 (1H, dd, J=1, 6 Hz), 7.44 (1H, dd, J=0.6, 8 Hz), 7.00–7.40 (5H, m), 2.76 (2H, q, J=7 Hz), 1.18 (3H, t, J=7 Hz,); ^{13}C NMR δ 160.2, 140.1, 137.6, 136.3, 131.5, 131.0, 128.1, 125.4, 124.6, 123.2, 122.6, 121.3, 120.4, 112.8, 103.4, 31.3, 15.3; MS [*m*/*z* (relative intensity)] 296 (M$^+$, 54), 235 (75), 153 (100). Anal. Calcd for $C_{17}H_{16}N_2OS$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.70; H, 5.55; N, 9.34.

4.2.2. Method B. To an N_2-flushed flask containing toluene (123 mL) was added trimethylaluminum (2.0 M in hexane, 21 mL, 42 mmol, 1.14 equiv) via a syringe dropwise. *CAUTION: pyrophoric.* This solution was cooled to 5 °C and 2-(ethylthio)aniline (5.7 g, 37 mmol) in toluene (18 mL) was added dropwise. After stirring 20 min at 5 °C, the solution was allowed to warm to room temperature over a 45-min period. To the resulting solution was added dropwise ethyl indole-2-carboxylate (7.0 g, 37 mmol) in toluene (62 mL) and CH_2Cl_2 (18 mL). When the addition was complete the reaction mixture was heated to reflux. After refluxing 16 h, the cooled solution was hydrolyzed by slow addition of 2% aq HCl (45 mL). The layers were separated and the aqueous layer extracted with EtOAc (3×50 mL). The combined organics were washed with saturated NaCl and then with H_2O, dried (Na_2SO_4), and the solvent evaporated in vacuo to yield a yellow solid (9.8 g, 92%) as a single spot on TLC, which was identical to the compound prepared above (^{1}H NMR and mixed melting point).

4.3. *N*-[2-(Ethylsulfinyl)phenyl]-1*H*-indole-2-carboxamide (2a)

To a well-stirred solution of **1a** (0.5 g, 1.5 mmol) in THF/MeOH (2.5 mL/1 mL) at 0 °C was added all at once a solution of Oxone® in H_2O (2.5 mL). The resulting mixture was stirred at 0 °C for 5 min then at room temperature for 2.5 h then extracted with CH_2Cl_2 (2×10 mL). The combined organics were washed with H_2O, dried (Na_2SO_4), and the solvent removed in vacuo to yield a light yellow solid, which

was recrystallized in MeOH to yield a very pale yellow solid, **2a** (0.3 g, 58%). Mp 156–157 °C; IR 3289, 3168, 1662, 1009 cm^{-1}; ^1H NMR (200 MHz) δ 11.84 (1H, s, br), 10.29 (1H, s, br), 8.80 (1H, dd, J=1, 8 Hz), 7.10–7.72 (8H, m, containing 1H at δ 7.45, dd, J=1, 8 Hz), 3.07–3.19 (2H, dm), 1.26 (3H, t, J=7 Hz); ^{13}C NMR δ 160.4, 141.6, 133.0, 131.2, 128.2, 127.7, 127.2, 127.1, 125.4, 125.1, 123.5, 122.9, 121.1, 112.4, 104.8, 48.9, 7.8; MS [m/z (relative intensity)] 312 (M^+, 63), 283 (20), 144 (100). Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.35; H, 5.33; N, 8.86.

4.4. *N*-[2-(*tert*-Butylsulfinyl)phenyl]-*N*-methyl-1*H*-indole-2-carboxamide (4b)

To an ice-cooled solution of **3b** (5.0 g, 14.8 mmol) in CH_2Cl_2 (150 mL) was added slowly a solution of *m*-CPBA (77%, 1.1 equiv, 21.1 mmol, 3.6 g) in CH_2Cl_2 (50 mL). The resulting mixture was stirred at 0 °C for 15 min and then put it in a freezer (−8 °C) overnight. The reaction mixture was then poured into 5% $NaHCO_3$ solution (150 mL) and extracted with CH_2Cl_2 (200 mL). The combined organic layer was washed with distilled water, dried, and concentrated in vacuo. Column chromatography (EtOAc/hexane, 9:1) gave a yellowish white solid, which was recrystallized (hexane) to give a white solid (3.68 g, 70%). Mp 114–116 °C; IR 3453, 1624 cm^{-1}; ^1H NMR and ^{13}C NMR was not well-resolved due to presence of rotational isomers; MS [m/z (relative intensity)] 144 (6), 56 (58), 41 (100).

4.5. *N*-[2-(Ethylthio)phenyl]-*N*,1-dimethyl-1*H*-indole-2-carboxamide (7a)

To a well-stirred suspension of **1a** (5.2 g, 17 mmol) and tetra-*n*-butylammonium sulfate (0.6 g, 2 mmol, 0.1 equiv) in toluene (22 mL) was added 50% aq NaOH solution (22 mL) in one portion. The resulting two-layer mixture was heated to reflux and a solution of CH_3I (5.4 g, 38 mmol, 2.2 equiv) in toluene (5 mL) added dropwise over 5 min. This mixture was refluxed for 24 h, cooled to room temperature and the layers separated. The organic layer was washed with H_2O several times (until washings were neutral to litmus), dried (Na_2SO_4), and the solvent evaporated in vacuo to yield a brown solid, which was filtered through a silica gel column (1:1 $CHCl_3$/hexane) to give **7a** (4.7 g, 82%) as a white solid. Recrystallization (acetone) gave pure **7a**. Mp 127–128 °C; IR 1635 cm^{-1}; ^1H NMR (200 MHz) δ 6.95–7.38 (8H, m), 6.07 (1H, s), 3.97 (3H, s), 3.41 (3H, s), 2.80 (2H, apparent qd, J=7.2, 4.9, 2.3 Hz,), 1.20 (2H, t, J=7.3 Hz); ^{13}C NMR δ 164.6, 143.1, 138.4, 136.5, 132.3, 129.0, 128.8, 128.6, 127.9, 126.5, 123.7 122.2, 120.1, 110.1, 107.1, 37.2, 32.0, 26.4, 14.2; MS [m/z (relative intensity)] 324 (M^+, 2), 158 (100). Anal. Calcd for $C_{19}H_{20}N_2OS$: C, 70.34; H, 6.21; N, 8.63. Found: C, 70.27; H, 6.34; N, 8.58.

4.6. 10,11-Dihydro-10-methyl-12*H*-indolo[3,2-*b*]-[1,5]benzothiazepin-11-one (9) from 4a

4.6.1. Method A (thermal cyclization). A solution of **4a** (1.7 g, 5 mmol) in *p*-xylene (66 mL) was heated under reflux for 12 h. Upon cooling to room temperature, the solution was filtered to give a green solid, **9** (0.8 g, 56%). Mp 290 °C (dec); IR 3228, 1618 cm^{-1}; ^1H NMR (200 MHz, DMSO-d_6) δ 12.13 (1H, s, br), 7.15–7.67 (8H, m), 3.51 (3H, s); MS [m/z (relative intensity)] 280 (M^+, 100). Anal. Calcd for $C_{16}H_{12}N_2OS$: C, 68.55; H, 4.31; N, 9.51. Found: C, 68.63; H, 4.65; N, 9.91.

4.6.2. Method B (electrophilic activation). The reaction was carried out as for **8a** (see Section 4.7) with TFAA (0.2 mL, 1.2 mmol, 3.75 equiv) in CH_2Cl_2 (2 mL), pyridine (0.1 mL, 1.2 mmol, 4 equiv), and **4a** (0.10 g, 0.3 mmol) in CH_2Cl_2 (1 mL). Stirring at 0 °C for 15 min, then at room temperature for 0.5 h, yielded **9** as a yellow solid (0.3 g, 75%).

4.7. 10,11-Dihydro-10-methyl-12*H*-indolo[3,2-*b*]-1,5-benzothiazepin-11-one (9) from 4b

4.7.1. Method A (thermal cyclization). A solution of **4b** (0.73 g, 2.1 mmol) in chloroform (75 mL) was heated under reflux for 64 h. The solution was cooled to room temperature precipitating a white solid (**9**, 0.33 g, 58%). Mp 295 °C (dec); IR 1619 cm^{-1}; ^1H NMR δ 10.61 (br, 1H), 7.56 (d, J=8.0 Hz, 1H), 7.42 (d, J=8.0 Hz, 1H), 7.28 (d, J=8.28 Hz, 1H), 7.17–7.19 (m, 2H), 7.11 (dt, J=6.99, 1.07 Hz, 1H), 6.95–7.03 (m, 2H), 3.44 (s, 3H); MS [m/z (relative intensity)] 280 (M^+, 100), 248 (27).

4.7.2. Method B (electrophilic activation). The reaction was carried out as for **8a** (see Section 4.7) with TFAA (0.45 g, 2.1 mmol, 3.75 equiv) in CH_2Cl_2 (20 mL), pyridine (0.18 g, 2.3 mmol, 4 equiv), and **4b** (0.20 g, 0.57 mmol) in CH_2Cl_2 (15 mL). Stirring at 0 °C for 15 min, then at room temperature for 30 min, yielded **9** (0.16 g, 100%).

4.8. 10,11-Dihydro-10,12-dimethylindolo[3,2-*b*]-[1,5]benzothiazepin-11-one (10) from 8a

4.8.1. Method A (thermal cyclization). A solution of **8a** (1.0 g, 3 mmol) in *p*-xylene (35 mL) was heated under reflux for 30 h. Solvent was removed in vacuo and the brown residue was passed through a silica gel column ($CHCl_3$) to give **10** (0.2 g, 22%). Mp 198–200 °C; IR 1627 cm^{-1}; ^1H NMR (200 MHz) δ 7.77 (1H, d, J=0.9 Hz), 7.73 (1H, d, J=0.9 Hz), 7.08–7.58 (6H, m), 3.91 (3H, s), 3.62 (3H, s); ^{13}C NMR δ 163.5, 146.0, 138.2, 137.4, 132.3, 131.0, 128.9, 126.2, 125.8, 125.5, 125.0, 120.6, 120.3, 117.5, 110.1, 38.6, 31.6; MS [m/z (relative intensity)] 294 (M^+, 100). Anal. Calcd for $C_{17}H_{14}N_2OS$: C, 69.36; H, 4.79; N 9.52. Found: C, 69.35; H, 4.89; N, 9.28.

4.8.2. Method B (electrophilic activation). To a well-stirred solution of TFAA (1.4 mL, 11 mmol, 3.75 equiv) in CH_2Cl_2 (17 mL) at 0 °C was added neat pyridine (1 mL, 12 mmol, 4 equiv) via syringe. To this solution was added, **8a** (1 g, 3 mmol) in CH_2Cl_2 (9 mL), which had been previously cooled to 0 °C. After stirring at 0 °C for 15 min then at room temperature for 3 h, the solution was poured into a 10% aq Na_2CO_3 (30 mL) and stirred for 5 min. The layers were separated and the aqueous layer washed with CH_2Cl_2 (1×30 mL). The combined organics were washed with 5% HCl (3×40 mL), 10% aq Na_2CO_3 (1×40 mL), H_2O, and dried (Na_2SO_4). The solvent removal in vacuo gave a yellow solid **10** (0.8 g, 90%). Mp 196–198 °C.

4.9. Trapping experiment

To a solution of **8b** (0.1 g, 0.27 mmol) in chloroform (50 mL) was added 2-mercaptobenzothiazole (1.0 equiv, 0.27 mmol, 45.0 mg) and the resulting mixture was heated under reflux for 72 h (until no starting material on TLC). The solution was allowed to cool to room temperature and the solvent was evaporated in vacuo to yield a brown solid. Column chromatography (CH_2Cl_2) gave **10** (0.025 g, 32%).

4.10. 3-[(2-Aminophenyl)thio]-1*H*-indole-2-carboxylic acid (11)

To a well-stirred suspension of NaH (1.1 g, 45 mmol, 3.0 equiv) in dry DMF (30 mL) under N_2 at room temperature was added dropwise a solution of indole-2-carboxylic acid (2.4 g, 15 mmol) in DMF (10 mL). After the evolution of H_2 had ceased, a solution of 2,2′-diaminodiphenyldisulfide (15 mmol) in DMF (5 mL) was added dropwise and the dark colored solution was heated at 50 °C for 24 h, then poured into H_2O (75 mL) and extracted with Et_2O (3×50 mL). The aqueous layer was acidified to pH~5–6 precipitating a light brown solid (**11**, 4.1 g, 93%). The solid was used in the next step without purification.

4.11. 10,11-Dihydro-10,12*H*-indolo[3,2-*b*][1,5]benzothiazepin-11-one (12)

A suspension of **11** (5 g, 17.6 mmol) and SiO_2 (column chromatographic grade, 20 g) in toluene (250 mL) was heated under reflux for 13 h under a Dean–Stark trap. The partially cooled reaction mixture was filtered through a sintered glass funnel and the SiO_2 washed with 1:1 CH_2Cl_2/MeOH (50 mL) and then with MeOH (2×30 mL). The combined organics were evaporated in vacuo and the light brown solid recrystallized to produce **12** (2.95 g, 63%) as an off-white solid. Mp 237–239 °C (50% EtOH); IR 3414, 3197, 1654 cm^{-1}; ^1H NMR (200 MHz) δ 12.14 (1H, s, br), 10.46 (1H, s, br), 7.12–7.70 (8H, m); ^{13}C NMR δ 164.7, 142.3, 137.6, 133.0, 131.5, 130.6, 130.3, 127.0, 126.9, 126.8, 126.3, 125.2, 121.8, 120.8, 114.0; MS [*m*/*z* (relative intensity)] 266 (M^+, 100). Anal. Calcd for $C_{15}H_{10}N_2OS$: C, 67.65; H, 3.78; N, 10.52. Found: C, 67.48; H, 4.12; N, 10.42.

4.12. *N*-[2-(Ethylthio)phenyl]-1*H*-indole-3-carboxamide (14a)

To a magnetically stirred solution of indole-3-carboxylic acid (1.5 g, 9 mmol) in THF (20 mL) at 0 °C was added dropwise neat oxalyl chloride (2.3 g, 18 mmol, 2 equiv). After 12 h at room temperature, the solvent was evaporated in vacuo and the yellow residue (in dichloroethane (40 mL)) was added to a mechanically stirred solution of 2-(ethylthio)-aniline (2.8 g, 18 mmol, 2 equiv) in dichloroethane (30 mL). After 5 h at room temperature, the mixture was washed with 5% HCl (3×50 mL), 5% $NaHCO_3$ (3×50 mL), H_2O, and dried (Na_2SO_4). The solvent was evaporated in vacuo to leave a dark brown oil. Column chromatography ($CHCl_3$) produced **14a** as a faint brown solid (0.9 g, 35%). Mp 103–105 °C; IR 3352, 3216, 1638 cm^{-1}; ^1H NMR (200 MHz) δ 9.31 (1H, s), 8.66 (1H, dd, *J*=1.3, 7 Hz), 8.31–8.36 (1H, m), 7.88 (1H, d, *J*=3 Hz), 7.58 (1H, dd, *J*=1.4, 6.2 Hz), 7.25–7.48 (4H, m), 7.07 (1H, td, *J*=1.4, 6.2 Hz), 2.78 (2H, q, *J*=7 Hz), 1.20 (3H, t, *J*=7 Hz); ^{13}C NMR δ 165.4, 141.5, 138.2, 136.8, 131.0, 130.8, 125.8, 125.1, 124.4, 124.3, 123.3, 121.8, 121.2, 113.9, 113.5, 31.7, 16.1; MS [*m*/*z* (relative intensity)] 296 (M^+, 12), 153 (100). Anal. Calcd for $C_{17}H_{16}N_2OS$: C, 68.89; H, 5.44; N, 9.45. Found: C, 68.49; H, 5.62; N, 9.44.

4.13. *N*-[2-(*tert*-Butylthio)phenyl]-1*H*-indole-3-carboxamide (14b)

Triphosgene (1.1 g, 3.66 mmol) in toluene (5 mL) was added to a well-stirred solution of indole (1.3 g, 11.0 mmol) and pyridine (0.88 g, 11.0 mmol) in CH_2Cl_2 (40 mL) dropwise over 30 min at 25 °C. The resulting dark red mixture was stirred for 3.5 h at 25 °C under drying tube. Solvent was evaporated in vacuo to half of its volume and CH_2Cl_2 (10 mL) was added followed by a solution of 2-(*tert*-butylthio)aniline (4.0 g, 22.1 mmol) in CH_2Cl_2 (25 mL) dropwise. The resulting dark green mixture was stirred at room temperature under a drying tube for 4 h. The reaction mixture was washed with 5% HCl (3×50 mL), 5% Na_2CO_3 (3×50 mL), H_2O (50 mL). Drying (Na_2SO_4) and solvent removal in vacuo and column chromatography (CH_2Cl_2) gave a white solid (**14b**, 1.20 g, 33%). Mp 185–187 °C; IR 3335, 1637 cm^{-1}; ^1H NMR δ 9.88 (br, 1H), 9.64 (br, 1H), 8.76 (d, *J*=7.88 Hz, 1H), 8.46 (d, *J*=7.88 Hz, 1H), 7.89 (d, *J*=2.64 Hz, 1H), 7.58 (d, *J*=7.74 Hz, 1H), 7.46 (t, *J*=7.03 Hz, 2H), 7.32 (t, *J*=7.03 Hz, 1H), 7.25 (t, *J*=7.74 Hz, 1H), 7.08 (t, *J*=7.74 Hz, 1H), 1.27 (s, 9H); ^{13}C NMR δ 163.6, 142.1, 138.7, 136.8, 130.8, 129.5, 124.3, 123.0, 121.8, 120.3, 120.2, 120.0, 112.6, 112.4, 48.5, 31.0, 30.8; MS [*m*/*z* (relative intensity)] 324 [M^+, 13], 268 (6), 144 (100), 125 (24), 57 (5).

4.14. *N*-[2-(Ethylsulfinyl)phenyl]-1*H*-indole-3-carboxamide (15a)

Yield 96%. Mp 60–61 °C; IR 3217, 3168, 1652, 1003 cm^{-1}; ^1H NMR (200 MHz) δ 11.15 (1H, s); 9.72 (1H, s), 8.71 (1H, d, *J*=8 Hz), 8.40–8.45 (1H, m), 7.90 (1H, d, *J*=3 Hz), 7.06–7.60 (6H, m), 3.02–3.24 (2H, dm), 1.18 (3H, t, *J*=7 Hz); ^{13}C NMR δ 164.9, 142.8, 137.8, 134.1, 128.8, 128.2, 127.3, 125.6, 124.4, 124.0, 123.8, 123.1, 122.7, 113.1, 113.0, 49.3, 8.8; MS [*m*/*z* (relative intensity)] 312 (M^+, 15), 144 (100). Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.48; H, 5.23; N, 8.99.

4.15. *N*-[2-(Ethylthio)phenyl]-*N*,1-dimethyl-1*H*-indole-3-carboxamide (16a)

To a stirred suspension of **14a** (1.8 g, 6.1 mmol) and tetra-*n*-butylammonium sulfate in toluene (10 mL) was added 50% aq NaOH (7 mL) in one portion. After refluxing for 2 h, a solution of CH_3I (1.9 g, 13.3 mmol, 2.2 equiv) in toluene (2 mL) was added and the mixture heated under reflux for an additional 17 h. The organics were collected, washed with H_2O until neutral to litmus, dried (Na_2SO_4), the volatiles removed in vacuo, and the brown solid chromatographed ($CHCl_3$) to produce **16a** (1.8 g, 90%) as an off-white solid. Mp 172–173 °C (acetone); IR 1621 cm^{-1}; ^1H NMR (200 MHz) δ 8.41–8.46 (1H, m), 7.12–7.34 (7H, m), 6.06 (1H, d, *J*=0.6 Hz), 3.49 (3H, s), 3.38 (3H, s), 2.90

(2H, apparent qd, J=7.1, 0.2 Hz), 1.27 (3H, t, J=7.0 Hz); ^{13}C NMR δ 166.7, 143.6, 138.4, 136.8, 132.6, 130.3, 124.4, 124.2, 127.5, 126.7, 123.5, 123.2, 122.0, 110.0, 109.8, 37.3, 33.8, 26.2, 14.5; MS [*m*/*z* (relative intensity)] 324 (M^+, 3), 158 (100). Anal. Calcd for $C_{19}H_{20}N_2OS$: C, 70.34; H, 6.21; N, 8.63. Found: C, 70.28; H, 6.41; N, 8.69.

4.16. *N*-[2-(*tert*-Butylthio)phenyl]-*N*,1-dimethyl-1*H*-indole-3-carboxamide (16b)

To a well-stirred suspension of **14b** (1.1 g, 3.4 mmol) and tetra-*n*-butylammonium hydrogensulfate (0.3 equiv, 1 mmol, 0.35 g) in toluene (100 mL) was added all at once 50% aq NaOH solution (100 mL). The resulting two-layer mixture was heated to reflux and a solution of iodomethane (2.5 equiv, 8.5 mmol, 1.20 g) in toluene (10 mL) was added dropwise over 5 min. The resulting two phase mixture was maintained at reflux for 87 h. After cooling, the organic layer was collected and washed with water several times (until washings were neutral to litmus), dried over Na_2SO_4, and evaporated in vacuo to yield an off-white solid. Purification by column chromatography (chloroform/ether 9:1) gave**16b** as a white solid (0.87 g, 73%). Mp 156–158 °C; IR 1630 cm^{-1}; ^{1}H NMR δ 8.34–8.41 (m, 1H), 7.59 (d, J=7.72 Hz, 1H), 7.31–7.39 (m, 2H), 7.28 (ddd, J=7.71, 2.12 Hz, 1H), 7.17–7.22 (m, 2H), 7.10–7.16 (m, 1H), 5.81 (s, 1H), 3.43 (s, 6H), 1.29 (s, 9H); ^{13}C NMR δ 166.1, 147.6, 136.5, 136.0, 131.6, 129.0, 128.9, 128.2, 127.3, 122.6, 122.3, 121.0, 109.8, 108.9, 46.7, 32.8, 31.6; MS [*m*/*z* (relative intensity)] 295 (12), 263 (21), 158 (100).

4.17. *N*-[2-(Ethylsulfinyl)phenyl]-*N*,1-dimethyl-1*H*-indole-3-carboxamide (17a)

Yield 72%; mp 188–189 °C (acetone); IR 1627, 1014 cm^{-1}; ^{1}H NMR (200 MHz, taken at 100 °C in DMSO-d_6) δ 8.25–8.31 (1H, m), 7.96–8.01 (1H, m), 7.19–7.60 (7H, m), 6.25 (1H, s), 3.54 (3H, s), 3.46 (3H, s), 2.56–2.80 (2H, m), 1.12 (3H, t, J=6.6 Hz); ^{13}C NMR δ 167.0, 143.3, 143.1, 137.4, 133.5, 133.2, 133.0, 130.3, 121.9, 124.3, 123.7, 123.1, 123.0, 110.6, 110.5, 50.8, 49.5, 34.5, 7.3; MS [*m*/*z* (relative intensity)] 340 (M^+, 0.2), 158 (100). Anal. Calcd for $C_{19}H_{20}N_2O_2S$: C, 67.03; H, 5.92; N, 8.23. Found: C, 67.25; H, 6.10; N, 8.27.

4.18. *N*-[2-(*tert*-Butylsulfinyl)phenyl]-*N*,1-dimethyl-1*H*-indole-3-carboxamide (17b)

To an ice-cooled solution of **16b** (0.82 g, 2.30 mmol) in CH_2Cl_2 (50 mL) was added slowly a solution of *m*-CPBA (77%, 1.1 equiv, 3.32 mmol, 0.57 g) in CH_2Cl_2 (10 mL). The resulting mixture was stirred at 0 °C for 15 min and then put it in a freezer (−8 °C) overnight. The reaction mixture was then poured into 5% aq $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (50 mL). The combined organic layer was washed with distilled water, dried, and concentrated in vacuo. Column chromatography (acetone/CH_2Cl_2, 1:1) gave white solid (0.42 g, 49%). Mp 159–160 °C; IR 1631, 1030 cm^{-1}; ^{1}H NMR and ^{13}C NMR were not well-resolved due to presence of rotational isomers; MS [*m*/*z* (relative intensity)] 294 (35), 158 (100).

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Supplementary data

Experimental procedures for 2-(ethylthio)-*N*-methylaniline, 2-(*tert*-butylthio)-*N*-methylaniline, ethyl *N*-methylindole-2-carboxylate, **1b**, **2b**, **3ab**, **4a**, **5ab**, **6ab**, **7bc**, **8abc**, and the thermal and TFAA-promoted cyclization of **8b**; ^{1}H NMR and ^{13}C NMR spectra for **1b–3b**, **5b–8b**, **7c**, **10**, **14b**, and **16b**; ^{1}H NMR for **4b** and **9**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.09.050.

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