Intramolecular Sulfoxide Electrophilic Sulfenylation in 1- and 3-Acylindoles

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Heating 1-(2-ethylsulfinyl)benzoylindole (**1**) in refluxing *p*-xylene [thermal Sulfoxide Electrophilic Sulfenylation (SES)] produces indolo[2,1-*b*][1,3]benzothiazin-12-one (**2**) in 66% yield. Similar treatment of 1-methyl-3-(2-ethylsulfinyl)benzoylindole (**8**) provides three products: sulfide **7** and cyclized products **9** and **10** in 10, 19 and 15% yield, respectively. Conversion of **10** to **9** under the reaction conditions is demonstrated and a spirocyclic intermediate **12**, which may form from both **9** and **10** but undergoes only preferential *S*-migration, is postulated to account for the rearrangement.

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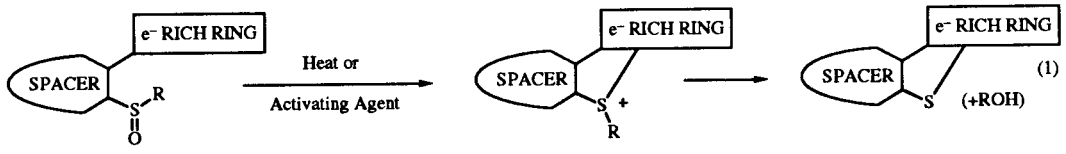
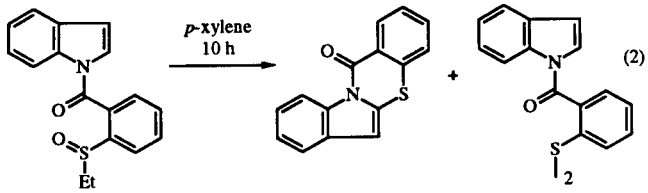
Use of sulfoxides as sulfenylating agents for electron-rich pyrroles is a useful technique for heterocyclic synthesis (eq 1) [1]. We now report the cyclization *via* sulfoxide electrophilic sulfenylation (SES) of simple 1- and 3- acyl indoles.



The 1-acylindole (**1**) was easily prepared from indole and 2-(ethylthio)benzoyl chloride followed by oxidation. Refluxing **1** in *p*-xylene for 10 hours caused a gradual replacement of starting material with a compound having a higher R_f value. Purification of the reaction mixture by column chromatography gave **2** as a bright yellow solid in 66% yield and a trace of a second compound thought to be the disulfide **3** (eq 2). The structure of **2** was apparent from spectroscopic data. In brief, peaks for the ethyl side-chain were absent from the ^1H and ^{13}C nmr spectra, the two doublets for the protons on C-2 and C-3 in the proton nmr of starting material were replaced by a singlet at δ 6.66 for the remaining C-3 proton, a very strong molecular ion peak appeared at m/z 251, and an amide carbonyl was evidenced by absorptions at 1680 cm^{-1} in the ir spectrum and at δ 159.8 in the ^{13}C nmr spectrum.



1 2 3

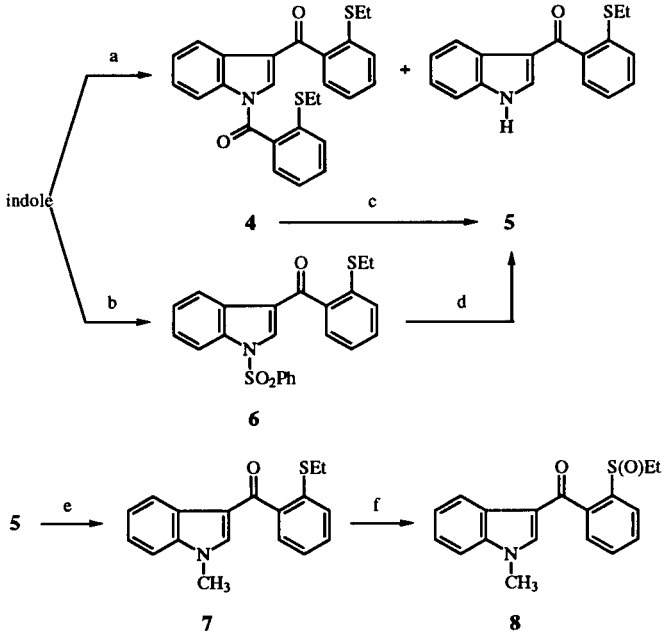
Encouraged by the straightforward preparation of **3**, we next turned our attention to 1-methyl-3-(2-ethylsulfinylbenzoyl)indole (**8**). Previous experience in our laboratory has shown that, generally, heterocycles having a free N-H proton do not cyclize as well nor are they or their cyclization products as readily soluble in common organic solvents as the *N*-alkylated counterpart. Indeed, the sulfoxide prepared from **5** decomposes to an intractable tar upon heating in *p*-xylene solution.

The sulfide precursor to **8**, compound **5**, was prepared by two routes as discussed below but neither gave a good yield of **5**. Although acylimidazolides are reported to have high reactivity towards Grignard reagents [2], in our hands indolyl magnesium bromide gave a low conversion to acylated indoles when treated with the *ortho*-substituted imidazolide, 1-(2-ethylthiobenzoyl)imidazole. Acylation reactions using indolyl magnesium bromide and acid chlorides produce large amounts of 1,3-diacylated product [3] and we had hoped use of the imidazolide would reduce the amount of this byproduct. However, nearly equal yields of 3-acyl, **5**, and 1,3-diacyl, **4**, products were formed (Scheme 1). Compound **4** could be converted to additional **5** by alkaline hydrolysis.

Alternatively, **5** could be prepared by Friedel-Crafts acylation of 1-phenylsulfonylindole [4] catalyzed by aluminum trichloride followed by removal of the phenylsulfonyl group from **6** by alkaline hydrolysis [5]. Although compound **6** could be isolated, purified and hydrolyzed to **5**, we found the yield to be significantly better if the crude acylation product was subjected directly to hydrolysis due to large losses of **6** during chromatography. Methylation to **7** followed by oxidation [6] gave **8**.

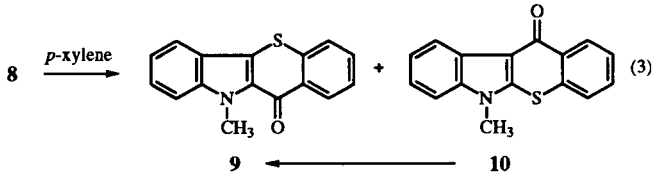
When **8** was heated in refluxing *p*-xylene until starting material was no longer detected by tlc (16 hours), **10** and rearranged compound **9** were formed (in 19% and 15% yield, respectively). The only other product isolated was

Scheme 1



reagents: (a) 1. EtMgBr, Et_2O. 2. 1-(2-ethylthiobenzoyl)imidazole. (b) 1. $PhSOCl_2$. 2. $AlCl_3$, CH_2Cl_2. 3. 2-ethylthiobenzoyl chloride. (c) $NaOH/CH_3OH/H_2O/CH_2Cl_2$. (d) $K_2CO_3/CH_3OH/H_2O$. (e) CH_3I, TBA HSO_4. (f) $NaIO_4$, CH_3OH/H_2O.

the deoxygenated compound **7** (10%). Sulfoxide **8** was chosen for this study because both the expected cyclization product **10** [7] and its regioisomer **9** [8] are known compounds. They were expected to be readily differentiated from each other; the reported melting points differ by 31° and the reported nmr spectra show very different *N*-methyl environments [9].

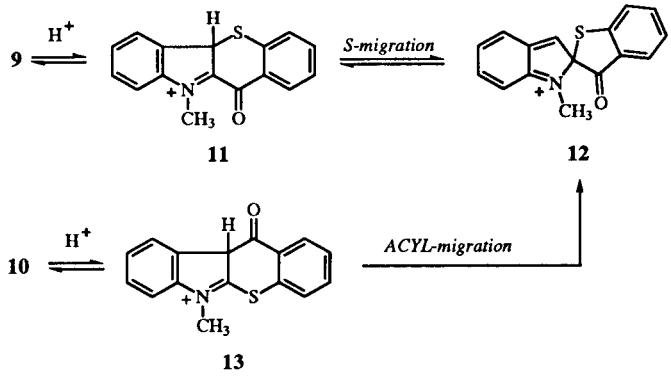


Having both compounds available was important because of possible structural ambiguity due to substituent migration during reaction and acid-catalyzed isomerization of the products after cyclization. There are many examples in the indole literature of skeletal rearrangement causing confusion about the structures of products formed in seemingly straightforward reactions [10].

In order to gain some insight into whether **9** was formed during the cylization process (*via* a spirocyclic intermediate [11]) or formed from **10** after cyclization, each of these compounds was returned to refluxing *p*-xylene. Compound **10** was partially converted into **9** over 14 hours, but the reverse process *i.e.*, conversion of **9** into **10** did not occur. Since **9** may arise from **10** under the reaction conditions, no conclusions may be made about a spirocyclic intermediate during the cyclization. However the rearrangement after cyclization is interesting and unexpected and provides indirect support for a spirocyclic intermediate.

Under acidic conditions, 2-acetyl [12] and 2-benzoyl [13] indole rearrange to corresponding 3-isomer, while 3-thioalkylindoles [14] rearrange to 2-thioalkylindoles (but not *vice versa*). These rearrangements depend on the rate of formation and stability of protonated 2*H*- and 3*H*-indoles such as **11** and **13** (Scheme 2) and on the migratory aptitude of a thioalkyl or an acyl group *relative to a proton* in these intermediates. The interconversion of **9** and **10** depends not only on these factors but also upon the formation of a spirocyclic intermediate, **12**, and the migratory aptitude of *arylthio relative to acyl* in this intermediate. The intermediacy of **12** readily accounts for the apparent contradictory rearrangement of **10** to **9**. Indoles **9** and **10** would be expected to protonate predominantly at C-3 [15] giving **11** and **13**, respectively (Scheme 2). Each

Scheme 2



could then transform into the same spirocyclic intermediate **12** by migration of their respective 3-substituents [16]. However **12**, once formed, has only one pathway available, *i.e.*, preferential sulfur migration to give **9** *via* **11** [17]. Consequently one would predict that **9** would be stable to the reaction conditions whereas **10** would be converted into **9**, as observed. Intermediate **13** is expected to be particularly easily formed relative to **11** due to the ability of the sulfur substituent at C-2 to assist stabilization of the adjacent charge [18]. The conversion of **10** into **9** is slow due to the small amount of acid available in the system. The probable source is the glass wall of the reaction vessel; added acid promotes decomposition as well as migration.

Although these arguments call for the intermediacy of spirocyclic intermediates, much if not all previous work

Table

Summary of Selected Physical and Spectral Data

Compound No. Molecular formula	mp (°C)	Partial ^{13}C nmr C=O	N-CH_3	CH_2	CH_3	M^+ m/z	Base peak m/z	Calcd./Found C	H	N
1 [a]								68.66	5.08	4.71
$C_{17}H_{15}NO_2S$	118-120	165.8		50.7, 6.5		297	181	68.72	5.07	4.75
2 [b]				159.8, 135.6, 133.4, 133.1, 131.2,				71.69	3.61	5.60
$C_{15}H_9NOS$	167-170			129.0, 126.3, 126.0, 125.1, 124.6, 123.6, 123.4, 118.9, 117.0, 104.0 [c]		251	251	71.71	3.77	5.59
4		191.4						70.08	5.20	3.14
$C_{26}H_{23}NO_2S_2$	134-135	167.8		28.5, 27.8, 14.1, 13.8		294	181	69.97	5.36	3.01
5 [d]								72.57	5.37	4.98
$C_{17}H_{15}NOS$	130-132	192.5		28.5, 14.5		251	251	72.50	5.45	4.80
7	205-207	191.4	34.2	28.6, 14.6		295	266	—	—	—
8								62.23	6.09	4.03
$C_{18}H_{17}NO_2S \cdot 2H_2O$	152-155	189.2	34.3	51.3, 7.1		311	146	62.06	6.06	4.00

[a] Ir (potassium bromide): 1660, 1340, 1450 cm^{-1}. [b] Ir (potassium bromide): 1680 cm^{-1}. [c] All peaks reported. [d] Ir (potassium bromide): 3200, 1600 cm^{-1}.

proposing the intermediacy of spirocyclic intermediates in pyrrole and indole sulfides [19] must be considered suspect in view of the recent work of Hamel [14b], Muchowski [9a] and others [14a,20] in which 2-thioalkylindoles and thioalkylpyrroles were found to readily undergo sulfur side-chain migration under acidic conditions. In the literature, presumed spirocyclic intermediates were generated by acyl cyclization in compounds containing a C-S bond, a bond quite prone to alkylthio side chain migration. In the "corresponding" sulfoxide system however, a spirocycle may be generated by C-S bond formation in a "migration-free" acyl derivative (various benzoyl indole derivatives are recovered unchanged after prolonged reflux in *p*-xylene solution). Our current work focuses on further establishing the intermediacy of spirocycles in this and related sulfoxide-containing indole systems.

EXPERIMENTAL

Melting points are reported uncorrected. The nmr spectra were recorded at 200 MHz for ^1H and 75 MHz for ^{13}C in deuteriochloroform solutions unless otherwise specified. The term "work-up" refers to the following sequence: Filtration of the reaction mixture, partitioning of the filtrate between water and dichloromethane in a separatory funnel followed by drying of the organic layer over sodium sulfate and solvent evaporation on a rotary evaporator *in vacuo*. Elemental analyses were performed by Spang Microanalytical Laboratory in Eagle Harbor, MI, or Galbraith Laboratory, Inc. in Knoxville, TN. Physical and spectral data are summarized in the Table.

1-(2-Ethylthio)benzoylindole.

To a well stirred solution of indole (2.11 g, 18 mmoles) and tetrabutylammonium hydrogensulfate (0.0610 g, 0.18 mmoles) in dichloromethane (60 ml) was added 2 g (50 mmoles) of sodium hydroxide (powdered), followed by 2-ethylthiobenzoyl chloride (5.40 g, 27 mmoles). The reddish brown mixture was stirred in an ice bath for 35 minutes at which time tlc indicated the reaction was complete. After work-up, the crude product was chromatographed (silica gel, dichloromethane:hexane (1:1)) to yield 7.82 g (56%) of the pure 1-acylated product: mp 80-81°; ir (potassium bromide): 1740 cm^{-1}; ^1H nmr: δ 8.43 (d, J = 8 Hz, 1H), 7.64-7.28 (m, 7H), 7.05 (d, J = 4 Hz, 1H), 6.60 (d, J = 4 Hz, 1H), 2.93 (q, J = 7 Hz, 2H), 1.25 (t, J = 7 Hz, 3H).

Anal. Calcd. for $C_{17}H_{15}NOS$: C, 72.57; H, 5.37; N, 4.98. Found: C, 72.59; H, 5.27; N, 5.03.

Preparation of Sulfoxides.

The procedure of Leonard and Johnson [6] was used.

1-(2-Ethylsulfinyl)benzoylindole (**1**).

This compound was obtained in 73% yield; ^1H nmr: δ 8.32 (d, J = 8 Hz, 1 H), 8.23 (d, J = 8 Hz, 1 H), 7.85-7.25 (m, 6 H), 7.08 (d, J = 4 Hz, 1 H), 6.63 (d, J = 4 Hz, 1 H), 3.28 (dq, 1 H), 2.93 (dq, 1 H), 1.32 (t, J = 7 Hz, 3 H).

1-Methyl-3-(2-ethylsulfinyl)benzoylindole (**8**).

This compound was obtained in 91% yield; ^1H nmr: δ 8.32 (m, 1H), 8.23 (dd, J = 1.5 Hz, 8.18 Hz, 1H), 7.77-7.31 (m, 7H), 3.82 (s, 3H), 3.36 (dq, 1H), 2.94 (dq, 1H), 1.32 (t, J = 7.49 Hz, 3H).

Indolo[2,1-*b*][1,3]benzothiazin-12-one (**2**).

Sulfoxide **1** (2.40 g) was dissolved in 90 ml of *p*-xylene and refluxed until there was no spot for starting material on tlc (8 hours). Within 30 minutes of the reaction, the mixture became orange-red and gradually changed to red then to black-red. Solvent evaporation followed by column chromatography (silica gel, methylene chloride/hexane) gave two compounds: The first was compound **2** (1.34 g, 66%); ^1H nmr: δ 8.81 (m, 1H), 8.54 (d, J = 8 Hz, 1H), 7.72-7.23 (m, 6H), 6.66 (s, 1H).

The second compound (110 mg) was not fully characterized but the nmr and mass spectra support the disulfide structure **3**.

3-[2-(Ethylthio)benzoyl]indole (**5**).

a. *via* 1-(2-Ethylthio)benzoylimidazole.

Freshly prepared (2-ethylthio)benzoyl chloride (8.00 g, 40

mmoles) in 20 ml of freshly distilled tetrahydrofuran was added to a stirred solution of imidazole (4.97 g, 70 mmoles, 1.75 equivalents) in tetrahydrofuran (150 ml) at 0° under nitrogen over a period of 1 hour. After an additional 1 hour at 0°, the mixture was filtered and the precipitate was washed with tetrahydrofuran. Evaporation of the filtrate gave 10.20 g of the liquid imidazolide as a single spot on tlc; ^{1}H nmr: δ 7.86 (s, 1 H), 7.54-7.26 (m, 5 H), 7.13 (d, J = 1.52 Hz, 1H), 2.92 (q, J = 7.38 Hz, 2H), 1.24 (t, J = 7.25 Hz, 3H); ms: m/z 232 (M^+, 5), 165 (100). This compound was used directly in the next reaction.

Ethyl magnesium bromide (from magnesium (0.48 g, 20 mmoles) and bromoethane (2.20 g, 20 mmoles) in 10 ml of anhydrous ether and indole (2.34 g, 20 mmoles in 5 ml of ether) were mixed and refluxed for 30 minutes. After cooling, the imidazolide (4.64 g, 20 mmoles) in ether (15 ml) was added dropwise with stirring to the reaction mixture. With the addition of each drop of imidazolide, the mixture turned cloudy yellow which disappeared with stirring. Gradually a reddish thick creamy solid formed at the bottom. After stirring 12 hours at room temperature, the reaction mixture was decomposed with ice. The crude solid was extracted with chloroform, washed with 1% hydrochloric acid then 5% sodium hydrogensulfate, dried (sodium sulfate) and the solvent evaporated. Chromatography (silica gel) gave two products, **4** and **5**, along with recovered indole (1.25 g). Compound **4** (17%), is a white crystalline solid; ^{1}H nmr: δ 8.27 (m, 1H), 8.18 (m, 1H), 7.47-7.13 (m, 11H), 2.87 (q, J = 7.35 Hz, 4H), 1.21 (t, J = 7.17 Hz, 6H).

Compound **5** was obtained in 22% yield; ^{1}H-nmr: δ 9.53 (brs, 1 H), 8.36 (m, 1H), 7.43-7.15 (m, 8H), 2.85 (q, J = 7.41 Hz, 2H), 1.17 (t, J = 7.39 Hz, 3H).

b. *via* Friedel-Crafts Reaction of 1-Phenylsulfonyl-3-(2-ethylthio)benzoylindole (**6**).

To a mechanically stirred suspension of aluminum trichloride (8.00 g, 60 mmoles) in 100 ml of dichloromethane at 25° was added 2-(ethylthio)benzoyl chloride (6.00 g, 30 mmoles) and the mixture was stirred for 15 minutes. A solution of 1-phenylsulfonylindole (2.57 g, 10 mmoles) in 20 ml of dichloromethane was added dropwise and the mixture stirred for 2 hours at 25° and then poured into crushed ice (160 ml). After work-up and column chromatography (silica gel, dichloromethane/hexane), **6** was obtained as a greenish yellow powder (0.82 g, 20%), mp 182-185°; ^{1}H nmr: δ 8.39-8.35 (m, 1H), 7.98-7.84 (m, 4H), 7.56-7.29 (m, 9H), 2.88 (q, J = 7 Hz, 2H), 1.22 (t, J = 7 Hz, 3H); ms: m/z 421 (M^+, 17.6), 144 (100.0).

The phenylsulfonyl group of compound **6** was removed as follows: A magnetically stirred solution of **6** (2.50 g of crude product from the previous reaction), potassium carbonate (1.66 g, 12 mmoles), methanol (80 ml) and water (20 ml) was refluxed under nitrogen for 2.5 hours. The methanol was evaporated *in vacuo* and the remaining aqueous mixture was extracted thoroughly with dichloromethane. After work-up and recrystallization (methylene chloride/hexane), **5** was obtained as a yellowish green powder (0.57 g, 33% from 1-phenylsulfonylindole).

1-Methyl-3-(2-ethylthio)benzoylindole (**7**).

A mixture of 3-(2-ethylthio)benzoylindole (**5**) (0.70 g, 2.5 mmoles), methyl iodide (0.71 g, 5 mmoles, 2 equivalents), tetrabutylammonium hydrogensulfate (0.08 g, 0.25 mmole, 0.1 equivalent), crushed sodium hydroxide (0.30 g, 7.5 mmoles, 3 equivalents) and 10 ml of dichloromethane was stirred at room temperature overnight. Filtration and concentration of the filtrate gave the crude product which was recrystallized from ether/hexane to give the *N*-methylindole derivative **7** (0.73 g, 99%); ^{1}H nmr: δ 8.38 (m, 1H), 7.47-7.18 (m, 8H), 3.75 (s, 3H), 2.90 (q, J = 7.38 Hz, 2H), 1.23 (t, J = 7.37 Hz, 3H). This compound was oxidized directly to sulfoxide **8**.

Cyclization of Sulfoxide **8**.

A 0.09 *M* solution of 0.63 g **8** in *p*-xylene was refluxed for 16 hours. Column chromatography (silica gel, dichloromethane) gave three products, **7**, **9** and **10**.

Compound **9** was obtained in 19% yield, mp 170-171° (lit mp 165° [8]); ^{1}H nmr: δ 8.73 (dd, J = 2.0, 7.69 Hz, 1H), 7.88-7.49 (m, 6H), 7.31-7.23 (m, 1H), 4.42 (s, 3H); uv (ethanol): [λ max (nm)] 206, 234, 290, 326, 404 [lit uv (methanol): 231 (4.44), 287 (4.35), 323 (4.30), 400 (3.87).

Compound **10** was obtained in 15% yield, mp 193-195° (lit mp 196° [7]); ^{1}H nmr: δ 8.81-8.76 (m, 1H), 8.70-8.64 (m, 1H), 7.67-7.57 (m, 3H), 7.39 (d, J = 3.5 Hz, 3H), 3.83 (s, 3H); uv (ethanol): [λ max (nm)] 206, 224, 244, 282.

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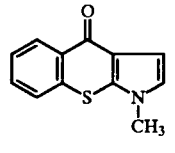
[9] The reported value is δ 3.46 in **10** for the *N*-methyl signal. This value, however, is not consistent with the observed *N*-methyl chemical shift for the closely related pyrrole derivative **i** which has a value of δ 3.72 [9a]. The value we observe for **10** (δ 3.83) more closely matches the latter value. This leads us to believe the published value for the *N*-Me signal of **10** is a misprint in the original article [7]. The value we observe for **9** (δ 4.42) is consistent with both the literature value (δ 4.38) [8] and that observed for **ii** (δ 4.26) [9b]; [a] J. DeSales, R. Greenhouse, and J. M. Muchowski, *J. Org. Chem.*, **47**, 3668 (1982); [b] K. A. Tafel, Ph.D. Thesis, Michigan Technological University, 1992, p 120.



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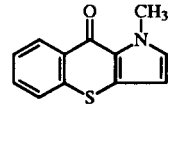

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