Nonreductive Desulfenylation of 3-Indolyl Sulfides. Improved Syntheses of 2-Substituted Indoles and 2-Indolyl Sulfides

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Desulfenylation of 3-indolyl sulfides to the corresponding 3-unsubstituted indoles is usually carried out under reductive conditions, thus accommodating only substituents which are resistant to reduction. We have developed a nonreductive procedure for removal of a sulfide at the 3-position of indoles, using trifluoroacetic acid in the presence of a thiol as trapping agent, which is compatible with a large array of functionalities on the indole ring. In addition, the desulfenylation occurs selectively at the 3-position of the indole, and sulfide groups at other positions of the molecule remain untouched. Thus, indole 2,3-bis-sulfides are selectively desulfenylated at the 3-position, affording 3-unsubstituted 2-indolyl sulfides. This methodology broadens the use of sulfide as a protecting group for the 3-position of indoles.

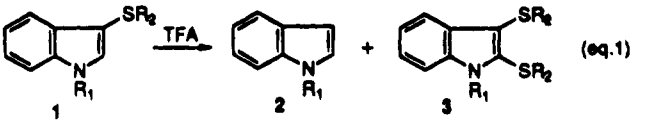
Introduction

The quest for efficient methods of preparing indoles unsubstituted in the 3-position remains a major objective in indole chemistry. In particular, much effort is directed toward the design of general approaches to 2-substituted indoles in which the most nucleophilic 3-position is available for subsequent substitution, as can be seen by the number of recent publications addressing this subject.[1]

Recently,[2] our uncovering of an unexpected, intermolecular mechanism for the acid-catalyzed isomerization of 3-indolyl sulfides to corresponding 2-indolyl sulfides[3] led us to the discovery of a novel nonreductive method for the desulfenylation of 3-indolyl sulfides.[4] We present herein a detailed account of the discovery of this methodology and of its usefulness in the preparation of a wide variety of 2-substituted indoles, previously unattainable by classical desulfurization techniques (e.g. Gassman synthesis).[5] In addition, we demonstrate how the selectivity of the process allows efficient access to 2-indolyl sulfides via preferential desulfenylation of the easily obtainable indole 2,3-bis-sulfides.

Results and Discussion

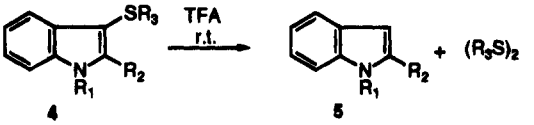
We recently[2] demonstrated that the predominant mechanism of the TFA-catalyzed rearrangement of 3-indolyl sulfides **1** to the isomeric 2-indolyl sulfides[3] features an initial rapid disproportionation of the 3-sulfide into a 2,3-unsubstituted indole **2** and a corresponding indole 2,3-bis-sulfide **3** (eq 1). This proceeds via an initial desulfenylation of the protonated form of **1**, with transfer of the sulfide to a molecule of nonprotonated substrate, while the unsubstituted **2** suffers reversible dimerization in the strongly acidic medium.



1 2 3

With the aim of exploring the potential utility of the desulfenylation step, we reasoned that the presence of a substituent at the 2-position of the 3-indolyl sulfide should prevent the dimerization of the desulfenylated product, thus allowing its isolation. Although this process would be expected to favor resulfenylation of the product **5** (eq 2, top), we anticipated that slow concomitant decomposition of the acyloxy sulfide CF_3COOSR_3 to the corresponding disulfide[6] $(R_3S)_2$ might eventually drive the equilibrium in the desired direction. Initial applications of this concept, listed in Table 1, convinced us that the sluggishness of the process ruled out its synthetic usefulness.

Table 1. TFA-Catalyzed Desulfenylation of 3-Indolyl Sulfides



4 5

substrate	R_1	R_2	R_3	time (h)	% **5**	% R_3SSR_3
a	H	CH_3	CH_3	5.5	35	–
b	H	CH_3	Ph	23	49	59
c	H	Ph	Ph	20	62	65
d	CH_3	CH_3	Ph	23	9	54

Since the sole driving force for this desulfenylation resided in the slow breakdown of the acyloxy sulfide, we considered the possibility of introducing an exogenous nucleophile, which would react irreversibly with the acyloxy sulfide, thus greatly favoring the desulfenylation (eq 2, bottom). Initial studies (Table 2) using anisole (5 equiv) or toluene (as cosolvent) did not lead to appreciable improvement, presumably due to the fact that **5** is a

† This paper is dedicated to the memory of Nicolas Zajac, who died in a tragic sports accident in June 1992. He performed a portion of the work during a student work term.

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(1) The following are representative of the many recent papers on the subject: (a) Sadanandan, E. V.; Srinivasan, P. C. *Synthesis* **1992**, 648. (b) Izumi, T.; Sugano, M.; Konno, T. *J. Heterocycl. Chem.* **1992**, *29*, 899. (c) Somei, M.; Kobayashi, T. *Heterocycles* **1992**, *34*, 1295. (d) Nagarathnam, D. *J. Heterocycl. Chem.* **1992**, *29*, 1371.

(2) Hamel, P.; Girard, Y.; Atkinson, J. G. *J. Org. Chem.* **1992**, *57*, 2694.

(3) Plate, R.; Ottenheijm, H. C. J. *Tetrahedron* **1986**, *42*, 4511.

(4) Hamel, P.; Zajac, N.; Atkinson, J. G.; Girard, Y. *Tetrahedron Lett.* **1993**, *34*, 2059.

(5) Gassman, P. G.; van Gergen, T. J.; Gilbert, D. P.; Cue, B. K., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 5495.

(6) (a) Barton, D. H. R.; Nakano, T.; Sammes, P. G. *J. Chem. Soc. (C)* **1968**, 322. (b) Morishita, T.; Furukawa, N.; Oae, S. *Tetrahedron* **1981**, *37*, 3115. (c) Haas, A.; Lieb, M.; Zhang, Y. *J. Fluorine Chem.* **1985**, *29*, 297.

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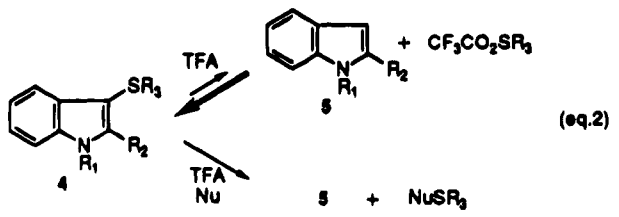
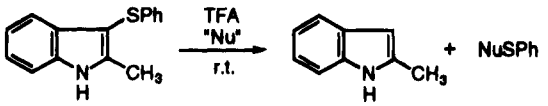


(eq.2)

much stronger nucleophile than either of these aryls. However, thiols proved to be very efficient trapping agents (entries 4–7) as demonstrated by the reduced reaction times and improved yields of the desulfenylated product **5**. The selection of these thiols was based on the ease of separating the excess of trapping agent as well as trapping product (mixed disulfide) from **5** via simple extraction with dilute aqueous acid or alkali. The results obtained with thiosalicyclic acid (entries 6 and 7) led us to select it as the trapping agent of choice in further studies, since it is an inexpensive, nonvolatile solid, and hence not very odorous.

Table 2. TFA-Catalyzed Desulfenylation with Trapping Agent



4b **5b**

example	"Nu" (equiv)	time (h)	% **5b**
1	none	23	49
2	$PhOCH_3$ (5)	17	63
3	$PhCH_3$ (cosolvent)	17	50
4	$HSCH_2CH_2NH_2$ (5)	5	87
5	$HSCH_2CH_2COOH$ (5)	1	88
6	*o*-HSC_6H_4COOH (5)	0.75	90
7	*o*-HSC_6H_4COOH (2)	0.5	88

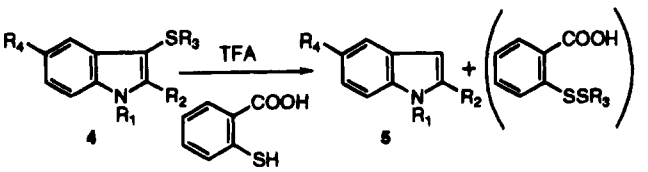
The most striking advantage of this desulfenylation process is that it is performed under nonreductive conditions, in contrast to previous desulfurization techniques (e.g. Raney Nickel). We undertook a study of the applicability of our method to substrates bearing functionalities which would be incompatible with Raney Nickel conditions, with emphasis on a variety of substituents on the phenyl portion of the indole ring.

This variety was provided by the use of two complementary indole syntheses: condensation of β-keto sulfides with appropriately substituted anilines (Gassman synthesis) and phenylhydrazines (Fisher indole synthesis).[8] The former approach is preferred when the ring substituent is electron-withdrawing, such as nitro or nitrile, whereas electron-rich substituents are best provided by the Fischer indolization. These results are easily rationalized by examination of the respective reaction mechanisms. The preparation of these substrates, most of which are novel compounds, is detailed in the Experimental Section.

Typical conditions for the desulfenylation of 3-indolyl sulfides were as follows: a mixture of 1 mmol of 3-indolyl sulfide **4** and 2 mmoles of thiosalicyclic acid in 7 mL of TFA was stirred at room temperature or reflux until TLC monitoring showed completeness of the reaction. In many cases, the desulfenylation proceeded very rapidly,

(7) For a review of indole dimerization see: Smith, G. G. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R.; Ed.; Academic Press: New York, 1963; Vol. 2, pp 300–09.
(8) Wieland, T.; Ruehl, K. *Chem. Ber.* **1963**, *96*, 260.

Table 3. Desulfenylation of 3-Indolyl Sulfides with TFA and Thiosalicylic Acid



4 **5**

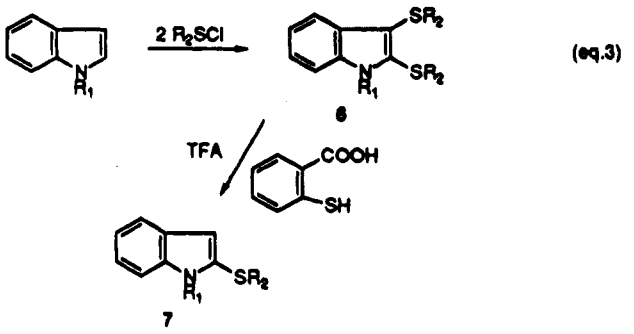
example	R_1	R_2	R_3	R_4	temp (°C)	time (h)	% **5**
a	H	CH_3	CH_3	H	72	0.5	90
b	H	CH_3	Ph	H	rt	0.5	88
c	H	Ph	Ph	H	72	1	66
d	CH_3	CH_3	Ph	H	72	0.5	94
e	CH_3	Ph	t-Bu	H	72	1.5	84
f	H	CH_3	CH_3	NO_2	72	0.25	67
g	H	CH_3	Ph	NO_2	72	0.25	51
h	H	CH_3	Ph	OCH_3	rt	1.5	96
i	H	CH_3	CH_3	$COCH_3$	rt	0.5	59
j	H	CH_3	Ph	SCH_3	rt	0.25	93
k	H	CH_3	Ph	SO_2CH_3	rt	0.25	83
l	H	CH_3	Ph	CN	rt	0.25	83
m	H	CH_3	Ph	O-Allyl	rt	1.5	94
n	H	CH_3	Ph	Br	rt	0.5	91
o	H	CH_3	Ph	I	72	0.25	81
p	CH_2Ph	CH_3	Ph	H	rt	1	86
q	H	CO_2CH_3	Ph	H	60	0.25	91

within minutes at room temperature. Other substrates required heating and/or longer reaction times. A simple workup consisting of evaporation of the TFA followed by partition of the residue between an organic solvent and dilute aqueous alkali afforded crude **5**, which were purified by column chromatography. The generally excellent yields obtained with the broad array of substrates studied, as listed in Table 3, illustrate the wide applicability and usefulness of the process, which offers several advantages over Raney Nickel desulfurization, the most notable of which is its nonreductive nature, so that functionalities such as nitro, halogen (even iodide), nitrile, olefin, etc., are unaffected. In addition, there is no handling of messy, pyrophoric materials and the desulfenylation occurs exclusively at the 3-position of the ring, so that a sulfide at another position remains untouched (e.g. substrate **4j**). It should also be noted that substrate **4q** bearing the electron-withdrawing carbomethoxy substituent in the 2-position also undergoes smooth desulfenylation.

The use of 2 mol equiv of thiosalicyclic acid is based on preliminary experiments and was retained for consistency in comparison of the results. A slight excess of 1 mol equiv would most likely afford acceptable results, as demonstrated by the experiment described below in which 1.1 equiv of methyl thiosalicylate was used in order to isolate and identify the mixed disulfide trapping product. An experiment on substrate **4b** using 0.25 equiv of thiol resulted in slow desulfenylation, barely more rapid than in the absence of thiol. In a control experiment, where TFA was replaced by CH_2Cl_2, in the presence of 2 equiv of thiosalicyclic acid, no desulfenylation of **4b** occurred on prolonged stirring at room temperature.

One major limitation of the process resides in the fact that a substituent must be present in the 2-position of the substrate, since absence of a substituent could lead to isomerization of the 3-sulfide to the 2-sulfide and/or dimerization of the 2,3-unsubstituted indole[7] after desulfenylation.

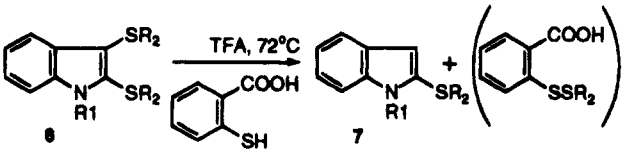
Selective Desulfenylation of Indole 2,3-Bis-Sulfides to 2-Indolyl Sulfides. The selectivity of our



(eq.3)

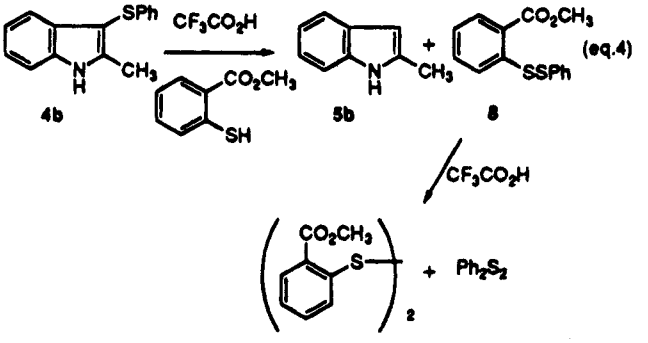
desulfenylation technique at the 3-position of the indole ring prompted us to examine a further useful application. To date, two approaches are available for the synthesis of 3-unsubstituted 2-indolyl sulfides: acid-catalyzed isomerization of 3-indolyl sulfides, affording variable yields of rearranged product depending on the nature of the sulfide, and alkylation of thioindoles,[9] requiring the tedious and unpleasant preparation of the required thioindoles from the corresponding oxindoles. However, indole 2,3 bis-sulfides **6** are readily obtained in one step[10] by double sulfenylation of indole using 2 equiv of a sulfenyl chloride easily generated from an appropriate disulfide and sulfuryl chloride. When subjected to the desulfenylation conditions described above, these bis-sulfides suffer selective removal of the sulfide at the 3-position of the ring, while the sulfide at the 2-position remains untouched. The result is a simple, efficient two-step synthesis of 3-unsubstituted 2-indolyl sulfides **7** as outlined in eq 3. The efficiency of the selective desulfenylation is demonstrated by the results listed in Table 4.

Table 4. Selective Desulfenylation of Indole 2,3-Bis-Sulfides



example	R_1	R_2	time (h)	% 7
a	H	CH_3	2.5	94
b	H	CH_2CH_3	1.5	82
c	H	$CH_2CH_2COOCH_3$	1.0	80
d	H	Ph	0.5	91
e	H	4-ClPh	0.25	87
f	H	4-CH_3OPh	0.25	94
g	H	2-naphthyl	1.0	90
h	CH_3	CH_3	1.5	91
i	CH_3	Ph	0.25	92
j	CH_3	4-CH_3OPh	0.25	94
k	CH_2Ph	Ph	0.25	87

Isolation of Trapping Product. Initial attempts at isolating the mixed disulfide trapping product via esterification gave very low yields. An alternative was found in the use of methyl thiosalicylate as the trapping thiol (eq 4). When 2-methyl-3-phenylthioindole (**4b**) was stirred at room temperature in TFA with 1.1 equiv of methyl thiosalicylate for 45 min, after evaporation of the TFA, chromatography of the residual material afforded 84% of 2-methylindole (**5b**) and 43.5% of the expected mixed disulfide **8**;[11] both diphenyl disulfide and bis(o-carbomethoxyphenyl) disulfide were also observed but not quantified. The low yield of isolated **8** led us to examine its stability in TFA solution: when a sample of **8** was stirred at room temperature in TFA, TLC showed both diphenyl disulfide and bis(o-carbomethoxyphenyl) disulfide being generated within minutes, thus indicating that the trapping product **8** is slowly decomposed during the course of the desulfenylation. This would appear to also occur when thiosalicyclic acid is used as trapping agent, as invariably, in all the cases studied, the disulfide corresponding to the SR_3 group is observed in the crude reaction product.



(eq.4)

The 3-Sulfide as Protecting Group. An interesting corollary to the application of this method is that the 3-sulfide group may be considered as a built-in protecting group for the 3-position of the indole. Indeed, various transformations can be effected at other positions on the ring without complications arising from the nucleophilicity of the 3-position. The concept of utilizing the sulfide as a protecting group has had very limited application,[12] in view of the reductive conditions that were previously required for its removal. The desulfenylation method that we present herein, which permits the presence of a much wider array of substituents on the indole ring, allows novel flexibility in the manipulation of indole derivatives. As a possible extension to this concept, a 3-unsubstituted indole may be easily sulfenylated, transformations effected elsewhere on the molecule, and the sulfide protecting group subsequently removed, liberating the 3-position for further modifications.

As an illustration of this concept, the sulfide group at the 3-position can be used to block C-alkylation and allow successful N-alkylation of the indole ring, especially in cases where the alkylating agent is valuable. Substrate **4p** of Table 3 was prepared by initial sulfenylation[13] of 2-methylindole (90%) and subsequent N-alkylation with benzyl bromide using NaH in DMF (95%); desulfenylation by our method led to **5p** in 86% yield.

Conclusion

We have developed an efficient, nonreductive method for the desulfenylation of 3-indolyl sulfides, by treatment with trifluoroacetic acid in the presence of a thiol trapping agent. This method affords good to excellent yields of 2-substituted indoles, and since it features a nonre-

(9) (a) Nakagawa, N.; Hino, T. *Tetrahedron* **1970**, *26*, 4491. (b) Baudin, J.-B.; Bekhazi, M.; Julia, S. A.; Ruel, O.; deJong, R. L. P.; Brandsma, L. *Synthesis* **1985**, 956.

(10) Anzai, K. *J. Heterocycl. Chem.* **1979**, *16*, 567.

(11) Modena, T.; Pavanetto, F.; Montanari, L.; Mazza, M.; Conti, B. *Farmaco, Ed. Sc.* **1985**, *40*, 803.

(12) (a) Mohan, B.; Nagarathnam, D.; Vedachalam, M.; Srinivasan, P. C. *Synthesis* **1985**, 188. (b) Rajeswaran, W. G.; Srinivasan, P. C. *Synthesis* **1992**, 835.

(13) Atkinson, J. G.; Hamel, P.; Girard, Y. *Synthesis* **1988**, 480.

ductive medium, it is applicable to substrates bearing substituents which most likely would not survive previous desulfurization techniques and allows the use of sulfide as protecting group for the 3-position of the indole ring. In addition, the desulfenylation occurs selectively at the 3-position of the indole ring, so that sulfide groups elsewhere in the molecule are not removed. This property allows efficient synthesis of 2-indolyl sulfides from easily obtainable indole 2,3-bis-sulfides.

Experimental Section

All reagents and solvents from commercial sources were used without further purification or drying. The use of an inert atmosphere was not required. Melting points were recorded using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer Model 681 spectrophotometer, and the values reported correspond to the largest or most characteristic absorptions. The 300 MHz proton NMR data were collected using a Bruker instrument. Chemical shifts are reported in ppm relative to TMS. Elemental analyses were provided by Galbraith Laboratories Inc., Knoxville, TN. The necessary anilines and phenylhydrazines were all commercially available, except for 4-(methylthio)phenylhydrazine which was prepared by the method of Demers and Klaubert.[14]

The β-keto sulfides were prepared by treatment of corresponding halomethyl ketones with appropriate thiols in the presence of Hunig's base and are known compounds.

Synthesis of 3-Indolyl Sulfides (4). Gassman Method: Preparation of 5-Cyano-2-Methyl-3-(phenylthio)-indole (4l). The method of P. Gassman[5] et al. was used. To a solution of 354 mg of 4-aminobenzonitrile (3 mmol) in 20 mL of CH_2Cl_2 at −70 °C there was slowly added a solution of 434 mg of *tert*-butyl hypochlorite (4 mmol) in 1 mL of CH_2Cl_2, resulting in a yellow solution. After 20 min, there was added dropwise a solution of 664 mg of 1-(phenylthio)-2-propanone (4 mmol) in 2 mL of CH_2Cl_2, and the resulting yellow-brown solution was kept at −70 °C for 1.5 h. There was added 404 mg of triethylamine (4 mmol) and, after 10 min at −70 °C the mixture was allowed to warm up to room temperature. After dilution with 20 mL of CH_2Cl_2, the mixture was washed twice with water, dried with $MgSO_4$, and evaporated to a residue which was chromatographed on silica gel, eluting with a 2:1 mixture of ether and hexane, to afford 672 mg (85%) of **4l** as a yellow solid: mp 157−159 °C; IR (KBr) 3308 (NH) 2220 (CN) 1470 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.57 (s, 3H, CH_3), 7.10 (m, 5H, arom), 7.42 (m, 2H, H_6 and H_7), 7.87 (s, 1H, H_4), 8.60 (br, NH). Anal. Calcd for $C_{16}H_{12}N_2S$: C, 72.70; H, 4.58; N, 10.60; S, 12.13. Found: C, 72.45; H, 4.48; N, 10.50; S, 11.92.

This method was also followed to prepare the following compounds:

5-Nitro-2-methyl-3-(methylthio)indole (4f): dark yellow solid (33%) mp 197−199 (lit.[5] 197.5−198.5 °C).

5-Nitro-2-methyl-3-(phenylthio)indole (4g): yellow orange solid (89%) mp 208−210 °C; IR (KBr) 3320, 1475, 1320 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.56 (s, 3H, CH_3), 7.04 (m, 3H, arom), 7.16 (m, 2H, arom), 7.37 (d, J = 8.8 Hz, 1H, arom), 8.10 (dd, J = 8.8 and 2.1 Hz, 1H, arom), 8.47 (d, J = 2.1 Hz, 1H, arom), 8.60 (br, NH). Anal. Calcd for $C_{15}H_{12}N_2O_2S$: C, 63.36; H, 4.25; N, 9.85; S, 11.28. Found: C, 63.04; H, 4.14; N, 9.71; S, 11.26.

5-Acetyl-2-methyl-3-(methylthio)indole (4i): cream-colored solid (78%) mp 140−142 °C; IR (KBr) 3225, 1650, 1302 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.29, 2.57 and 2.71 (3s, $3CH_3$), 7.32 (d, J = 8.5 Hz, 1H, H_7), 7.86 (dd, J = 8.5 and 1.6 Hz, 1H, H_6), 8.32 (d, J = 1.6 Hz, H_4), 8.38 (br, NH). Anal. Calcd for $C_{12}H_{13}NOS$: C, 65.72; H, 5.98; N, 6.39; S, 14.62. Found: C, 65.52; H, 5.95; N, 6.30; S, 14.81.

2-Methyl-5-(methylsulfonyl)-3-(phenylthio)indole (4k): light pink solid (65%) mp 175−177 °C; IR (KBr) 3300, 1290, 1140, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.53 and 3.05 (2s, $2CH_3$), 7.10 (m, 5H, arom), 7.47 (d, J = 8.7 Hz, 1H, H_7), 7.75 (dd, J = 8.7 and 1.8 Hz, 1H, H_6), 8.19 (d, J = 1.8 Hz, 1H, H_4), 8.63 (br, NH). Anal. Calcd for $C_{16}H_{15}NO_2S_2$: C, 60.54; H, 4.76; N, 4.41; S, 20.20. Found: C, 60.30; H, 4.71; N, 4.47; S, 20.11.

5-Bromo-2-methyl-3-(phenylthio)indole (4n): light brown crystals (47%), mp 160−162 °C (ether−hexane); IR (KBr) 3405, 1580, 1474, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 (s, 3H, CH_3), 7.04 (m, 3H, arom), 7.12 (m, 4H, arom), 7.63 (s, 1H, H_4), 8.28 (br, NH). Anal. Calcd for $C_{15}H_{12}BrNS$: C, 56.61; H, 3.80; N, 4.40; Br, 25.11; S, 10.07. Found: C, 56.44; H, 3.54; N, 4.32; Br, 24.76; S, 10.17.

5-Iodo-2-methyl-3-(phenylthio)indole (4o): tan solid (42%), mp 164−166 °C; IR (KBr) 3405, 1580, 1475, 1445 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.51 (s, 3H, CH_3), 7.10 (m, 6H, arom), 7.45 (dd, J = 8.4 and 1.6 Hz, 1H, H_6), 7.88 (d, J = 1.6 Hz, 1H, H_4), 8.28 (br, NH). Anal. Calcd for $C_{15}H_{12}INS$: C, 49.33; H, 3.31; N, 3.83; I, 34.75; S, 8.78. Found: C, 49.35; H, 3.26; N, 3.64; I, 34.36; S, 9.09.

Fischer Indolization Type I: Preparation of 2-Methyl-5-(methylthio)-3-(phenylthio)indole (4j). A mixture of 762 mg of 4-(methylthio)phenylhydrazine hydrochloride[14] (4 mmol) and 581 mg of 1-(phenylthio)-2-propanone (3.5 mmol) in 12 mL of *tert*-butyl alcohol was refluxed for 0.5 h. After cooling, the mixture was diluted with water and partitioned between water and ethyl acetate. The crude product from the organic phase was chromatographed on silica gel, eluting with a 1:3 mixture of ethyl acetate and hexane to afford a yellow oil which after trituration with a 1:2 mixture of ether and hexane afforded a yellow solid which was filtered. There was obtained 890 mg of **4j** (89%): mp 132−134 °C; IR (KBr) 3405, 1580, 1478 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.47 and 2.51 (2s, $2CH_3$), 7.05 (m, 3H, arom), 7.18 (m, 3H, arom), 7.28 (d, J = 8.4 Hz, 1H, H_7), 7.50 (s, 1H, H_4), 8.22 (br, NH). Anal. Calcd for $C_{16}H_{15}NS_2$: C, 67.33; H, 5.30; N, 4.91; S, 22.46. Found: C, 67.51; H, 5.32; N, 4.85; S, 22.74.

The above method was also utilized to provide the following compounds:

5-Methoxy-2-methyl-3-(phenylthio)indole (4h): tan solid (85%) mp 129−130 °C (lit.[12a] 125−126 °C).

5-(Allyloxy)-2-methyl-3-(phenylthio)indole (4m): light yellow solid (91%), mp 78−80 °C; IR (KBr) 3390, 1475, 1188 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.49 (s, CH_3), 4.50 (m, 2H, CH_2), 5.30 (m, 2H, CH_2), 6.06 (m, 1H, CH), 6.86 (dd, J = 8.7 and 2.4 Hz, H_6), 7.15 (m, 7H, arom), 8.17 (br, NH). Anal. Calcd for $C_{18}H_{17}NOS$: C, 73.19; H, 5.80; N, 4.74; S, 10.85. Found: C, 73.04; H, 5.86; N, 4.61; S, 10.76.

Fischer Indolization Type II: Synthesis of 3-(*tert*-Butylthio)-1-methyl-2-phenylindole (4e). A mixture of 732 mg of 1-methyl-1-phenylhydrazine (6 mmol), 1.04 g of α-(*tert*-butylthio)acetophenone (5 mmol), 820 mg of sodium acetate (10 mmol), 20 mL of toluene, and 10 mL of acetic acid was stirred at room temperature for 3 h. The solvents were evaporated away under vacuum, and the residue was partitioned between ether and water. The crude product from the organic phase was chromatographed on silica gel, eluting with a 1:19 mixture of ethyl acetate and hexane, to afford 950 mg of **4e** (64%) as a light yellow solid: mp 102−104 °C; IR (KBr) 2965, 1468, 1372 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.04 (s, 9H, $3CH_3$), 3.68 (s, 3H, CH_3), 7.21 (m, 2H, arom), 7.38 (d, J = 7.8 Hz, 1H arom), 7.46 (m, 5H, arom), 7.87 (d, J = 7.6 Hz, 1H, H_4). Anal. Calcd for $C_{19}H_{21}NS$: C, 77.24; H, 7.16; N, 4.74; S, 10.85. Found: C, 76.93; H, 7.21; N, 4.70, S, 11.20.

Compounds **4a**[5], **4b**[13], **4c**,[13] and **4q**[13] were prepared by published procedures.

1,2-Dimethyl-3-(phenylthio)indole (4d) was prepared by N-methylation of **4b** with MeI using NaH in DMF (90% yield): mp 113−114 °C; IR (KBr) 1580, 1470, 1390 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52 and 3.77 (2s, $2CH_3$), 7.04 (m, 3H, arom), 7.13 (m, 3H, arom), 7.24 (m, 1H, arom), 7.35 (d, J = 8 Hz, 1H, H_7), 7.57 (d, J = 7.7 Hz, 1H, H_4). Anal. Calcd for $C_{16}H_{15}NS$: C, 75.85; H, 5.97; N, 5.53; S, 12.65. Found: C, 75.95; H, 6.23; N, 5.39; S, 12.98.

1-Benzyl-2-methyl-3-(phenylthio)indole (4p) was obtained by N-alkylation of **4b** with benzyl bromide using NaH in DMF. It was obtained in 95% yield as a beige solid: mp 94−96 °C (hexane); IR (KBr) 1478, 1448, 730 cm^{-1}; ^1H NMR

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($CDCl_3$) δ 2.46 (s, CH_3), 5.40 (s, 2H, CH_2), 7.02 (m, 5H, arom), 7.16 (m, 5H, arom), 7.28 (m, 3H, arom), 7.26 (d, J = 8 Hz, 1H, H_4). Anal. Calcd for $C_{22}H_{19}NS$: C, 80.20; H, 5.81; N, 4.25; S, 9.73. Found: C, 80.13, H, 5.96; N, 4.21; S, 9.73.

General Procedure for Desulfenylation of 3-Indolyl Sulfides Using TFA and Thiosalicyclic Acid: Desulfenylation of 4j to 2-Methyl-5-(methylthio)indole (5j). A suspension of 285 mg of **4j** (1 mmol) and 308 mg of thiosalicyclic acid (2 mmol) in 7 mL of TFA was stirred at room temperature for 15 min. The TFA was evaporated away, the residue was taken up in ethyl acetate, washed twice with 1 N aqueous NaOH and then three times with water, dried, and evaporated down. The residue was chromatographed on silica gel, eluting with a 1:3 mixture of ethyl acetate and hexane, to afford 166 mg of **5j** (93%) as a yellow solid: mp 51–53 °C (ether–hexane); ^1H NMR ($CDCl_3$) δ 2.43 and 2.50 (2s, $2CH_3$), 6.16 (s, 1H, H_3), 7.14 (dd, J = 8.4 and 1.6 Hz, H_6), 7.21 (d, J = 8.4 Hz, H_7), 7.52 (d, J = 1.6 Hz, H_4), 7.83 (br, NH). Anal. Calcd for $C_{10}H_{11}NS$: C, 67.76; H, 6.25; N, 7.90; S, 18.09. Found: C, 67.74; H, 6.08; N, 7.58; S, 18.31.

This compound gradually decomposes on prolonged standing.

This procedure was followed for all the examples of Table 3; appropriate temperatures and reaction times are listed therein. Compounds **5a/5b** (2-methylindole), **5c** (2-phenylindole), **5d** (1,2-dimethylindole), and **5q** (methyl indole-2-carboxylate) corresponded to commercially available samples.

1-Methyl-2-phenylindole (5e): white solid, mp 97–99 °C. NMR data consistent with published values.[15]

2-Methyl-5-nitroindole (5f/5g): yellow solid, mp 169–171 °C (lit.[16] 175–176 °C).

5-Methoxy-2-methylindole (5h): beige solid, mp 86–88 °C (ether–hexane) (lit.[17] 89–90 °C).

5-Acetyl-2-methylindole (5i): cream-colored solid, mp 136–138 °C (lit.[18] 140.5–141 °C).

For this compound, evaporation of the TFA affords lower yields; it is preferable to pour the reaction mixture onto water, extract with ethyl acetate, and wash with aqueous base to remove the TFA.

2-Methyl-5-(methylsulfonyl)indole (5k): cream-colored solid, mp 145–147 °C (EtOAc–hexane); IR (KBr) 3350, 1290, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.50 (s, CH_3), 3.07 (s, CH_3), 6.37 (s, 1H, H_3), 7.40 (d, J = 8.6 Hz, H_7), 7.65 (dd, J = 6 and 1.7 Hz, H_6), 8.14 (d, J = 1.7 Hz, H_4), 8.22 (br, NH). Anal. Calcd for $C_{10}H_{11}NO_2S$: C, 57.40; H, 5.30; N. 6.69; S, 15.32. Found: C, 57.12; H, 5.28; N, 6.48; S, 14.99.

5-Cyano-2-methylindole (5l): cream-colored crystals, mp 134–135 °C (ether–hexane); IR (KBr) 3320 (NH), 2220 (CN), 1470 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.48 (s, 3H, CH_3), 6.30 (s, 1H, H_3), 7.34 (m, 2H, H_6 and H_7), 7.85 (s, 1H, H_4), 8.20 (br, NH). Anal. Calcd for $C_{10}H_8N_2$: C, 76.90; H, 5.16; N, 17.94. Found: C, 76.68; H, 5.07; N, 17.78.

5-(Allyloxy)-2-methylindole (5m): tan solid, mp 40–42 °C; IR (KBr) 3400, 1480, 1178 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42 (s, 3H, CH_3), 4.56 (m, 2H, CH_2), 5.35 (m, 2H, CH_2), 6.10 (m, 1H, CH), 6.13 (s, 1H, H_3), 6.78 (dd, J = 8.7 and 2.4 Hz, 1H, H_6), 7.00 (d, J = 2.4 Hz, 1H, H_4), 7.16 (d, J = 8.7 Hz, H_7), 7.74 (br, NH). Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 76.76; H, 7.04; N, 7.33.

5-Bromo-2-methylindole (5n): white needles, mp 104–106 °C (ether–hexane) (lit.[17] 104–105 °C).

5-Iodo-2-methylindole (5o): tan crystals, mp 89–91 °C (ether–hexane); IR (KBr) 3400, 1445, 1303, 795 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.44 (s, 3H, CH_3), 6.14 (s, 1H, H_3), 7.06 (d, J = 8.5 Hz, 1H, H_7), 7.35 (d, J = 8.5 Hz, 1H, H_6), 7.83 (s, 1H, H_4), 7.90 (br, NH). Anal. Calcd for C_9H_8IN: C, 42.05, H, 3.14; N, 5.45; I, 49.36. Found: C, 42.31; H, 3.18; N, 5.49; I, 49.27.

1-Benzyl-2-methylindole (5p): cream-colored solid, mp 48–50 °C (lit.[19] 49 °C).

Synthesis of 2,3-Indole Bis-Sulfides: The procedure of K. Anzai[10] was followed to prepare all of the bis-sulfides as follows:

2,3-Bis[(4-methoxyphenyl)thio]indole (6f). To a solution of 2.02 g of bis(4-methoxyphenyl) disulfide (7.27 mmol) in 18 mL of 1,2-dichloroethane at room temperature there was added 0.89 g of sulfuryl chloride (0.54 mL, 6.6 mmol) and the resulting red solution was stirred for 20 min, affording an assumed 0.67 M solution of the sulfenyl chloride. This solution (18 mL, 12 mmol) was added to a solution of 585 mg of indole (5 mmol) in 10 mL of DMF. After stirring at room temperature for 1 h, the mixture was concentrated under vacuum to remove the dichloroethane, and the residue was partitioned between ether and water. The crude product from the organic phase was chromatographed on silica gel, eluting with a 2:3 mixture of ether and hexane, to afford 1.77 g (90%) of **6f** as a beige solid: mp 133–135 °C (EtOH); IR (KBr) 3340, 1490, 1252, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.72 and 3.77 (2s, $2CH_3$), 6.70 (d, J = 8.9 Hz, 2H, arom), 6.81 (d, J = 8.9 Hz, 2H, arom), 7.16 (m, 2H, H_5 and H_6), 7.12 (d, J = 8.9 Hz, 2H, arom), 7.23 (d, J = 7.1 Hz, 1H, H_7); 7.33 (d, J = 8.9 Hz, 2H, arom), 7.56 (d, J = 8.2 Hz, 1H, H_4), 8.08 (br, NH). Anal. Calcd for $C_{22}H_{19}NO_2S_2$: C, 67.15; H, 4.87; N, 3.56; S, 16.29. Found: C, 66.96; H, 4.93; N, 3.51; S, 16.26. Also prepared were the following:

2,3-Bis(methylthio)indole[2] (6a): colorless oil (81% yield). This reaction is preferably run at 0 °C.

2,3-Bis(ethylthio)indole (6b): yellow oil (76% yield); IR (neat) 3390, 1435, 1335 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 and 1.27 (2t, 2 CH_3), 2.78 and 2.95 (2q, $2CH_2$), 7.21 (m, 2H, H_5 and H_6), 7.32 (m, 1H, H_7), 7.72 (d, J = 7.3 Hz, 1H, H_4), 8.28 (br, NH). Anal. Calcd for $C_{12}H_{15}NS_2$: C, 60.72; H, 6.37; N, 5.90; S, 27.01. Found: C, 60.42; H, 6.52; N, 5.61; S, 26.65.

2,3-Bis[(2-carbomethoxyethyl)thio]indole (6c): white solid (95% yield), mp 65–67 °C; IR (KBr) 3350, 1732, 1715, 1168 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.54 (t, J = 7.4 Hz, 2H, CH_2), 2.66 (t, J = 7.4 Hz, 2H, CH_2), 2.99 (t, J = 6.7 Hz, 2H, CH_2), 3.16 (t, J = 6.7 Hz, 2H, CH_2), 3.60 and 3.71 (2s, $2CH_3$), 7.21 (m, 2H, H_5 and H_6), 7.36 (d, J = 7.6 Hz, 1H, H_7), 7.70 (d, J = 8.4 Hz, 1H, H_4), 9.08 (br, NH). Anal. Calcd for $C_{16}H_{19}NO_4S_2$: C, 54.37; H, 5.42; N, 3.96; S, 18.14. Found: C, 54.36; H, 5.36; N, 3.96; S, 18.24.

2,3-Bis(phenylthio)indole (6d): off-white solid (94% yield), mp 97–99 °C lit.[10] 98–99 °C).

2,3-Bis[(4-chlorophenyl)thio]indole (6e): beige solid (90% yield), mp 75–77 °C; IR (KBr) 3390, 1468, 1088 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.98 (d, J = 8.7 Hz, 2H, arom), 7.09 (d, J = 8.7 Hz, 2H, arom), 7.27 (m, 7H, arom), 7.57 (d, J = 8 Hz, 1H, H_4), 8.45 (br, NH). Anal. Calcd for $C_{20}H_{13}Cl_2NS_2$: C, 59.70; H, 3.26; N, 3.48; S, 15.94; Cl, 17.62. Found: C, 59.33; H, 3.28; N, 3.54; S, 15.94; Cl, 17.70.

2,3-Bis(2-naphthylthio)indole (6g): white solid (66% yield), mp 188–190 °C (EtOAc–hexane); IR (KBr) 3385, 1500, 1338, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.13 (m, 1H, arom), 7.24 (m, 2H, arom), 7.32 (m, 4H, arom), 7.40 (m, 2H, arom), 7.49 (m, 2H, arom), 7.57–7.72 (m, 6H, arom), 7.76 (s, 1H, arom), 8.40 (br, NH). Anal. Calcd for $C_{28}H_{19}NS_2$: C, 77.56; H, 4.42; N, 3.23; S, 14.79. Found: C, 77.70; H, 4.62; N, 3.18; S, 14.70.

1-Methyl-2,3-bis(methylthio)indole[2] (6h) was obtained by N-methylation of **6a** using NaH–MeI in DMF (84% yield), as a yellow oil.

1-Methyl-2,3-bis(phenylthio)indole (6i): obtained in the same manner from **6d** (88%); tan crystals, mp 108–109 °C (ether–hexane (lit.[2] 107–108 °C).

1-Methyl-2,3-bis[(4-methoxyphenyl)thio]indole (6j): obtained in the same manner from **6f** (91% yield); beige solid, mp 95–96 °C; IR (KBr) 1590, 1490, 1246 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.71, 3.73 and 3.78 (3s, $3CH_3$), 6.70 (m, 4H, arom), 7.12 (m, 5H, arom), 7.29 (m, 2H, arom), 7.67 (d, J = 7.9 Hz, 1H, H_4). Anal. Calcd for $C_{23}H_{21}NO_2S_2$: C, 67.78; H, 5.19; N, 3.44; S, 15.73. Found: C, 67.86; H, 5.17; N, 3.36; S, 15.78.

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1-Benzyl-2,3-bis(phenylthio)indole (6k) was obtained by N-alkylation of **6d** using NaH and benzyl bromide in DMF (86% yield): white crystals, mp 78–80 °C, IR (KBr) 1472, 1434, 739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.52 (s, 2H, CH_2), 6.97–7.31 (m, 18H, arom), 7.67 (d, J = 7.7 Hz, 1H, H_4). Anal. Calcd for $C_{27}H_{21}NS_2$: C, 76.55; H, 5.00; N, 3.31; S, 15.14. Found: C, 76.32; H, 4.97; N, 3.34; S, 14.93.

Selective Desulfenylation of Indole 2,3-Bis-Sulfides to 2-Indolyl Sulfides: 2-[(4-Methoxyphenyl)thio]indole (7f). To a mixture of 197 mg of **6f** (0.5 mmol) and 154 mg of thiosalicyclic acid (1 mmol) there was added 3 mL of TFA. The mixture was refluxed for 15 min and the TFA was evaporated off. The residue was diluted with ether, washed twice with 1 N aqueous NaOH and three times with water, dried, and evaporated down. The residue was chromatographed on silica gel to afford 120 mg of **7f** (94%) as a tan solid: mp 67–69 °C (lit.[2] 68–70 °C) along with 48 mg of bis(4-methoxyphenyl) disulfide.

Compounds **7a–e and 7g–i** were obtained by the same procedure. Yields are listed in Table 4 and data on isolated compounds correspond to those from ref 2.

1-Methyl-2-[(4-methoxyphenyl)thio]indole (7j): white solid, mp 58–60 °C (hexane); IR (KBr) 1485, 1230, 1015 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.67 and 3.75 (2s, $2CH_3$), 6.76 (d, J = 5Hz, 2H, arom), 6.85 (s, 1H, H_3), 7.12 (d, J = 5Hz, 2H, arom), 7.25 (m, 3H, arom), 7.61 (d, J = 7.3 Hz, H_4). Anal. Calcd for $C_{16}H_{15}NOS$: C, 71.34; H, 5.61; N, 5.20; S, 11.91. Found: C, 71.72; H, 5.91; N, 5.19; S, 12.02.

1-Benzyl-2-(phenylthio)indole (7k): white crystals, mp 104–105 °C; IR (KBr) 1570, 1470, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.38 (s, 2H, CH_2), 6.96 (m, 3H, arom), 7.02–7.25 (m, 11H, arom), 7.69 (d, J = 7.6 Hz, H_4). Anal. Calcd for $C_{21}H_{17}NS$: C, 79.96; H, 5.43; N, 4.44; S, 10.17. Found: C, 79.82; H, 5.50; N, 4.39; S, 9.89.

Desulfenylation of 4b with TFA Using Methyl Thiosalicylate as Trapping Agent: Isolation of Trapping Product. To a mixture of 239 mg of **4b** (1 mmol) and 185 mg of methyl thiosalicylate (1.1 mmol) there was added 6 mL and TFA. The mixture was stirred at room temperature for 45 min. The TFA was evaporated away under vacuum at 30 °C, the residue was dissolved in ethyl acetate, and the solution was washed four times with water, dried, and evaporated down. The residue was chromatographed on silica gel, eluting with a 1:5 mixture of EtOAc and hexane to afford 52 mg of diphenyl disulfide, 120 mg (43.5%) of *o*-carbomethoxyphenyl phenyl disulfide **8**, mp 52–53 °C (lit.[11] 54–55 °C), and 110 mg of 2-methylindole (84%). Bis(*o*-carbomethoxyphenyl) disulfide was observed but not quantified.

Stability of 8. When 5 mg of **8** was stirred in 0.5 mL of TFA at room temperature, monitoring by TLC showed that after 15 min, significant amounts of Ph_2S_2 and bis(*o*-carbomethoxyphenyl) disulfide had been formed.