A New Synthesis of 3-Arylthioindoles

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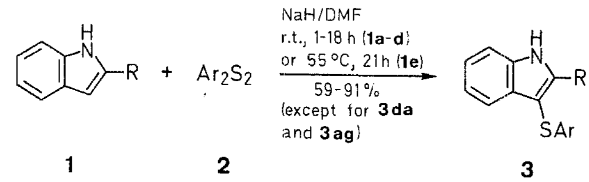
The reaction of the anions of indoles with diaryl disulfides in dimethylformamide at room temperature gives the 3-arylthioindoles in 59–91 % yield.

The discovery of novel rearrangement reactions of 3-thioindoles in our laboratories[1] led to a need for a series of 3-arylthioindoles **3**. Such compounds have been prepared by the Fischer indole synthesis,[2] but separate syntheses of the carbonyl component are required for each variation of R and Ar. Syntheses based on the reaction of arenesulfenic chlorides with indoles have also been described.[3,4] Although satisfactory, arenesulfenic chlorides possess the modest drawback of requiring their prior or *in situ* preparation (usually from the corresponding diaryl disulfides) using corrosive reagents (e.g., chlorine or sulfuryl chloride), and of being very reactive electrophilic reagents that can bring about disulfenylation of the indole nucleus.[3] A third major synthesis involves the reaction of indoles, arenethiols and potassium triiodide in aqueous alcoholic media.[5,6,7] We initially tried the latter procedure,[7] but obtained only a 20 % yield of 3-phenylthioindole **3aa**. Methyl(phenyl)succinimidosulfonium chloride was found to react with indole, and pyrolysis of the resulting sulfonium salt yielded 3-phenylthioindole, but the requirement for a pyrolytic step renders this approach less attractive.[8] Recently, 2-phenylindole and diphenyl disulfide were reported to react efficiently under UV irradiation to form 2-phenyl-3-phenylthioindole,[9] but the generality of this mild reaction remains to be demonstrated.

A widely used procedure for the preparation of α-thiolated carbonyl compounds employs the reaction of enolates with disulfides;[10] hindered phenol anions react with diaryl disulfides to yield (arylthio) phenols.[11] It occurred to us that the indole anion might undergo a similar reaction at C-3, and gratifyingly, such proved to be the case. As shown in the Scheme and the Table, a variety of 3-arylthioindoles has been synthesized by this simple methodology. (The two letters in the designation for **3** refer first to the identity of R and second to the identity of Ar.)



1	R	2	Ar	2	Ar
a	H	**a**	C_6H_5	**f**	3-$NO_2C_6H_4$
b	CH_3	**b**	4-ClC_6H_4	**g**	2-$CH_3O_2CC_6H_4$
c	C_6H_5	**c**	2-$CH_3C_6H_4$	**h**	2-naphthyl
d	CO_2CH_3	**d**	3-$CH_3OC_6H_4$	**i**	2-pyridyl
e	CO_2H	**e**	4-$CH_3OC_6H_4$		

The method possesses the practical advantage over the other approaches reviewed above of utilizing, as sulfenylating agents, the very stable diaryl disulfides, a large number of which are commercially available or are readily prepared from the corresponding thiols. Furthermore, disulfides are very weak electrophilic reagents, in contrast to the corresponding sulfenyl chlorides, so that no disulfenylation[3] is observed. The method is complementary to the use of sulfenyl chlorides in that the latter do react with *N*-substituted indoles,[3] whereas the disulfides do not, again a reflection of their milder electrophilic nature. The present reaction proceeds to over 50 % completion within two hours, and after 18 hours, the yields are over 80 % in some of the cases examined. Not all the yields in the Table have been optimized.

It is to be noted that the reaction also functions well with 2-substituted indoles (**1b–e**) to give good to excellent yields (**3ba**, **3ce**, **3ea**). The low yield of **3da** was found to be due to a competing ester cleavage, with formation of thioanisole. The problem was circumvented by using the acid **1e**, from which an acceptable yield (66 %) of **3ea** was obtained. The same explanation may hold for the low yield of **3ag**.

An initially attempted reaction of the indole anion with a dialkyl disulfide (dimethyl disulfide) was unsuccessful, even upon heating at 120 °C (see Ref. 11 for a similar experience). In contrast, the diaryl disulfides react efficiently at room temperature, presumably because of the better leaving-group capability of the arenethiolate anion, giving rise to an effective and broadly useful synthesis of 3-arylthioindoles.

Solvents were of reagent grade and used without further purification. TLC monitoring of the reactions was carried out with E. Merck # 15327 silica gel plates, eluted with EtOAc/hexane (1 : 3). E. Merck # 9385 silica gel, 230–400 mesh, was used for flash column chromatography; elution was with EtOAc/hexane (1 : 3). Indoles **1a–c**, **e** and disulfides **2a**, **f**, **i** were purchased from Aldrich Chemical Co. and used as such. Esterification of **1e** afforded **1d**, and disulfides **2b**,[12] **2c**,[13] **2d**,[13] **2e**,[14] **2g**,[15] and **2h**[16] are described in the literature.

Table. 3-Arylthioindoles **3** Prepared

Product	Reaction Time (h)	Yield[a] (%)	mp (°C)[b] (solvent)	Molecular Formula[c] or Lit. mp (°C)	IR (KBr)[d] ν(cm^{-1})	^{1}H-NMR (CDCl$_3$/TMS)[e] δ, J(Hz)
3aa	18	89	151–153 (toluene/hexane)	152–153[3]		
3ab	18	91	137–138 (Et_2O/hexane)	134–135[6]		
3ac	21	84	121–122 (Et_2O/hexane)	$C_{15}H_{13}NS$ (239.3)	3420 (NH); 1582 (arom); 1460	2.50 (s, 3H, CH_3); 6.75–7.50 (m, 7H$_{arom}$); 7.47 (d, 1H, J = 3, collapses to s on D_2O exch., H-2); 7.63 (dd, 1H, J = 2, 7, H-4); 8.40 (br, 1H, NH)
3ad	1.5	66	88–90 (Et_2O/hexane)	$C_{15}H_{13}NOS$ (255.3)	3415 (NH); 1590 (arom); 1475; 1230 (C–O)	3.69 (s, 3H, OCH_3); 6.55–6.82 (m, 3H$_{arom}$); 6.98–7.48 (m, 4H$_{arom}$); 7.43 (d, 1H, J = 3, collapses to s on D_2O exch., H-2); 7.68 (dd, 1H, J = 2, 7, H-4); 8.47 (br, 1H, NH)
3ae	1.5	59	110–112 (Et_2O/hexane)	$C_{15}H_{13}NOS$ (255.3)	3400 (NH); 1490 (arom); 1238 (C–O)	3.73 (s, 3H, OCH_3); 6.76 (d, 2H$_{arom}$, J = 9); 7.18 (d, J = 9, 2H$_{arom}$); 7.05–7.50 (m, 3H$_{arom}$); 7.45 (d, 1H, J = 2, collapses to s on D_2O exch., H-2); 7.70 (dd, 1H, J = 2, 7, H-4); 8.30 (br, 1H, NH)
3af	1	81	133–135 (CH_2Cl_2)	132–133.5[4]		
3ag	48	29	160–162 (Et_2O/hexane)	$C_{16}H_{13}NO_2S$ (283.3)	3360 (NH); 1690 (C=O); 1258 (C–O)	4.02 (s, 3H, OCH_3); 6.78–7.67 (m, 7H$_{arom}$); 7.53 (s, 1H, H-2); 8.06 (m, 1H$_{arom}$); 8.78 (br, 1H, NH)
3ah	1.5	62	185–186 (Et_2O/hexane)	$C_{18}H_{13}NS$ (275.4)	3410 (NH); 1585 (arom); 1452	7.10–7.80 (m, 11H$_{arom}$); 7.55 (d, 1H, J = 2, collapses to s on D_2O exch., H-2); 8.45 (br, 1H, NH)
3ai	18	67	135–137 (Et_2O/hexane)	128[5]		
3ba	1.5	89	129–131 (Et_2O/hexane)	130[2]		
3ce	18	80	160–161 (Et_2O/hexane)	$C_{21}H_{17}NOS$ (331.4)	3330 (NH); 1230 (C–O)	3.70 (s, 3H, OCH_3); 6.77 (d, J = 9, 2H$_{arom}$); 7.08 (d, J = 9, 2H$_{arom}$); 7.05–7.90 (m, 9H$_{arom}$); 8.53 (br, 1H, NH)
3da	18 (80°)	22	178–180 (Et_2O/hexane)	$C_{16}H_{13}NO_2S$ (283.3)	3300 (NH); 1685 (C=O); 1255 (C–O)	3.97 (s, 3H, OCH_3); 7.0–7.72 (m, 9H$_{arom}$); 9.42 (br, 1H, NH)
3ea	21 (55°)	66	160–162 (AcOH)	$C_{15}H_{11}NO_2S$[f] (269.3)	3600–2500 (OH); 3320 (NH); 1665 (C=O)	6.70 (br, 1H, OH); 7.21 (s, 5H$_{arom}$); 7.25–7.80 (m, 4H$_{arom}$); 9.85 (br, 1H, NH)

[a] Yield of isolated product based on **1**.

[b] Measured on a Thomas Hoover apparatus and uncorrected.

[c] Satisfactory microanalyses obtained: C ±0.37, H ±0.34, N ±0.21, S ±0.35 (Guelph Chemical Labs, Guelph, Ontario).

[d] Recorded on a Perkin-Elmer model 681 grating infra-red spectrophotometer.

[e] Recorded on a EM-360 90 mHz Varian spectrometer.

[f] Satisfactory analyses were not obtained, but the spectral data are in agreement with the expected structure.

3-Arylthioindoles (3); General Procedure:

To a suspension of powdered NaH (540 mg, 22.5 mmol) in dry DMF (40 mL), under N_2, there is added in portions the indole **1a–d** (15 mmol) and the mixture is stirred at room temperature until evolution of H_2 has ceased. There is then added, in portions, the disulfide **2a–i** (16.5 mmol) and the resulting mixture is stirred at room temperature, with TLC monitoring, usually for 1–18 h. The mixture is diluted with H_2O (300 mL) and extracted with Et_2O (3 × 45 mL). The combined extracts are washed with H_2O until the washings are neutral, dried (Na_2SO_4), and evaporated to dryness. Compounds **3aa**, **3ab**, **3ac**, **3ai**, **3ba**, and **3da** are purified by crystallization; the remainder are purified by flash chromatography followed by crystallization (for solvents of crystallization, see Table).

When indole **1e** is the starting material, an additional 1.5 equiv of NaH is used and heating is required (55 °C, 21 h); on work-up, acidification of the aqueous phase affords crude **3ea**, which is filtered and crystallized from AcOH.

Received: 2 September 1987; revised: 7 January 1988

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