

Novel Intramolecular Radical Displacement Reactions of 2-Indolyl Aryl Sulfides and Sulfoxides

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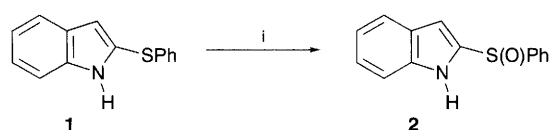
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A novel radical substitution reaction is described; the reaction involves the intramolecular addition of carbon-centred radicals to aryl sulfoxide and aryl sulfide substituted indoles.

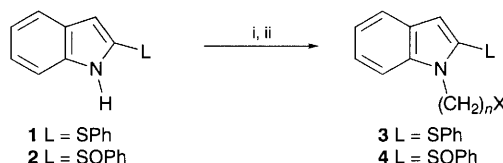
The efficiency of free radical chain reactions has made them attractive for the construction of carbon-carbon bonds.¹ Whilst numerous radical addition reactions have been developed and gained widespread use in synthesis, development of radical substitution reactions has progressed at a much slower rate. Recent reported transformations involve: allylic transposition resulting from addition-elimination sequences utilising allyl halides, stannanes and sulfides;² *ipso* substitution using vinyl and acyl stannanes and germanes; and aromatic *ipso* substitution using sulfones and sulfonamides.³ As part of our interest in developing free-radical based methodologies, we have been investigating a range of functional groups which participate in



Scheme 1 L = leaving group.

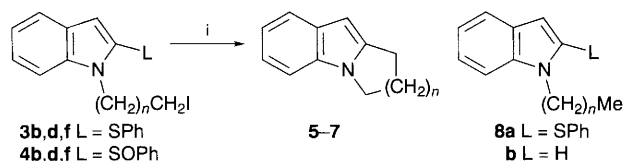


Scheme 2 Reagents: i, OxoneTM,⁷ THF, MeOH, H₂O (1:1:0.05), 0 °C, 50–64%.



Scheme 3 Reagents: i, Br(CH₂)_nBr, KOH, DMF, room temp.; ii, NaI, acetone, room temp.

X = Br (%)	X = I (%)
3a n = 3(41)	3b n = 3(60)
3c n = 4(54)	3d n = 4(68)
3e n = 5(57)	3f n = 5(63)
4a n = 3(67)	4b n = 3(70)
4c n = 4(69)	4d n = 4(61)



Scheme 4 Reagents: i, Bu₃SnH (2.2 equiv.), AIBN (0.2 equiv.), toluene, slow addition (4 h).

Iodide	Product (%)	Iodide	Product (%)
3b	5 (24)	4b	5 (40)
3d	6 (50)	4d	6 (50)
3f	8a/8b (59%)	4f	7 (30)

aromatic *ipso* substitution reactions under free radical chain conditions (Scheme 1).⁴

In this paper we detail our preliminary investigations using aryl sulfide and sulfoxides in intramolecular radical substitution reactions with carbon-centred radicals.⁵ In this work we have examined the process using indole substituted aryl sulfides and sulfoxides.

In order to prepare the substrates required for the investigation we utilised 2-phenylthioindole **1**,[†] prepared *via* acid promoted rearrangement of 3-phenylthioindole.⁶ Oxidation of 2-phenylthioindole **1** was accomplished using 1 equiv. of Oxone⁷ at 0 °C leading to the isolation of sulfoxide **2** in reasonable yield (50–64% yield), Scheme 2.

The sulfide and sulfoxide intermediates were further elaborated by *N*-alkylation⁸ using a dihaloalkane and bromide displacement (NaI, acetone, room temp.) to give the key cyclisation precursors as shown in Scheme 3.

Treatment of the aryl sulfide precursors **3b** and **3d** with tri-*n*-butyltin hydride under standard free radical conditions furnished the desired cyclisation products **5** and **6** in moderate yields (24–50%). Attempted cyclisation of **3f** under similar conditions led to reduction products **8a** and **8b** in 59% yield (1:2 ratio) with none of the desired cyclisation product **7** isolated. We believe that the rate of cyclisation is slow because of the electron donating character of the aryl sulfide moiety. In agreement with this hypothesis we found that treatment of the corresponding aryl sulfoxides **4b** and **4d** also provided the products **5** and **6** with improved isolated yields (40–51%). It is particularly noteworthy that **4f** is transformed into **7**, albeit in modest yields (20–30%).

As far as we are aware these are the first examples of intramolecular *ipso*-substitution using aryl sulfides and aryl sulfoxides as leaving groups. Work is currently underway to evaluate the synthetic utility of this type of process and to identify other groups which may undergo related radical displacement reactions.

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Footnote

[†] All compounds gave spectroscopic (IR, ¹H and ¹³C NMR) and MS data in accordance with their structure.

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