Rapid and Mild Generation of Carbon Radicals from o-(o-Iodophenyl)phenylthio Derivatives by an Anchimeric Approach

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Alkyl halides, especially iodides and bromides, are frequently utilized as precursors to generate various carbon-centered radicals. The usefulness

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of these halo derivatives in radical reactions has been demonstrated in numerous synthetic examples and often reviewed in the chemical literature. [1] There is, however, an inevitable drawback to the use of such reactive alkyl halides for radical reactions, and this is mainly due to the troublesome intervention of internal and/or external nucleophiles (e.g., alkoxides, amines, cyanide, enolates, etc.). To overcome this intrinsic problem, we initiated the search for a reactive alkyl iodide equivalent that is stable for ordinary nucleophilic attack. Herein we wish to report that o-(oiodophenyl)phenylthio derivatives of the type 1a (Figure 1) are highly effective with various functional group compatibility for the rapid generation of carbon radicals under mild conditions. This approach expands the scope of radical chemistry, since a variety of nucleophilic thiolations (thioacetalization, conjugate addition, epoxide opening, etc.) using arythiol 1b can be readily combined with the present radical generation process.

The requisite o-(o-iodophenyl)phenylthiol $1\,b$ is conveniently prepared from o-(o-iodophenyl)aniline in a two-step sequence: (i) aqueous HCl, NaNO₂; then Na₂S₂; [2] and (ii) LiAlH₄ in THF via the corresponding disulfide.

The relative reactivity of a series of alkyl derivatives, R-X [$R = (CH_2)_5OCH_2Ph$] including **1a**

$$= \bigcap_{\substack{1 \\ S \\ R}}$$

1a: $R = -(CH_2)_5OCH_2Ph$ **1b**: R = H

Figure 1. Structures of 1 a and 1 b

(Scheme 1) has been examined by the radical reduction with Bu_5SnH (1.2 equiv) in the presence of catalytic Et_5B as radical initiator,^[5] and selected

data are listed in Table 1. Alkyl iodide is rapidly reduced by $\mathrm{Bu}_{5}\mathrm{SnH}$ (entry 1), but the reduction rate of the corresponding alkyl bromide is moderate (entry 2). Attempted reduction of other hetero-atom derivatives possessing phenylseleno and phenylthio groups results in recovery of most of the starting materials (entries 3 and 4). [4] In marked contrast, however, the o-(o-iodophenyl)phenylthio derivative 1a cleanly generates the corresponding carbon radicals under similar reaction conditions in very high yield (entry 5). [5] The rapid generation of carbon radicals from 1a is apparently ascribable to the facile formation of stable dibenzothiophene (2) [6] as well as the higher reactivity of the iodobiphenyl moiety than that of ordinary aromatic iodides (entry 6 vs. 7). [7,8]

Ph O X
$$\frac{5 \text{ mol } \% \text{ Et}_3 \text{B}}{\text{Bu}_3 \text{SnH}}$$
 Ph O CH₂Cl₂ $-78 \, ^{\circ}\text{C}$, 30 min

Scheme 1. Evaluation of the relative reactivities of alkyl derivatives

Several characteristic features of the present approach have been noted. First, the *o*-(*o*-iodophenyl)-phenylthio group of **3** is tolerant to the amino functionality. Obviously, the corresponding iodo derivative **4** is quite unstable, and hence synthetically not obtainable due to the facile intramolecular attack

Table 1. Relative reactivity in the reduction of R–X $[R = (CH_2)_5OCH_2Ph]$ and related iodides with cat. $Et_5B/Bu_5SnH^{[a]}$

entry	substrate, RX	reduction yield $(\%)^{[b]}$
1	R–I	95
2	R–Br	60
3	R-SePh	3 (96% recovery)
4	R-SPh	3 (96% recovery) 0 (>99% recovery) ^[c]
5	1 a	98
6	o-iodobiphenyl	98
7	OBn	12 (85% recovery)

 $^{^{[}a]}$ The reduction of RX was carried out with cat. Et $_5B$ (5 mol %) and Bu_5SnH (1.2 equiv) in CH_2Cl_2 at $-78\,^{\circ}C$ for 30 min.

of the β-amino moiety. Use of the simple phenylthio group sacrifices its reactivity to a great extent. Indeed, the attempted reaction of 5 a with Bu₃SnH (1.2 equiv) and catalytic Et₃B in CH₂Cl₂ at room temperature for several hours resulted in almost total recovery of the starting material.^[9] However, the radical cyclization of 3a under similar reaction conditions proceeded smoothly to give the desired cyclic amine 6 in 87% yield (Scheme 2). A similar tendency was observed in the cyclization of secondary amino derivatives. Initial treatment of 3b with Bu₃SnH and Et₅B (1.1 equiv) in CH₂Cl₂ at room temperature for 1 h and subsequent acetylation afforded the corresponding cyclic amide 7 in 85% yield, while none of the cyclization product was obtained from the simple phenvlthio derivative **5 b**.^[9]

Scheme 2. Efficient intramolecular cyclization of amines

Second, the efficient intramolecular cyclization of the monothio acetal 8 appears feasible without applying

typical conditions for this type of substrate (heat to $80\text{--}100\,^{\circ}\text{C}$ in benzene or toluene with Bu_3SnH and a radical initiator such as AIBN) $^{[10,11]}$ to afford the tetrahydrofuran derivative 9 in 84% yield as illustrated in Scheme 3. Monothio acetals of types 8 and 10, differing from the corresponding α -iodo ethers, are stable and isolable in the usual manner, thereby allowing further functionalization prior to the radical cyclization process. In a similar manner, the sugar anomeric radicals, which were previously generated from unstable glycosyl iodides, $^{[12,13]}$ can be prepared from the stable monothio acetal 10 under mild radical conditions, giving the bicyclic C-glycoside 11 in high yield.

Scheme 5. Facile generation of anomeric carbon radicals and subsequent intramolecular addition to double bonds

Third, the o-(o-iodophenyl)phenylthio moiety can be easily introduced to a wide variety of substrates (α , β unsaturated carbonyls, epoxides, acetals, etc.) by nucleophilic thiolation to furnish the corresponding o-(o-iodophenyl)phenyl sulfides which, in turn, are useful radical precursors for a further carbon-carbon bond formation process. For instance, treatment of cyclohexenone with dimethylaluminum o-(o-iodophenyl)phenylthiolate (1.1 equiv)^[14] in CH₂Cl₂ at -78 °C gave rise to the corresponding 1,4-adduct 12 in good yield^[15] and subsequent exposure to the radical conditions in the presence of excess t-butyl acrylate in CH₂Cl₂ resulted in the rapid and clean formation of the keto ester 13 in 82% yield as shown in Scheme 4. It seems clear that the present transformation, in contrast to halo precursors, can be realized even in the presence of internal and/or external nucleophiles (e.g., amines).

Scheme 4. Nucleophilic thiolation-radical conjugate addition sequence

In addition to practical and general utility in organic synthesis, we further expected that it would be possible to generate carbon radicals from usually unreac-

[[]b] Yield of isolated product.

 $^{^{[}c]}$ The reduction with Bu₅SnH and cat. AIBN in refluxing benzene was very sluggish (4% yield after 4 h; 94% recovery of R–SPh).

tive sulfoxides such as 14 through the homolytic C–S=O bond cleavage by taking advantage of the remarkable reactivity of this system. ^[16] Indeed, on reaction of 14 with Bu₃SnH (2 equiv) and cat. Et₅B (30 mol %) in CH₂Cl₂ at -78 °C for 30 min the corresponding reduction product was obtained in 93% yield (Scheme 5).

Scheme 5. Radical generation from a sulfoxide through homolytic C–S=O bond cleavage

Experimental Section

Intramolecular Radical Cyclization of 3 a (Scheme 2)

To a solution of *tertiary* amine **3a** (280 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was added Bu_3SnH (160 μ L, 0.6 mmol) and a 1 M hexane solution of Et_3B (50 μ L, 0.05 mmol) sequentially at room temperature under argon. The mixture was stirred for 1 h at room temperature and then poured into saturated NaHCO₅. Extractive workup was performed with ether and the combined extracts were dried over Na₂SO₄. Evaporation of the solvents and purification of the residual oil by column chromatography on silica gel (ether/hexane = 1:3 as eluant) gave the cyclic amine **6**; yield: 108.4 mg (0.435 mmol; 87%; E/Z = 56:44).

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References and Notes

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