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Homolytic Substitution at Selenium: A Convenient Synthesis of Benzoselenophenes

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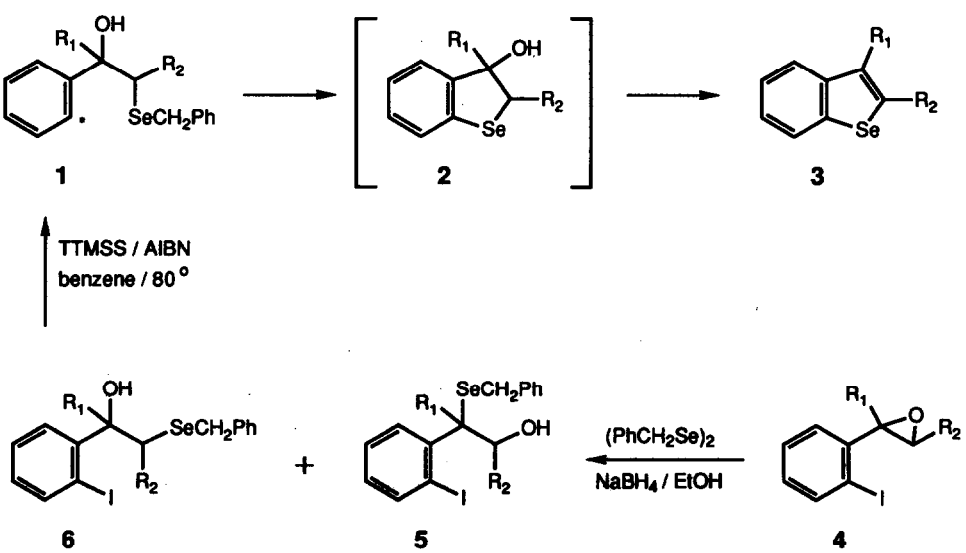
Abstract: *Substituted 2-benzylseleno-1-(2-iodophenyl)ethanols (6) react smoothly with tris(trimethylsilyl)silane (TTMSS) in benzene at 80° (AIBN initiator) to give benzo[b]selenophenes (3) in 80-86% yield. Interestingly, when the parent selenide (6: $R_1 = R_2 = H$) is reacted with tri-n-butyltin hydride under similar conditions, 3-hydroxydihydrobenzo[b]selenophene (2: $R_1 = R_2 = H$) is isolated as the only product of radical cyclization.*

Intramolecular free-radical homolytic substitution reactions at the sulfur atom in alkyl sulfides and sulfoxides offer an efficient and convenient entry point into a variety of sulfur-containing ring systems[1-6]. While this technique has been available for some time now, no similar methods for the construction of ring systems containing heteroatoms other than sulfur have, to the best of our knowledge, been reported. Recently, work in our laboratories has been directed toward the development and understanding of free-radical homolytic substitution at the selenium atom in alkyl selenides. We have shown that selenium-containing heterocycles can efficiently be prepared by the intramolecular attack of carbon-centred free-radicals at selenium and that these processes most probably involve T-shaped transition structures as opposed to hypervalent 9-Se-3 intermediates[7-9].

Scheme 1



In an attempt to expand the synthetic utility of these reactions we have examined the ring-closure of a variety of substituted 2-(2-benzylseleno-1-hydroxyethyl)phenyl radicals (**1**) with the aim of preparing substituted benzoselenophenes.

Radical precursors (**6**) were conveniently prepared according to Scheme 1. Thus, the epoxides[10,11] (**4**) were treated with dibenzyldiselenide-sodium borohydride in ethanol to produce a mixture of isomeric alcohols[12] (**5, 6**) which were separated by flash chromatography. Product yields are displayed in Table 1 and clearly indicate that the required isomer (**6**) is isolated as the sole product when the benzylic site of attack is blocked by a substituent ($R_1 \neq H$). Unfortunately, when **4** ($R_1 = H$, $R_2 = CH_3$) was reacted in the usual fashion, the sole product isolated (**5**: $R_1 = H$, $R_2 = CH_3$) was that of incorrect regiochemistry. We attribute this to the activation of the benzylic position toward nucleophilic attack over the alternative (secondary) site of attack.

When the precursors (**6**) were treated with tris(trimethylsilyl)silane (TTMSS, 0.005M) in benzene at 80° (AIBN initiator), the benzoselenophenes (**3**) were isolated in good yield (Table 1). Presumably the radicals (**1**), once generated, undergo homolytic substitution at selenium to give the alcohols (**2**) which subsequently dehydrate to produce the aromatic heterocycles (**3**). Interestingly, the benzoselenophenes appeared to elute with trace amounts of benzyl iodide upon flash chromatography. We found it convenient to remove the benzyl iodide by reaction with triethylamine prior to flash chromatography. When treated in this fashion, the products could be isolated free of contamination and were consistent with previous reports[13-16]. This procedure represents one of the highest yielding methods for the preparation of benzoselenophenes[13-21].

Table 1 Isolated Percentage Yields of the Free-Radical Precursors and Cyclized Products in this Study.

Substituent		Percentage Yield		
R_1	R_2	**5**	**6**	**3**
H	H	24	52	80
H	CH_3	85	-	-
H	Ph	47	33	86
CH_3	H	-	64	82
Ph	H	-	85	83

A typical procedure is presented:

3-Phenylbenzo[b]selenophene (**4**: R_1=Ph, R_2=H)

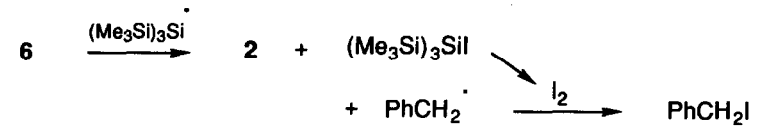
Sodium borohydride (70 mg, 1.8 mmol) was added to a solution of dibenzyl diselenide[22] (290 mg, 860 μmol) in ethanol (5 mL) and the mixture stirred, under nitrogen, until the characteristic yellow diselenide colour had disappeared. 2-(2-Iodophenyl)-2-phenyloxirane[11,12], (**4**: R_1=Ph, R_2=H) was added and the mixture stirred, under nitrogen, overnight. Water (5 mL) was added, the phases separated and the aqueous layer extracted with ether. The combined organic phases were washed with satd. sodium chloride, water and dried ($MgSO_4$). The solvent was removed *in vacuo* and the resulting oil purified by flash chromatography (10% ether: petroleum ether) to give 2-benzylseleno-1-(2-iodophenyl)-1-phenylethanol (**6**: R_1=Ph, R_2=H) as a colourless oil (650 mg, 85%). ^1H NMR ($CDCl_3$) δ 7.90 (d:d; J=8Hz, 1Hz; 1H), 7.59 (d:d; J=8Hz, 1Hz; 1H),

7.37 (d:t; J=8Hz, 1Hz; 1H), 7.20-7.34 (m, 10H), 6.95 (d:t; J=8Hz, 1Hz; 1H), 3.80 (d; J=13Hz, 1H) 3.59-3.69 (m, 2H), 3.35 (d; J=13Hz, 1H). MS, m/e 367 ($M-I^+$), calcd. for $C_{21}H_{19}OISe$: $M-I^+$ = 367.0600. Found:$M-I^+$ = 367.0617.

The alcohol (**6**: R_1=Ph, R_2=H) (130mg, 265 μmol) and TTMSS (82 μL, 265 μmol) were dissolved in benzene (50 mL) and AIBN (a few crystals) added. The solution was heated at reflux, under nitrogen, overnight, the solvent removed *in vacuo* and the residue stirred with triethylamine (100 μl, 800 μmol) in dichloromethane (10 mL) for 24h to remove trace amounts of benzyl iodide. After washing with 10% hydrochloric acid (2x) and drying ($MgSO_4$), the solvent was removed *in vacuo* and the residue separated by flash chromatography (petroleum ether) to give 3-phenylbenzo[b]selenophene[16] (56 mg, 83%) as a low melting solid. ^1H NMR ($CDCl_3$) δ 6.75-8.0 (m, 2H), 7.88 (s, 1H), 7.22-7.56 (m, 7H). ^{77}Se NMR ($CDCl_3$) δ 505.

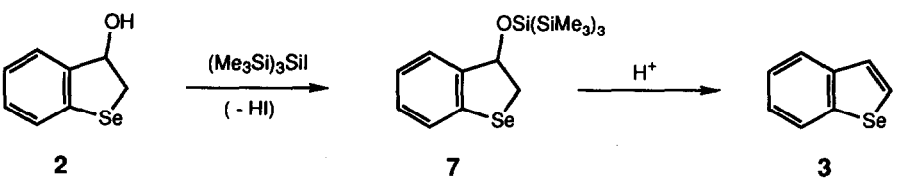
The trace amounts of benzyl iodide formed in these reactions is unlikely to directly arise from the radical chain mechanism involving homolytic substitution at selenium. Rather, we believe that tris(trimethylsilyl)silyl iodide, a byproduct of the radical chain mechanism, is unstable and decomposes to give small amounts of molecular iodine which are subsequently trapped by the chain-carrying benzyl radicals (Scheme 2).

Scheme 2



When the synthesis was repeated on the parent system ($R_1 = R_2 = H$) using tri-n-butyltin hydride instead of the silane (TTMSS), 3-hydroxydihydrobenzo[b]selenophene[23] (**2**; $R_1 = R_2 = H$; 73%) was the only product of radical ring-closure isolated. Clearly the silane or its products must catalyse the elimination process (**2** → **3**) in a way in which the tin-derived products cannot. We speculate that the elimination of **2** in the former process is a result of the reaction of tris(trimethylsilyl)silyl iodide and the alcohol (**2**). The silylated product (**7**), once formed, then undergoes acid catalysed elimination to give the product (**3**) (Scheme 3). We would not expect tri-n-butyltin iodide to become involved in a similar process.

Scheme 3



We are currently investigating the synthesis of other heterocycles by homolytic substitution and thank the Australian Research Council for financial support.

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