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Homolytic Substitution by Iminyl Radical at Selenium: A Free-Radical Route to 1,2-Benzoselenazoles

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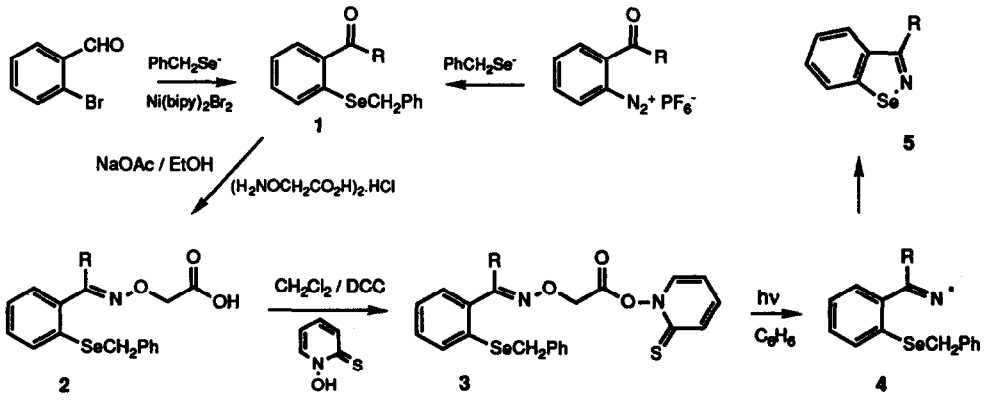
Key Words: Homolytic Substitution; Iminyl Radical; 1,2-Benzoselenazoles; Selenium; O-Carboxymethyl oximes.

Abstract: Thiohydroxamic esters (3) derived from the O-carboxymethyl oxime derivatives (2) of 2-(benzylseleno)-benzaldehyde (1: R = H), 2-(benzylseleno)acetophenone (1: R = Me) and 2-(benzylseleno)propiophenone (1: R = Et) decompose smoothly, upon irradiation, with the loss of carbon dioxide and formaldehyde to give the 1,2-benzoselenazoles (5). The reaction presumably involves the iminyl radical intermediate (4) which undergoes intramolecular free-radical homolytic substitution at selenium to afford the product (5).

Intramolecular free-radical homolytic substitution reactions offer a convenient method for the preparation of higher heterocycles. For example, several procedures have been reported in which sulfur-containing ring systems have been prepared by intramolecular attack of alkyl and aryl radicals at the sulfur atom in alkyl sulfides.[3-8] Despite the ease in which sulfur-containing rings can be formed by this method, no application of this technique to the preparation other higher heterocycles has, until recently, been reported.

Work in our laboratories has been directed toward the design and understanding of synthetic methods involving free-radical homolytic substitution at heteroatoms other than sulfur. To that end, we recently reported for the first time that carbon-centred free-radicals undergo rapid and efficient intramolecular attack at the selenium atom in alkyl selenides to produce saturated selenium-containing heterocycles[9,10], selenophenes[11] and benzoselenophenes[11,12] in excellent yield. In addition, *ab initio* calculations have provided support for a reaction mechanism involving a T-shaped transition structure in which the attacking and leaving groups adopt a co-linear arrangement in these reactions at selenium.[13]



In order to further extend this methodology to the construction of other related heterocyclic systems we have examined the decomposition of the thiohydroxamic esters (3) derived from the O-carboxymethyl oxime derivatives (2) with the aim of preparing 1,2-benzoselenazoles (5).

2-(Benzylseleno)benzaldehyde[14] (1: R = H) was readily prepared in large quantities as a white crystalline solid from 2-bromobenzaldehyde by the method of Cristau and co-workers[15] using sodium benzylselenoate[9,10] as reagent. Generation of the iminyl radical (4) was achieved using a slight modification of the method developed by Zard and co-workers[16]. The aldehyde (1: R = H) was converted to the O-carboxymethyl oxime (2) using carboxymethoxylamine hemihydrochloride in ethanol buffered with sodium acetate. We found it convenient to convert the oxime (2) into the thiohydroxamic ester (3) through the action of N-hydroxypyridine-2-thione and dicyclohexylcarbodiimide (DCC) in dichloromethane.[17] Subsequent photolysis of a solution of 3 in benzene under reflux, using a 150W tungsten lamp yielded 1,2-benzoselenophene (5: R = H) in about 70% yield as determined by ^{1}H and ^{77}Se NMR spectroscopy (δ 1033 ppm)[18] and was isolated in 54% yield after flash chromatography (8% ether in petroleum ether). By-products in this reaction include bibenzyl and 2-(benzylthio)pyridine. Presumably 3 decomposes to give the iminyl radical (4), as described by Zard and co-workers[16], followed by intramolecular free-radical homolytic substitution at the selenium atom with the loss of benzyl radical to afford the selenazole (5). To the best of our knowledge, this represents the first example of the involvement of iminyl radicals in homolytic substitution chemistry.

Unfortunately, 2-bromoacetophenone did not react with sodium benzylselenoate under the conditions described by Cristau, however, we were able to prepare the benzylseleno ketones (1: R = Me, Et) by the decomposition of the diazonium salts derived from 2-aminoacetophenone and 2-aminopropiophenone in the presence of sodium benzylselenoate in ethanol in yields ranging from 10-35%.

In similar fashion to that previously described, 2 (R = Me, Et) was converted to 3-methyl-1,2-benzoselenazole (5: R = Me) and 3-ethyl-1,2-benzoselenazole (5: R = Et) in yields in of about 70% as determined by ^{1}H NMR spectroscopy, and isolated in 45% and 60% yield respectively. Previous reported procedures for the preparation of 1,2-benzoselenazoles involve several steps, giving the required product in overall yields of 33 - 43% from diselenosalicylic acid.[14,19] The procedure thus described represents an effective alternative to the existing methods for the preparation of 1,2-benzoselenazoles.

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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