Utilization of *o*-[(*E*)-2-Trimethylsilyl-2-iodovinyl]phenylthio Derivatives as Carbon Radical Precursors by Anchimeric Approach

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Abstract: o-[(*E*)-2-Trimethylsilyl-2-iodovinyl]phenylthio derivatives have been introduced as effective precursors for the generation of carbon centered radicals even in the presence of certain nucleophiles; this provides useful information about the structural requirement for inducing an efficient anchimeric effect under mild conditions.

Key words: anchimeric effect, carbon radicals, cyclizations, reductions, vinyl iodides

Along with the integration of free radical chemistry into the general knowledge of organic reactions from the conceptual as well as methodological viewpoints, radical reactions have become a valuable and even indispensable tool for both the selective bond-forming and cleavage reactions, which play an important role in the construction of biologically active molecules with complex structures.^{1,2} Although alkyl halides, especially iodides and bromides, are generally used as precursors to generate various carbon radicals, such reactive alkyl halides have an inherent tendency of suffering from undesired reaction processes represented by displacement with internal and/ or external nucleophiles. Recently, we reported our own solution to this longstanding problem by introducing o-(oiodophenyl)phenylthio derivatives 1 as highly effective carbon radical precursors with various functional group compatibility.³ One of the key elements of our approach is the employment of a biphenyl framework that assures the strong participation of an initially generated biphenyl rad-





ical into facilitating the subsequent homolytic cleavage of a carbon-sulfur bond;⁴ this has stimulated our interest in the structural requirement to induce such an anchimeric effect. Here we wish to disclose that o-[(*E*)-2-trimethylsilyl-2-iodovinyl]phenylthio derivatives of type **2** exhibit the similar reactivity, thereby enabling rapid generation of carbon centered radicals under mild reaction conditions (Scheme 1).

As already reported,³ radical reduction of simple phenylthio derivative with Bu₃SnH (1.2 equiv) and catalytic amount of Et₃B (5 mol%)⁵ in toluene at -78 °C for 30 min resulted in almost total recovery of the starting material (Scheme 2).⁶ In sharp contrast, however, treatment of **2** with Bu₃SnH/*cat*. Et₃B in toluene at -78 °C for 30 min gave rise to the corresponding reduction product **3** in 91% isolated yield. This eminent reactivity stems from the rapid intramolecular radical translocation with the preferable formation of a five-membered heterocycle as illustrated in Scheme 2.^{7,8}





Based on the results, we synthesized several vinyl iodide analogues **4-6** and evaluated their ability as a carbon radical precursor in the radical reduction. Sequential addition of Bu₃SnH (1.2 equiv) and catalytic Et₃B (5 mol%) at -78 °C to a solution of **4** in toluene and subsequent stirring at -78 °C for 2 h and at -40 °C for 1 h gave only a trace amount of the desired **3** with predominant formation of **7** as a result of simple vinyl iodide reduction. Although the yield of **3** was improved to 36% when the reaction was performed at room temperature, **7** was still obtained as a major product. Reaction of **5** with Bu_3SnH/cat . Et_3B , in contrast, furnished **3** in 82% yield, though stirring for 1 h at room temperature was required. These results revealed that the trimethylsilyl group played a role in enhancing the reactivity of vinyl iodide, and the conjugation with aromatic moiety was necessary to facilitate the participation of initially generated vinyl radical into the subsequent homolytic S-C bond cleavage process. This observation seems consistent with the fact that attempted reaction of **6**, which possesses an additional methylene carbon between the sulfur atom and aromatic ring, afforded unknown compounds under similar conditions.⁹



Synthetic utility of the o-[(E)-2-trimethylsilyl-2-iodovinyl]phenylthio group was highlighted by the remarkably facile intramolecular radical cyclization of amino derivatives 8. Although simple phenylthio group is usually employed as a radical precursor in this type of reaction mainly due to the difficulty in preparation and isolation of the corresponding iodide, it unfortunately diminishes the reactivity to a great extent. For instance, attempted reaction of **11a** with Bu₃SnH/cat. Et₃B in toluene at -78 °C for 1.5 h showed no evidence of the product formation and resulted in 81% recovery of the starting material.¹⁰ However, smooth cyclization of 8a was observed under the similar reaction conditions producing the desired cyclic amine 9 in 83% yield. Moreover, the cyclization of secondary amino derivative 8b also appeared feasible with the present approach giving the corresponding cyclic amide 10 in 88% yield after acetylation in the usual manner, whereas none of the cyclization product was obtained from the simple phenylthio derivative 11b (Scheme 3).

A typical experimental procedure is as follows (radical reduction of **2**): To a solution of **2** (290 mg, 0.57 mmol) in toluene (5.7 mL) was added Bu₃SnH (183 μ L, 0.68 mmol) and Et₃B (28 μ L, 28 μ mol) sequentially at -78 °C under argon. The reaction was monitored by thin-layer chromatography (TLC) analysis. The mixture was stirred at -78 °C for 30 min and poured into saturated NaHCO₃. Extractive workup was performed with ether and the organic extracts were dried over Na₂SO₄. Evaporation of solvents and purification of the residual oil by column chromatography on silica gel (ether/hexane = 1:50 as eluent) furnished **3** (92.3 mg, 0.52 mmol, 91% yield) as a colorless oil.



Scheme 3

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References and Notes

- Reviews: (a) B. Giese, Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds; Pergamon Press: New York, 1986. (b) G. Pattenden, Chem. Soc. Rev. 17, 361, 1988.
 (c) D. P. Curran, In Comprehensive Organic Synthesis, Trost, B. M.; Fleming, I.; Semmelhock, M. F. Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p. 715. (d) C. P. Jasperse, D. P. Curran, and T. L. Fevig, Chem. Rev. 91, 1237, 1991. (e) W. B. Motherwell, D. Crich, Free-Radical Reactions in Organic Synthesis, Academic Press: London, 1992. (f) A. L. J. Beckwith, Chem. Soc. Rev. 22, 143, 1993. (g) G. G. Melikyan, Synthesis 833, 1993. (h) G. A. Molander, C. R. Harris, Chem. Rev. 96, 307, 1996. (i) B. B. Snider, *ibid.* 96, 339, 1996. (j) S. Z. Zard, Angew. Chem. Int. Ed. Engl. 36, 673, 1997.
- (2) (a) B. Giese, Angew. Chem. Int. Ed. Engl. 28, 969, 1989.
 (b) N. A. Porter, B. Giese, D. P. Curran, Acc. Chem. Res. 24, 296, 1991. (c) T. V. RajanBabu, *ibid.* 24, 139, 1991.
 (d) W. Smadja, Synlett 1, 1994. (e) D. P. Curran, N. A. Porter, and B. Giese, Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications; VCH: Weinheim, 1996.
- (3) T. Ooi, M. Furuya, D. Sakai, K. Maruoka, *Adv. Synth. Catal.* in press.
- (4) For the pioneering work on the utilization of intramolecular homolytic substitution at sulfur for the generation of acyl radicals, see: (a) D. Crich, Q. Yao, *J. Org. Chem.* 61, 3566, 1996. (b) D. Crich, X. L. Hao, *J. Org. Chem.* 62, 5982, 1997. For other radical translocation methodologies, see: D. P. Curran, A. C. Abraham, H. Liu, *J. Org. Chem.* 56, 4335, 1991; D. P. Curran, A. C. Abraham, *Tetrahedron* 49, 4821, 1993.
- (5) H. Nozaki, K. Oshima, K. Utimoto, J. Am. Chem. Soc. 109, 2547, 1987.
- (6) Only a trace amount of the desired reduction product 3 was obtained even when the reaction was carried out in refluxing benzene in the presence of *cat*. AIBN for several hours.

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- (7) Although we utilized (*E*)-vinyl iodide, (*Z*)-isomer would also exhibit similar reactivity because configurationally isomeric vinyl radicals with bent structure rapidly interconvert through a linear structure shown in Scheme 2.⁸ See: (a) B. Giese, J. A. Gonzalez-Gomez, S. Lachhein, J. O. Metzger, *Angew. Chem. Int. Ed. Engl.* **26**, 479, 1987. (b) T. Ooi, Y. Hokke, E. Tayama, and K. Maruoka, *Tetrahedron* **57**, 135, 2001.
- (8) A linear structure of the trimethylsilyl vinyl radicals has been previously claimed. See, for example: P. C. Montevecchi, M. L. Navacchia, P. Spagnolo, *Tetrahedron* 53, 7929, 1997.
- (9) Abstraction of the benzylic proton by the initially generated vinyl radical seemed to be involved.
- (10) Exposure of **11a** to Bu₃SnH/*cat*. AIBN in refluxing benzene for 2.5 h afforded a deteriorated mixture.

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