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2,3-Disubstituted Tetrahydrofuran Synthesis via Radical and Anionic Cyclization

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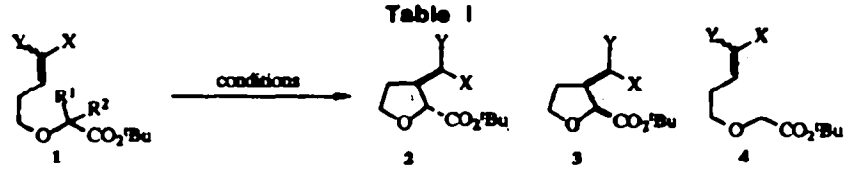
Key Words: substituted tetrahydrofurans; captodative stabilization; radical cyclization; anionic cyclization

Abstract: *Cyclization of the radicals derived from C-S bond homolysis as well as via 1,5-hydrogen atom transfer afforded tetrahydrofurans in high yield. An alternative anionic cyclization method provided the anti diastereomer preferentially.*

Hydropyran and hydrofuran subunits are prevalent in natural polyether-ionophore antibiotics.[1] We have developed two complementary approaches for the preparation of tetrahydropyrans: the dioxanone-to-dihydropyran route, leading to the formation of *syn* 2,3-substituted hydropyrans,[2] and a radical cyclization method, affording *anti* 2,3-substituted tetrahydropyrans.[3] Reported herein are examples of newly developed tetrahydrofuran syntheses[4] via radical[5] and anionic cyclizations.[6]

Table I



substrate	conditions (yield)	products (ratio)
1a; X = $SiMe_2Ph$, Y = R^1 = H, R^2 = SPh (*E*/*Z* = 4/1)	Ph_3SnH, AIBN, PhH reflux, 15 h (95%)	**2a** : **3a** (2:1)
1b; X = R^2 = SPh, Y = R^1 = H (*E*/*Z* = 1/1)	Ph_3SnH, AIBN, PhH reflux, 14 h (95%)	**2b** : **3b** : **4b** (4.7:2.3:1)
1c; X = R^1 = R^2 = SPh, Y = H (*E*/*Z* = 1/1)	2 eq. Ph_3SnH, Et_3B $PhCH_3$, 25 °C, 20 h (89%)	**2b** : **3b** (1:1.5)
1d; X = Y = SPh, R^1 = R^2 = H	LiHMDS, THF, -78 °C, 1 h; aq. NH_4Cl, -78 °C (81%)	**2d** (exclusive)
2d	Ph_3SnH, AIBN, PhH reflux, 22 h (84%)	**2b** (exclusive)

The first two examples in **Table I** feature the cyclization of stabilized radicals arising from C-S bond homolysis.[7] Treatment of vinylsilane **1a** with triphenylstannane resulted in the exclusive formation of tetrahydrofurans **2a** and **3a** via 5-*exo* cyclization, in a ratio of 2:1.[8] Vinyl sulfide **1b** led to the formation of tetrahydrofurans **2b** and **3b** as well as simple reduction product **4b** in a ratio of 4.7:2.3:1, respectively. Although radical cyclizations of analogous all-carbon systems afford *syn* diastereomers as major products,[9] *anti* isomers were observed as the major cyclization products in our systems.[10] We invoke a relatively late, compact transition structure for these cyclizations, reflecting the captodative stabilization of the radicals, the shortened C-O bonds, and the compressed C-O-C bond angle.[11] Non-bonded interactions should thus be more important in determining energies so that the chair transition state **6** with the *t*-butyl ester group in a pseudo-axial position would be favored over the other chair conformer **5** with the ester group in a pseudo-equatorial position (**Figure I**).[12]

Figure I

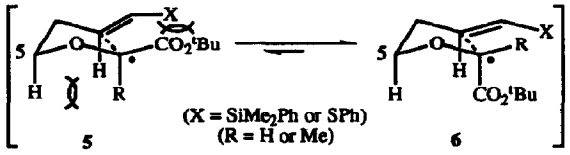


Figure II

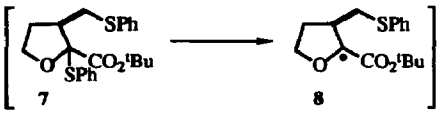
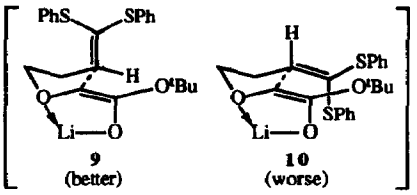


Figure III



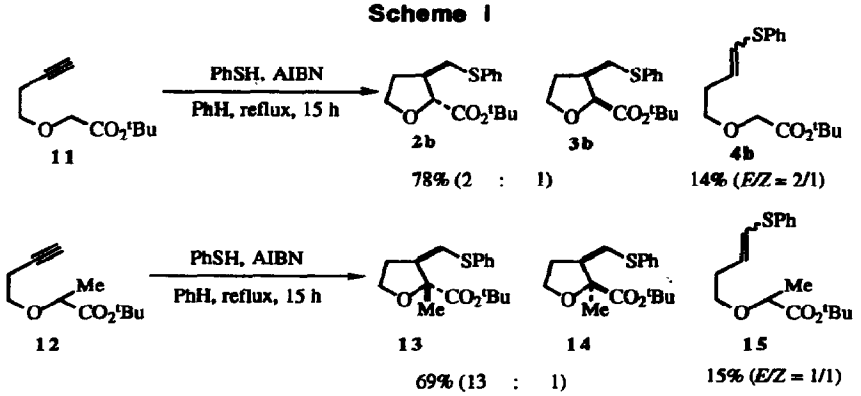
In an attempt at diastereoselectivity reversal, the radical precursor **1c** was treated at 25 °C[13] with two equivalents of triphenylstannane, yielding tetrahydrofurans **2b** and **3b** in a 1:1.5 ratio. The modest stereochemical reversal arises from preferential α-face hydrogen atom transfer from triphenylstannane to the radical species **8** which was, in turn, derived from the C-S bond homolysis of the initial cyclization product **7** (**Figure II**).[14] As an example of anionic cyclization,[6] intramolecular Michael type addition of the enolate derived from ester **1d** gave rise to the exclusive formation of the *anti* tetrahydrofuran **2d** in 81% yield (57% conversion). Alkoxy enolate chelation would suggest [3.3.0] bicyclic conformations **9** and **10** for cyclization, where the olefinic substituents in the transition state **10** would be sterically encumbered,[6c,d] rendering this conformation energetically disfavored (**Figure III**). Interestingly, conversion of **2d** to **2b** under the conditions employed in the radical cyclization reactions was carried out without any isomerization, strongly implying irreversibility in the radical cyclization of **1b**.

As an alternative radical generation method, the translocation of radical sites by intramolecular 1,5-hydrogen atom transfer[15] was achieved as shown in **Scheme I**. Slow addition of thiophenol to the refluxing benzene solution of the alkyne **11** and AIBN resulted in a very similar result to the radical cyclization of thioether **1b**, implying the presence of the same reacting species. The rationale for this observation is that the intramolecular 1,5-hydrogen atom transfer in the incipient radical took place after the addition of the phenylthio radical to the triple bond terminus of **11**. This method provides

shorter sequences leading to tetrahydrofuran formation than the C-S bond homolysis route. Remarkably, the alkyne **12** delivered the tetrahydrofurans **13** and **14** in a 13:1 ratio under the same conditions.[10] The enhanced diastereoselectivity was rationalized by comparing two chair transition conformers **5** and **6** (**Figure 1**), where the unfavorable conformer **5** leading to the formation of the minor cyclization product would involve the added 1,3-diaxial repulsion between the hydrogen at the C(5) center (tetrahydrofuran numbering) and the axially disposed methyl group.[16]

As demonstrated, the cyclization protocols discussed herein constitute new methods for the facile construction of a variety of tetrahydrofurans, and their application to natural product synthesis is described in the succeeding letter.

Scheme I



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REFERENCES AND NOTES

1. (a) Westley, J. W., Ed. *Polyether Antibiotics*; Marcel Dekker: New York, 1983; Vols. I and II. (b) Doblem, M. *Ionophores and Their Structures*; Wiley-Interscience: New York, 1981. (c) Robinson, J. A. *Prog. Chem. Org. Nat. Prod.* **1991**, *58*, 1.
2. (a) Burke, S. D.; Armistead, D. M.; Schoenen, F. J.; Fevig, J. M. *Tetrahedron* **1986**, *42*, 2787. (b) Burke, S. D.; Piscopio, A. D.; Kort, M. E.; Matulenko, M. A.; Parker, M. H.; Armistead, D. M.; Shankaran, K. *J. Org. Chem.* **1994**, *59*, 332. (c) Burke, S. D.; Lee, K. C.; Santafianos, D. *Tetrahedron Lett.* **1991**, *32*, 3957. (d) Burke, S. D.; Buchanan, J. L.; Rovin, J. D. *Tetrahedron Lett.* **1991**, *32*, 3961.
3. Burke, S. D.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 2335.
4. For recent reviews on tetrahydrofuran synthesis, see: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (b) Harmange, J.-C.; Figadère, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711.
5. For recent comprehensive reviews, see: (a) Curran, D. P. *Synthesis* **1988**, 417 and 489. (b) Giese, B. *Radicals in Organic Synthesis; Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986. (c) Hart, D. J. *Science* **1984**, *223*, 883. (d) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (e) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. For recent

examples of tetrahydrofuran synthesis via radical cyclization, see: (f) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741. (g) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564. (h) Rawal, V. H.; Singh, S. P.; Dufour, C.; Michoud, C. *J. Org. Chem.* **1991**, *56*, 5245. (i) Lolkema, L. D. M.; Hiemstra, H.; Al Ghouch, A. A.; Speckamp, W. N. *Tetrahedron Lett.* **1991**, *32*, 1491.

6. For recent examples of tetrahydrofuran synthesis via anionic cyclization, see: (a) Kalantar, T. H.; Sharpless, K. B. *Acta Chem. Scand.* **1993**, *47*, 307. (b) Fujisawa, T.; Okumura, Y.; Sato, T. *Chem. Lett.* **1990**, 593. (c) Broka, C. A.; Lee, W. J.; Shen, T. *J. Org. Chem.* **1988**, *53*, 1336. (d) Broka, C. A.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981.
7. Beckwith, A. L. J.; Pigou, P. E. *Aust. J. Chem.* **1986**, *39*, 77.
8. The preparation of cyclization substrates and conditions will be discussed in detail elsewhere.
9. (a) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373. (b) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. (c) Houk, K. N.; Paddon-Row, M. N.; Spellmeyer, D. C.; Rondan, N. G.; Nagase, S. N. *J. Org. Chem.* **1986**, *51*, 2874. (d) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.
10. The structures and stereochemistry of cyclization products were elucidated spectroscopically and by chemical transformation: See the succeeding paper. The structure of tetrahydrofuran **2b** was determined by single crystal X-ray analysis.
11. For captodative stabilization, see: (a) Bordwell, F. G.; Bausch, M. J.; Cheng, J.-P.; Cripe, T. H.; Lynch, T.-Y.; Mueller, M. E. *J. Org. Chem.* **1990**, *55*, 58. (b) Viehe, H. G.; Merényi, R.; Stella, L.; Janousek, Z. *Angew. Chem.* **1979**, *91*, 982. (c) Viehe, H. G.; Janousek, Z.; Merényi, R. *Acc. Chem. Res.* **1985**, *18*, 148. For the rotational barrier around the C-O bond due to spin delocalization, see: (d) Beckwith, A. L. J.; Glover, S. A. *Aust. J. Chem.* **1987**, *40*, 157.
12. (a) Reference 3. For the stereochemical comparison with all-carbon systems varying substituents, see: (b) Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140 and references cited therein.
13. (a) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547. (b) Ichinose, Y.; Matsunaga, S.; Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1989**, *30*, 3155. (c) Takeyama, Y.; Ichinose, Y.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1989**, *30*, 3159. It is believed that trace oxygen reacts with triethylborane to initiate the radical chain process: (d) Brown, H. C.; Midland, M. M. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 692.
14. In the cases where the reaction was incomplete, the intermediate **7** was isolated as a diastereomeric mixture.
15. (a) Curran, D. P.; Kim, D.; Liu, H. T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900. (b) Burgess, V. A.; Easton, C. J.; Hay, M. P. *J. Am. Chem. Soc.* **1989**, *111*, 1047.
16. In the preferred transition state, the methyl group would be located in a pseudo-equatorial position. In cyclohexane systems, the *A*-value of the methyl substituent is greater than that of the ester: (a) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper & Row Publishers: New York, 3rd ed., 1987, p. 139. (b) Jensen, F. R.; Bushweller, C. H.; Beck, B. H. *J. Am. Chem. Soc.* **1969**, *91*, 344.

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