Double Radical Cyclization/ β-Fragmentation of Acyclic ω-Yne Vinyl Sulfides. Synthesis of 3-Vinyldihydrothiophene and Dihydrothiopyran Derivatives. A New Example of a 5-*endo-trig* Radical Cyclization

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Free-radical chemistry has greatly expanded the repertoire of organic chemists over the last two decades and has proved to be a powerful method for tandem reactions that allow the formation of multiple carbon−carbon bonds in a one-pot reaction.[1] Radical cyclization and radical rearrangement−cyclization have been more and more utilized for the construction of elaborated molecules.[2] Herein, we report a new method for the synthesis of 3-vinyldihydrothiophene and dihydrothiopyran derivatives **2** via a double radical cyclization/β-fragmentation of acyclic ω-yne vinyl sulfides **1** regio-, chemo-, and stereoselectively (Scheme 1). This strategy involves five elemental processes: (i) intermolecular addition of a stannyl radical onto a terminal triple bond; (ii) 5- or 6-*exo-trig* cyclization of the *Z* vinyl radical;[3] (iii) β-fragmentation;[4] (iv) 5- or 6-*endo-trig* cyclization of the sulfur-centered radical; and (v) β-fragmentation of the tin radical. Although the 5-*endo-trig* cyclization ($n = 1$) is known to be a disfavored process,[5] the final fragmentation of the stannyl radical would drive the reaction toward the formation of the heterocycle **2**, terminating the radical chain. In this manner, the process is expected to be catalytic in tin hydride. In addition, it is noteworthy that the stereochemistry of **1** is of no consequence to the outcome with the formation of the less hindered *E* olefin.

The syntheses of the radical precursors (Table 1) were achieved in four steps from the commercially available 3-butyn-1-ol ($n = 1$) and 4-pentyn-1-ol ($n = 2$). The alcohols were first activated as the mesylates, which were displaced with a mixture of thiolacetic acid and cesium carbonate[6] in acetonitrile. Finally, deprotection with potassium carbonate in methanol afforded the thiols in

Scheme 1

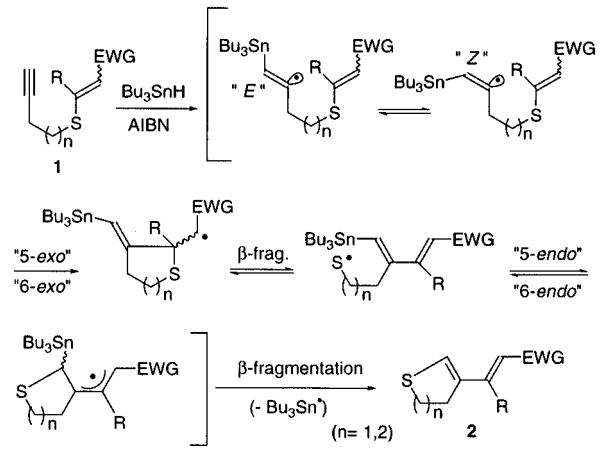
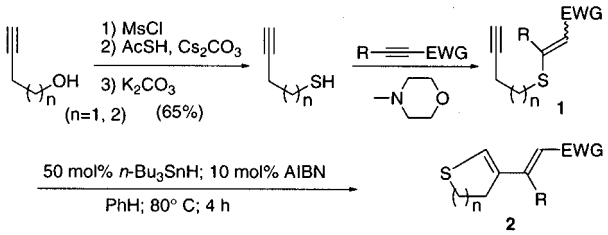


Table 1. Preparation of the Vinyl Sulfides 1 and Their Radical Cyclization to 2



entry	*n*	R	EWG	yield of **1** (%)[a]/*E*:*Z*	yield of **2** (%)[a]
a	1	H	CO_2Et	92/85:15[b]	64
b	1	n-C_4H_9	CO_2Et	65[c]/45:55[d]	62
c	1	H	SO_2-*p*-Tol	88/65:35[b]	0
d	2	H	CO_2Et	91/90:10[b]	73
e	2	n-C_4H_9	CO_2Et	62[c]/45:55[d]	78
f	2	CO_2Et	CO_2Et	86/37:63[d]	0

[a] Isolated yield (purified by silica gel chromatography). [b] Determined by the *J* coupling in the ^1H NMR. [c] The Michael addition of the thiol was achieved with a catalytic amount of sodium in ethanol.[8] [d] Determined by ^1H NMR−NOE experiment.

∼65% overall yield. Michael addition of the mercaptans onto an activated triple bond using *N*-methylmorpholine as the base in dichloromethane[7] gave **1** in good yields as a mixture of separable *E* and *Z* isomers.

Different chemical mediators, such as tris(trimethylsilyl)silane (TTMSS),[9] Et_3B−Ph_3SnH,[10] and thiophenol-AIBN were used to perform the radical cyclization but the best results were obtained when the reaction was carried out in a refluxing degassed benzene solution of **1a** and **1b** (or toluene at 80 °C) with 50 mol % of n-Bu_3SnH in the presence of AIBN catalyst at 0.02 M concentration for 4 h.[11] The reaction proceeded cleanly[12] with a regioselective 5-*endo-trig* cyclization, which gave the dihydrothiophene derivatives **2a** and **2b** in 64% and 62%

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(1) For reviews, see: (a) Curran, D. P. Radical Addition Reactions and Radical Cyclizations and Sequential Radical Reactions. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming I., Eds.; Pergamon: New York, 1992; Vol. 4, pp 715−831. (b) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev. (Washington, D.C.)* **1991**, *91*, 1237−1286. (c) Curran, D. P. *Synthesis* **1988**, 417−439 and 489−513. (d) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103−13159. (e) Malacria, M. *Chem. Rev. (Washington, D.C.)* **1996**, *96*, 289−306.

(2) For a recent example, see: Jung, M. E.; Rayle, H. L. *J. Org. Chem.* **1997**, *62*, 4601−4609 and references therein.

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(10) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547−2549.

(11) In a typical procedure, n-Bu_3SnH (135 μL, 0.5 mmol) was added to a degassed benzene solution (50 mL) containing AIBN (14 mg, 0.1 mmol) and **1** (1.0 mmol). The mixture was allowed to reflux (80 °C) under nitrogen for 4 h, cooled to room temperature, and concentrated in vacuo to give an oil that was flash chromatographed (silica) with a 5/95 mixture of ethyl acetate and hexane as eluent to give **2** as a colorless oil.

(12) Only the cyclized product **2** and tributyltin hydride could be evidenced in a clean crude ^1H NMR.

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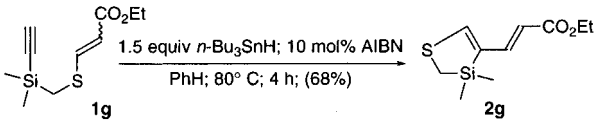
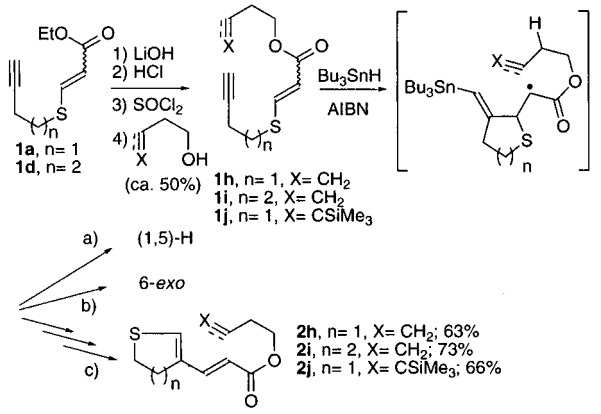
Scheme 2



Scheme 3

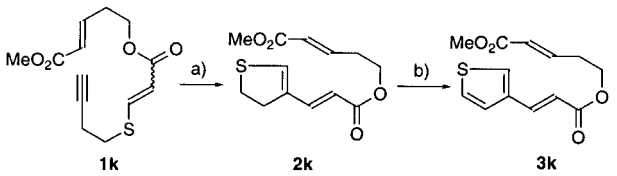


yield, respectively. The 6-*endo-trig* cyclization was also successfully accomplished with **1d** and **1e** to yield the dihydrothiopyran **2d** (73%) and **2e** (78%). As expected, the same result was obtained when the cyclization was run independently with the vinyl sulfide as a pure isomer or a mixture of both, leading to the *E* stereomer whose stereochemistry was assigned by ^{1}H NMR−NOE experiments for **2b** and **2e**. In the case of the sulfone[13] and the diester, no cyclization occurred; instead **1c** and **1f** underwent isomerization. Indeed, (*Z*)-**1c** gave (*E*)-**1c** under the reaction conditions. The tributyltin radical added chemoselectively to the strong electron-withdrawing vinyl sulfone (α to the divalent sulfur) instead of the terminal triple bond. For **1f**, the addition occurred probably at the less hindered *β* position, leading to a stable captodative radical.

This strategy was then used to synthesize an interesting new heterocycle **2g** containing both a sulfur and a silicon atom at the α and α′ positions of the endocyclic trisubstituted double bond in 68% isolated yield (Scheme 2). In this case, we preferred to use more tin hydride (1.5 equiv) due to the slow cyclization of **1g**[14] under the catalytic conditions.

This system is well-suited for a potentially new tandem radical cyclization/intramolecular [4 + 2] cycloaddition.[15] The cyclization was investigated with an *ω*-yne vinyl sulfide bearing extra unsaturation that would form the heterocycle **2** properly constituted to undergo an intramolecular Diels−Alder reaction (Scheme 3). The first cyclization would generate a *β*-sulfur radical that could further react through three different intramolecular pathways: (a) 1,5-hydrogen atom transfer;[16] (b) 6-*exo* cyclization; or (c) *β* -fragmentation followed by recyclization.

Scheme 4[a]



[a] Key: (a) 1.5 equiv of Bu_3SnH, 0.1 equiv of AIBN, PhH (80 °C), 4 h; 63%; (b) *o,o*-dichlorobenzene (180 °C), 80 h (ca. 40% conversion).

Addition of 3-buten-1-ol and 4-(trimethylsilyl)-3-butyn-1-ol to the acid chloride made from **1a** (*n* = 1) or **1d** (*n* = 2) provided a short and efficient access to the polyunsaturated precursors **1h**−**j**. The radical cyclizations of the alkenyl esters **1h** and **1i** proceeded as cleanly as the saturated cases with the same regio-, chemo-, and stereoselectivity. Nevertheless, the reaction was slower, and 1.5 equiv of tin hydride was required to reach completion within 4 h, leading to **2h** and **2i** in 63% and 73% yield, respectively, as the only isolable products of the reaction. Neither compound resulting from pathway a[17] or b or from a subsequent [4 + 2] cycloaddition was observed. The behavior of the alkynyl ester **1j**, under the catalytic conditions,[11] was identical, giving **2j** in 66% isolated yield.

The above conditions did not provide a subsequent Diels−Alder reaction with the unactivated dienophiles. Incorporating the requisite functional group, the ester **1k** was submitted to the radical cyclization for 4 h (with 1.5 equiv of *n*-Bu_3SnH), but the reaction temperature (80 °C) was not high enough for the cycloaddition to occur. Compound **2k** was isolated as the sole product in 63% yield (Scheme 4). Only aromatization[18] of **2k** into the thiophene **3k**[19] was evidenced (ca. 40% conversion) when harsher conditions were used (180 °C for 80 h).[20]

In conclusion, we have described a new synthesis of 3-vinyldihydrothiophenes, involving a rare 5-*endo-trig* cyclization, and dihydrothiopyran derivatives via a double radical cyclization/*β*-fragmentation of acyclic *ω*-yne vinyl sulfides regio-, chemo-, and stereoselectively. This new example demonstrates the usefulness of tandem radical cyclizations as a powerful tool in organic synthesis, and we believe that the straightforward simplicity of this one-step route may make it attractive for the synthesis of interesting sulfur-containing heterocyclic intermediates.

Acknowledgment. We thank Lisa DiMichele for the ^{1}H NMR−NOE experiments.

Supporting Information Available: Experimental procedure and characterization for the synthesis of the vinyl sulfides **1a**−**k** and their radical cyclization **2a**,**b**,**d**,**e**,**g**−**k**. Copy of ^{1}H NMR spectrum of compound **1g** (7 pages).

JO971787N

(13) For the synthesis of ethynyl *p*-tolyl sulfone, see: Waykole, L.; Paquette, L. A. *Org. Synth.* **1988**, *67*, 149−156.

(14) The synthesis of **1g** was achieved in four steps in 61% overall yield as a 9:1 mixture of *E* and *Z* stereomers: (i) addition of ethynylmagnesium bromide to (bromomethyl)chlorodimethylsilane; (ii) formation of the thioacetate by displacement of the bromide with thiolacetic acid and cesium carbonate;[6] (iii) hydrolysis of the acetate with 2 equiv of DiBal-H; (iv) Michael addition of the thiol to ethyl propiolate with *N*-methylmorpholine in dichloromethane.

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(17) An allylic radical would result from a 1,5-hydrogen atom transfer, which would be probably reduced as a primary radical with migration of the terminal double bond.

(18) The ^{1}H NMR spectrum showed that the alkenyl chain did not change, indicating that no cycloaddition had occurred. The formation of the thiophene **3k** was clearly evidenced by the appearance of its aromatic protons: 7.50 (d, *J* = 2.8 Hz, 1H), 7.34 (dd, *J* = 5.1 and 2.8 Hz, 1H), 7.29 (d, *J* = 5.1 Hz, 1H).

(19) 3-Substituted thiophenes are important key intermediates for the synthesis of natural products. For a review, see: Schulz, E.; Fahmi, M.; Lemaire, M. *Acros Organics Acta* **1995**, *1*, 10−17.

(20) An excess of the Lewis acid Et_2AlCl (>2 equiv) at 120 °C for 16 h also provided the thiophene **3k** in ca. 50% conversion as the only product.