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# New Cyclization of 4-Oxahepta-1,6-diynes Bearing Sulfur and Selenium Functional Groups

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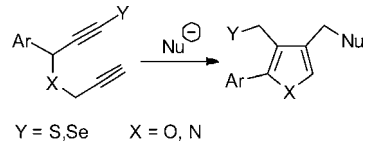
## ABSTRACT




**New cyclizations of 1-sulfanyl- and -selanyl-4-oxa-1,6-heptadiynes using sodium alkoxide or thiolates provided 4-alkoxymethyl-3-phenylsulfanyl- and 3,4-bis(sulfanylmethyl)furans in high yields.**

Furans are important heterocycles found in natural products and biologically active compounds. Accordingly, substantial attention has been paid to discover efficient synthetic routes to furans.[1] Cycloaddition or cycloisomerization is a powerful approach to synthesize aromatic heterocycles. The most widely used methods for the synthesis of furans proceed via cycloisomerization of alkynyl and allenyl ketones.[2] Alternative approaches to the synthesis of substituted furans involve a similar cyclization of the corresponding alcohols or epoxides.[3] The practical applicability of these methods depends on the ease of access to alkynyl and allenyl precursors and the precursor's stability under the isomerization conditions.[4] In general, alkynes are better starting materials because of the easy interconversion of alkyne to allenes under basic conditions.[5] Numerous strategies for the synthesis of furans from alkynyl ketones, alcohols, and epoxides exist; however, annulation of 4-oxahepta-1,6-diynes has been limited.[6] While searching for new strategies based upon the concept of a simple cyclization using nontransition metals, we investigated the cyclization of 4-oxahepta-1,6-diynes (bispropargyl ethers), which easily convert to allenic ethers under basic conditions. However, the cyclization of

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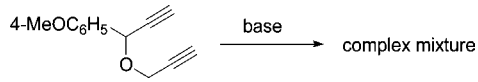
3-(*p*-methoxyphenyl)-4-oxahepta-1,6-diyne to furans did not succeed under some basic conditions, as shown in Scheme 1. Therefore, we selected 4-oxahepta-1,6-diynes bearing

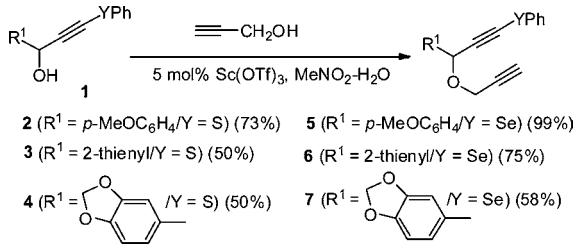
**Scheme 1.** Base-Promoted Cyclization of 4-Oxahepta-1,6-diyne




sulfur and selenium functional groups as a precursor because of the unique reactivity.[7] Here, we report a powerful tool for the synthesis of 3,4-disubstituted furans and pyrroles via 4-oxa- and 4-azahepta-1,6-diynes bearing sulfur and selenium functional groups.

In our initial study, we prepared diynes bearing sulfur or selenium functional groups by developing a new method for the formation of a direct C−O bond from the corresponding propargyl alcohols, which was modified on our original C−C bond formation or thiazole constructions.[8] Treatment of 1-*p*-methoxyphenyl-3-(phenylsulfanyl)propargyl alcohol **1** with 2-propyn-1-ol, scandium triflate (1−5 mol %) in $MeNO_2$−$H_2O$ (10:1) gave some type of sulfanyl and selanyl 4-oxaheptadiynes **2**−**7** (Scheme 2).

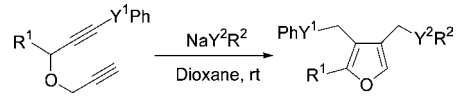
**Scheme 2.** Preparations of Sulfanyl and Selanyl 4-Oxohepta-1,6-diynes

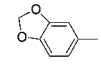
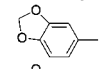
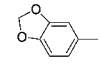
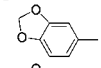
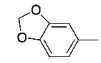



First, we selected 3-(*p*-methoxyphenyl)-4-oxahepta-1,6-diyne (**2**) as a substrate in order to determine the appropriate reaction conditions and examined the reaction with sodium methoxide in THF−MeOH. The reaction completed at 0 °C and afforded product **8a** in 99% yield. The structure of the compound **8a** was determined from the existence of two characteristic methylene groups at $\delta$ 3.82 and 4.18 in the $^1$H NMR spectrum. Furthermore, a singlet corresponding to the furyl proton was also observed at $\delta$ 7.35 ppm. The spectral data obtained indicated the presence of trisubstituted furans.

In order to elucidate the structure, we performed the desulfanylation of **8a** with $Bu_3SnH$/AIBN in toluene. The product, 4-methoxymethyl-2-(4-methoxyphenyl)-3-methylfuran, was obtained in 47% yield. These observations confirmed that the addition of $MeO^-$ took place at the nonsubstituted alkynyl group, while the alternative alkyne bearing sulfanyl group was found to act as a good electrophile. The optimization of this reaction was examined in 1,4-dioxane−alcohol (1:10), and the results of the reactions of 3-aryl-1-sulfanyl and 1-selanylhexa-1,6-diynes with simple alkoxides are shown in Table 1. Sodium ethoxide also gave

**Table 1.** Cycloisomerization of 4-Oxahepta-1,6-diynes




| run | $Y^1$ | alcohol **1** $R^1$ | $R^2$ | $Y^2$ | product (%yield)[a] |
|---|---|---|---|---|---|
| 1 | S | *p*-$MeOC_6H_4$ | Me | O | **8a** (99) |
| 2 | S | *p*-$MeOC_6H_4$ | Et | O | **8b** (73) |
| 3 | S | 2-thienyl | Me | O | **9** (99) |
| 4 | S |  | Me | O | **10** (73) |
| 5 | Se | *p*-$MeOC_6H_4$ | Et | O | **11** (80) |
| 6 | Se | 2-thienyl | Me | O | **12a** (99)[c] |
| 7 | Se | 2-thienyl | Et | O | **12b** (89)[c] |
| 8 | Se |  | Me | O | **13a** (99) |
| 9 | Se |  | Et | O | **13b** (91) |
| 10 | S | *p*-$MeOC_6H_4$ | Ph | S[b] | **14a** (73) |
| 11 | S | *p*-$MeOC_6H_4$ | *p*-$ClC_6H_4$ | S | **14b** (73) |
| 12 | S | *p*-$MeOC_6H_4$ | 2-PyS | S | **14c** (76) |
| 13 | S | 2-thienyl | Ph | S | **15a** (73) |
| 14 | S | 2-thienyl | 2-PyS | S | **15b** (76) |
| 15 | S | 2-thienyl | 2-NaphS | S | **15c** (93) |
| 16 | Se | *p*-$MeOC_6H_4$ | Ph | S | **16** (54) |
| 17 | Se |  | Ph | S | **17a** (61) |
| 18 | Se |  | 2-PyS | S | **17b** (45) |

[a] The reaction was carried out with sodium alkoxide (2−5 equiv) in 1,4-dioxane−alcohol (1:10) at 30 °C over 10−60 min. [b] The reaction was carried out in dioxane−alcohol using sodium alkoxide (2−3 equiv)−sodium thiolate (2 equiv) at 30 °C to reflux conditions. [c] The reactions provided 3,4-bis(selanylmethyl)furans in 2−3% yields.

the 4-ethoxymethyl furan **8b**, accompanied by a small amount of 3,4-bis(phenylsulfanylmethyl)furan **14a**. Both 2-(2-thienyl)-furan **9** and 2-(benzodioxol-5-yl) **10** were obtained in high yields. Cyclization of the selenium-substituted diynes bearing

(6) Dihydrofuran from diyne: Pd: Wang, F.; Tong, X.; Cheng, J.; Zhang, Z. *Chem.*−*Eur. J.* **2004**, *10*, 5338. Rh: (b) Tanaka, K.; Otake, Y.; Wada, A.; Noguchi, K.; Hirano, M. *Org. Lett.* **2007**, *9*, 2203. (c) Bartlett, A. J.; Laird, T.; Ollis, W. D. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1315. Furan from enyne: (d) Parsons, P. J.; Waters, A. J.; Walter, D. S.; Board, J. *J. Org. Chem.* **2007**, *72*, 1395. Hg: (e) Barluenga, J.; Aznar, F.; Bayod, M. *Tetrahedron Lett.* **1988**, *29*, 5029. Base: Diels−Alder type: (f) Kudoh, T.; Mori, T.; Shirahama, M.; Yamada, M.; Ishikawa, T.; Saito, S.; Kobayashi, H. *J. Am. Chem. Soc.* **2007**, *129*, 4939.

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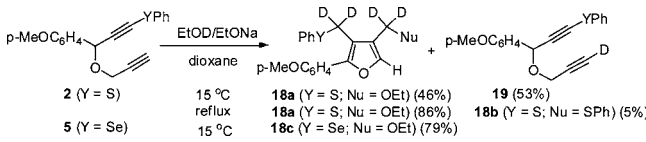
the similar substituents provided 3,4-disubstituted furans **12a**,**b** and **13a**,**b** (entries 5−9 of Table 1); however, 3,4-bis(phenylselanylmethyl)furan was formed from the reactions of the diynes containing diphenyl diselenide or diphenyl disulfide, which resulted from decomposition of the diynes under storing for a long time or a severe reaction conditions. This observation raises the possibility of using sodium thiolate as the nucleophile in the cyclization and prompted us to examine the cyclization using sodium thiolate, as shown in entries 10−18 of Table 1. The 3,4-bis(sulfanylmethyl)furans were efficiently obtained using a stoichiometric quantity of sodium thiolate and sodium alkoxide. A wide variety of thiolates generated the furans in high to excellent yields.

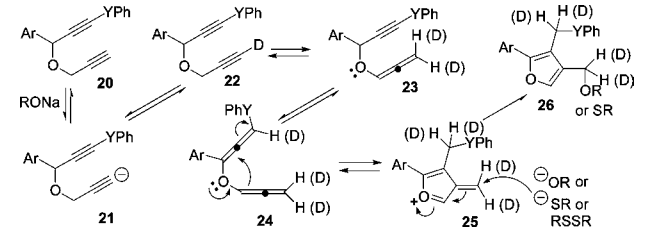
To gain additional support related to cyclization reactions, we attempted the reaction of sulfanyl- and selanyl-substituted diynes **2** and **5** with sodium ethoxide in EtOD (Scheme 3).

**Scheme 3.** Cyclization of 4-Oxaheptadiyne in EtONa/EtOD




The cyclized products obtained were tetradeuterated furans **18a**,**b**. Interestingly, in the reaction of **2**, the deuterated diyne **19** was recovered. Furthermore, the reaction of **2** under reflux condition gave both **18a** and **18b**. The structure of **18a** was determined by some spectral data showing two disappearing signals at $\delta$ 4.19 and 4.41 due to the methylene protons of **8b** in the $^1$H NMR spectrum and exhibiting the molecular ion due to $C_{21}H_{18}D_4O_3S$ at *m*/*z* 358 in the mass spectrum. These results suggest the cyclization sequence depicted in Scheme 4 as the

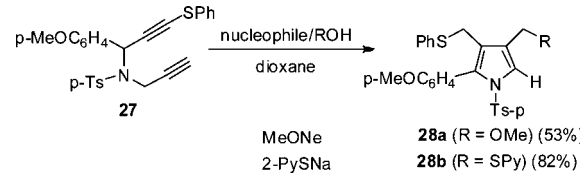
**Scheme 4.** Plausible Mechanism for Nucleophile-Initiated Cyclizations




possible reaction mechanism: (i) alkyne−allene isomerization of **22** first takes place via the acetylide **21** supported by the fact that the slow reaction of **2** with EtOD/EtONa gave rise to recovering the diyne **19**;[6f] (ii) second isomerization of **23**; (iii) intramolecular cyclization of 4-oxa-1,2,5,6-heptatetraene **24**; (iv) the successive addition of nucleophiles. Addition of alkoxide or thiolate to the cation intermediate **25** would regioselectively proceed to yield the trisubstituted furan **26** (Scheme 4). The alkoxide- or thiolate-initiated cyclization would also proceed on to the substituted alkynyl **23** or bisallenyl moiety **24**; however, it would be more probable that alkoxide or thiolate nucleophiles add to the cationic intermediate **25** because of the excellent regioselectivities of the products and the difficulty in attacking the terminal allenic carbon of the allene **23**, instead of the central carbon of the allene. However, we could not find whether the hypothesis reqired further confirmation. The 3,4-bis(selanylmethyl) and bis(sulfanylmethyl)furans **26** as byproduct (entries 5−9 in Table 1) would also be obtained through the addition of either diphenyl diselenide or diphenyl disulfide on to the cationic **25**.

Inspired by the successful synthesis of furans, we attempted the cyclization of 4-azahepta-1,6-diynes bearing sulfur-substituted **27** by almost the same procedure (Scheme 5). The reaction of **27** with sodium methoxide provided

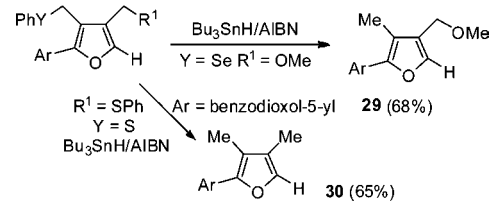
**Scheme 5.** Cyclization of 4-Azaheptadiynes




4-methoxymethylpyrrole **28a** in 53% yield. The reaction with sodium 2-pyridinethiolate also gave 3-phenylsulfanylmethyl-4-pyridylsulfanylmethylpyrrole **28b**.

We finally extended the functional transformation of the products. Desulfanylation of 3-sulfanylmethylfuran was improved using the selenium analogue as shown in Scheme 6. Furthermore, desulfanylation of bis(sulfanylmethyl)furan provided 3,4-dimethylfuran **30**.

**Scheme 6.** Transformations of Furans




In summary, we developed a powerful and novel protocol for the convergent synthesis of 3,4-disubstituted furans from 4-oxa- and 4-azahepta-1,6-diynes bearing sulfur or selenium functional groups. We also described the diverse mechanisms of cyclization. Further work, aimed at discovering the amide- or amino acid-promoted cyclizations of 4-oxa- and 4-azahepta-1,6-diynes, is in progress. These results will be reported elsewhere.

**Supporting Information Available:** Typical experiment procedures and spectral data for all of the new compounds, the copies for $^1$H and $^{13}$C NMR spectral data of **9**, **10**, **12b**, **14a**−**c**, **18a**,**b**, **28a**,**b**, **29**, and **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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