A New Synthesis of 2,3-Dihydrofurans: Cycloisomerization of Alkynyl Alcohols to Endocyclic Enol Ethers

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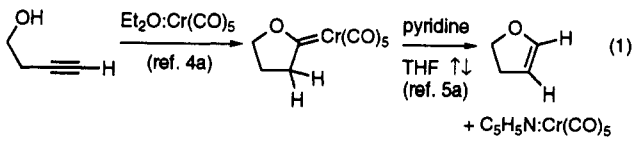
Summary: Molybdenum pentacarbonyl-trimethylamine promotes the cyclization of 1-alkyn-4-ols to the isomeric 2,3-dihydrofurans.

One of our research programs in cyclic ether synthesis requires a general cycloisomerization method for converting acyclic alkynols to endocyclic enol ethers. Applications of endocyclic enol ethers in synthetic organic chemistry include construction of glycoconjugates[2] as well as various polyether natural products.[3] A survey of the literature suggests a two-step procedure featuring cyclization of terminal alkynols to the corresponding pentacarbonylchromium oxacarbenes,[4a] followed by pyridine-induced conversion to enol ethers (eq 1).[5,6]



(1)

Herein we report our initial results with a reagent which mediates the cyclization of 1-alkyn-4-ols to the isomeric 2,3-dihydrofurans *in a single step.*

At the outset of our studies we proposed that tertiary amine-metal carbonyls[7] might serve as effective catalysts for the single-step conversion of alkynols to endocyclic enol ethers. We found that oxidative decarbonylation of chromium or tungsten hexacarbonyls with trimethylamine *N*-oxide (TMNO)[7] followed by addition of alkynyl alcohol **1**[8] gave facile conversion to the cyclic chromium and tungsten oxacarbenes **2** and **3** (Table I, entries 1 and 2), but the corresponding dihydrofurans were not observed. In contrast, the reaction of molybdenum hexacarbonyl/TMNO with **1** produced dihydrofuran **4**[9] without molybdenum oxacarbene formation.

This reaction is modestly catalytic, with the best preparative yield and reproducibility observed with 50 mol % of molybdenum hexacarbonyl and TMNO (entry 3).[10] Triethylamine as cosolvent accelerates the cycloisomerization reaction rate, whereas tetrahydrofuran or acetonitrile inhibits the reaction. Cycloisomerization is also promoted by the use of dimethyl sulfoxide (DMSO)[11] in place of TMNO, but no reaction occurs unless exogenous triethylamine is added. Substrates with C(3)-heteroatom substituents such as **10** and **12** tend to undergo elimination with both the molybdenum- and chromium-based systems to give furan derivatives **11** and **13**, respectively (entries 6 and 7).[12]

We presume that cycloisomerization proceeds by initial rearrangement of an η^2 metal-alkyne complex **14** to a vinylidene complex **15**.[13] Base-induced cyclization of the alcohol nucleophile might then afford the cyclic anionic intermediate **16** (Scheme I). Although protonation[14] of **16** at C2 would provide the neutral carbene **17** (as observed for the chromium and tungsten cases), protonation at C1 affords the dihydrofuran **4** and regenerates R_3N-$Mo(CO)_5$ as a potential catalyst. The formation of dihydrofurans at room temperature in the molybdenum-based system suggests that the activation barrier for **16** → **4** is signif-

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(8) 1: Brandsma, L. *Preparative Acetylenic Chemistry,* 2nd ed.; Elsevier: Amsterdam, 1988; p 67. **5**: from *rac*-glycidol and 2 equiv of lithium acetylide in THF, -78 °C to room temperature (Paterson, I.; Banks, B. J.; Gardner, M. *Tetrahedron* **1989**, *45*, 5283). **8**: from glycidyl pivaloate (Molander, G. A.; Bobbitt, K. L. *J. Org. Chem.* **1992**, *57*, 5031) and lithium acetylide/BF_3-etherate in THF, -78 °C to room temperature. **10**: from (*E*)-2-penten-4-yn-1-ol: (1) TBSCl, imidazole, DMF; (2) catalytic OsO_4, TMNO, aqueous acetone/THF. **12**: from (*E*)-2-penten-4-yn-1-ol: (1) *m*-CPBA, CH_2Cl_2, 0 °C. (2) Ti(O-*i*-Pr)$_4$, $TMSN_3$, toluene, 111 °C (Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 5185).

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(10) Addition of 1 to 10 mol % preformed Me_3N-$Mo(CO)_5$ complex[7b] provides compound **4** in 37% yield; substantial amounts of alkynol **1** are recovered after prolonged reaction times. While we cannot account for the complete balance of material in Table I, these reactions are generally clean by crude ^{1}H NMR. We attribute the loss of organic materials to entrainment or chemical incorporation in an insoluble byproduct which is produced in this reaction. All of the reactions in Table I should be run at room temperature; at elevated temperatures (i.e., refluxing ether) we observed only decomposition of organic materials.

(11) (a) Jeong, N.; Lee, S. J.; Lee, B. Y.; Chung, Y. K. *Tetrahedron Lett.* **1993**, *34*, 4027. (b) Chung, Y. K.; Lee, B. Y.; Jeong, N.; Hudecek, M.; Pauson, P. L. *Organometallics* **1993**, *12*, 220.

(12) Protection of the C(3) oxygen of **10** as a silyl ether (1 equiv of TBSCl, imidazole, DMF) provides low yields of the isomeric 2,3-dihydrofuran contaminated with furan **11**. The dihydrofuran product suffers partial elimination to the furan **11** upon silica gel chromatography.

(13) (a) Bruce, M. I.; Swincer, A. G. *Adv. Organomet. Chem.* **1983**, *22*, 59. (b) Bruce, M. I. *Chem. Rev.* **1991**, *91*, 197.

(14) Casey, C. P.; Brunsvold, W. R. *Inorg. Chem.* **1977**, *16*, 391.

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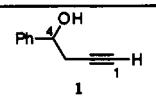
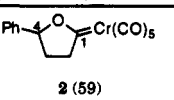
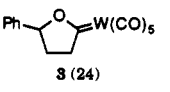
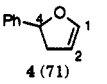
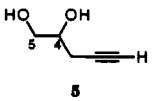
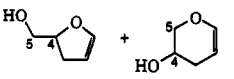
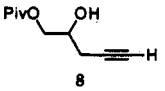
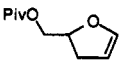
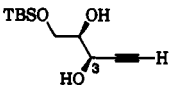
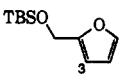
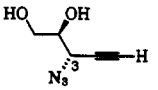
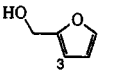
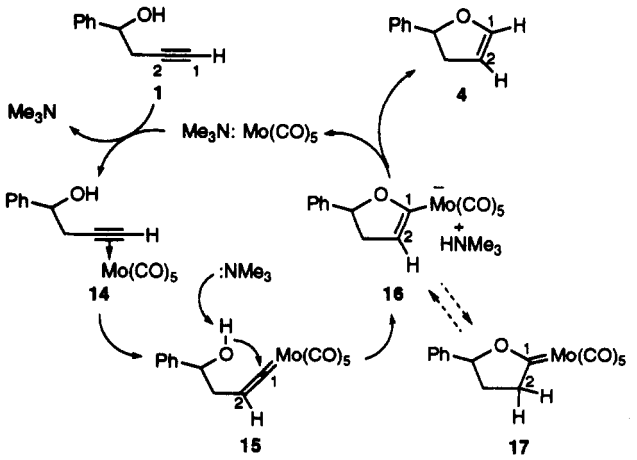
Table I. Products from Reaction of Alkynols with M(CO)$_6$/TMNO

entry	substrate[a]	conditions[a]	product (yield,[c] %)
1	 1	Me_3N-$Cr(CO)_5$[b] (1 equiv), Et_2O, 120 h	 2 (59)
2	1	$W(CO)_6$ (1 equiv), TMNO (1 equiv), Et_2O, 120 h	 3 (24)
3	1	$Mo(CO)_6$ (0.5 equiv), TMNO (0.5 equiv), Et_3N, Et_2O, 60 h	 4 (71)
4	 5	$Mo(CO)_6$ (0.5 equiv), TMNO (0.5 equiv), Et_3N, Et_2O, 92 h	 6 7 (ca. 9:1, combined yield 59%)
5	 8	$Mo(CO)_6$ (0.5 equiv), TMNO (0.5 equiv), Et_3N, Et_2O, 72 h	 9 (52)
6	 10	$Mo(CO)_6$ (1 equiv), TMNO (1 equiv), Et_3N, Et_2O, 19 h	 11 (58)
7	 12	$Mo(CO)_6$ (0.5 equiv), TMNO (0.5 equiv), Et_3N, Et_2O, 12 h	 13 (60)

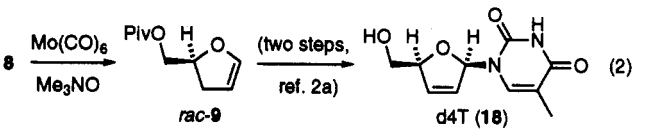
[a] $M(CO)_6$ and TMNO were dissolved in Et_2O (0.1 M) and Et_3N (0.03 M) under N_2 at 20 °C. The solution rapidly turned green (M = Cr), brown (M = Mo), or yellow (M = W), and after 30–60 min the alkynyl alcohol was added and stirred at 20 °C for the time indicated. Dihydrofuran products were isolated by evaporation of solvent followed by silica gel chromatography (pentane/Et_2O/1% diethylamine); carbene products were purified by silica gel chromatography (pentane/Et_2O) and recrystallized (pentane, −78 °C). [b] Preformed Me_3N-$Cr(CO)_5$ gave better yields than those obtained from *in situ* generation from $Cr(CO)_6$ and TMNO (1 → 2, 34% yield). [c] Isolated yields.

Scheme I. Proposed Mechanism for Cycloisomerization of 1 → 4



icantly lower for the molybdenum compounds than for chromium and tungsten analogs. Our observations may constitute another manifestation of the enhanced ligand lability of second-row organotransition metal compounds.[15,16]

Recent advances in asymmetric synthesis provide a variety of chiral, nonracemic 1-alkyn-4-ols as readily available substrates for the cycloisomerization process described herein.[17,18] For instance, our synthesis of furanoid glycal 9 from compound 8 represents a formal synthesis of the anti-AIDS nucleoside 2′,3′-didehydro-2′,3′-dideoxythymidine (d4T, 18; eq 2).[2a]



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Supplementary Material Available: A listing of NMR, IR, and analytical data for compounds 2–4, 6, and 9 (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(17) (a) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (b) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437.

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