[2 + 2 + 2]Cycloadditions of Alkynes to Furans and Thiophenes: A Cobalt-Mediated "Enol Ether Walk"

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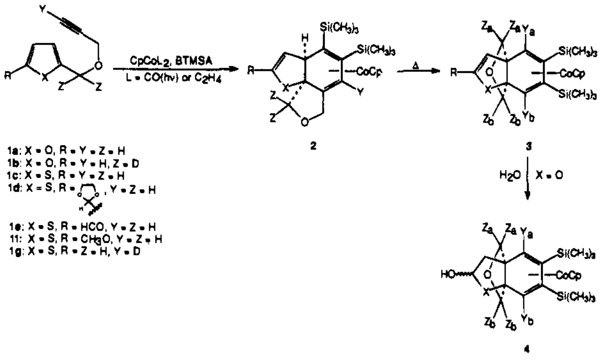
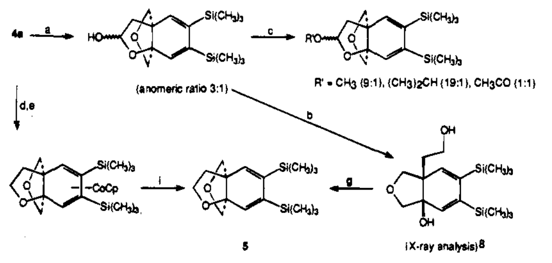
Involvement of the 2,3-double bond of furan and thiophene in cycloadditions is relatively uncommon, usually limited to specific substrates or by special conditions.[2,5a] Our finding that indoles,[3a] pyrroles,[3b] imidazoles,[3c] and uracils[3d] can be activated by CpCo to undergo cocyclizations with alkynes suggested an extension of these efforts to the title heterocycles, in particular because the latter constitute new brackets for the degree of aromaticity (furan lowest, thiophene highest)[4] that is subject to neutralization in these reactions and because the anticipated enol (thio)ether products exhibit potential synthetic utility.[5] Of concern with respect to the outcome of the proposed scheme were literature reports that indicated that, while transition metal π-complexation to the heteroaromatics in question was feasible, such treatment could lead to a number of alternative further reactions, including C−H activation and ring opening.[6]

Indeed, cobalt-mediated [2 + 2 + 2]cycloaddition of **1a** to solvent[3] bis(trimethylsilyl)acetylene (BTMSA, Scheme 1)[7] gave not the expected **2a** but rather the rearranged **3a** in the form of sensitive hemiacetal **4a** (47%, anomeric ratio 4:1), in which the spirofused enol ether bridge had migrated to furnish the less-strained (MM2 calculations on the free ligands) propellane framework.

Scheme 1

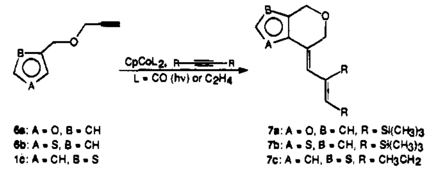


Scheme 2[a]



a (a) $CuCl_2{\cdot}2H_2O$) (4 equiv), CH_3CN, 81%; (b) $NaBH_4$ (4 equiv), $(CH_3)_2CHOH$, 79%; (c) CH_3OH, H_2SO_4, 80%, or $(CH_3)_2CHOH$, H_2SO_4, 84%, or $CH_3CO_2COCH_3$, $(CH_3CH_2)_3N$, 91%; (d) $NaBH_4$ (10 equiv), $(CH_3)_2CHOH$ (1H NMR characterization); (e) SiO_2, 80% from **4a**; (f) $CuCl_2$ (5 equiv), CH_3CN, 57%; (g) $BF_3{\cdot}(CH_3CH_2)_2O$ (6 equiv), CH_2Cl_2, 83%.

Scheme 3



Proof of the structure of **4a** was established by the extensive derivatization and correlation chemistry outlined in Scheme 2,[7] including an X-ray analysis.[8,9] It is of mechanistic relevance (vide infra) that **6a** transforms predominantly by seeming C_2−H activation[10] to **7a** (33%) and, remarkably, also (vide infra) to **4a** (4%) as the sole products (Scheme 3).[7] More telling is a labeling experiment with **1b**, providing **4b** with deuterium *extensively scrambled over positions a and b* [D_a:D_b = 2:1 (35 °C), 3.5:1 (90 °C); final ratios unchanged at 110 °C, 24 h].[11] Although D_a:D_b varies somewhat with the temperature of the cyclization, it remains unchanged in the product (110 °C, 24 h).[11]

A mechanism accommodating these results is shown in Scheme 4. It presupposes that the [2 + 2 + 2]cycloaddition proceeds initially as expected to generate **2** but that this species is capable of heterolytic ring-opening to the zwitterion **A**, featuring an enolate substituent attached to a relatively stable

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(1) (a) Universität-GH Essen. (b) University of California at Berkeley.

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(7) All new compounds isolated exhibited satisfactory analytical and/or spectroscopic or (**2d**, **3f**) X-ray data (see supplementary material). For the preparation of (or methods toward) starting materials, see: (a) Vereshchagin, L. I.; Kirillova, L. P.; Rechkina, A. V.; Kuimova, N. M. *Zh. Org. Khim.* **1971**, *7*, 907−912. (b) Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1975**, 3269−3270. (c) Benneche, T.; Strande, P.; Undheim, K. *Synthesis* **1983**, 762−763. (d) Carpenter, A. J.; Chadwick, D. J. *Tetrahedron* **1985**, *41*, 3803−3812. (e) Prugh, J. D.; Hartman, G. D.; Mallorga, P. J.; McKeever, B. M.; Michelson, S. R.; Murcko, M. A.; Schwam, H.; Smith, R. L.; Sondey, J. M.; Springer, J. P.; Sugrue, M. F. *J. Med. Chem.* **1991**, *34*, 1805−1818. (f) Sicé, J. *J. Am. Chem. Soc.* **1953**, *75*, 3697−3700. (g) Dowle, M. D.; Hayes, R.; Judd, D. B.; Williams, C. N. *Synthesis* **1983**, 73−75.

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(9) Similar results were obtained with **1** (X = O, R = CH_3), 2-(4-pentynyl)furan, and with **1a** and dimethyl butynedioate.

(10) For analogies, see: (a) Yamazaki, H.; Wakatsuki, Y. *J. Organomet. Chem.* **1978**, *149*, 377−393. (b) Selnau, H. E.; Merola, J. S. *Organometallics* **1993**, *12*, 3800−3801. (c) Robertson, M. J.; White, C. J.; Angelici, R. J. *J. Am. Chem. Soc.* **1994**, *116*, 5190−5195.

(11) The position of the label was detected by ^1H NMR experiments, most conveniently on **5**, in which assignments were readily made by NOE experiments.

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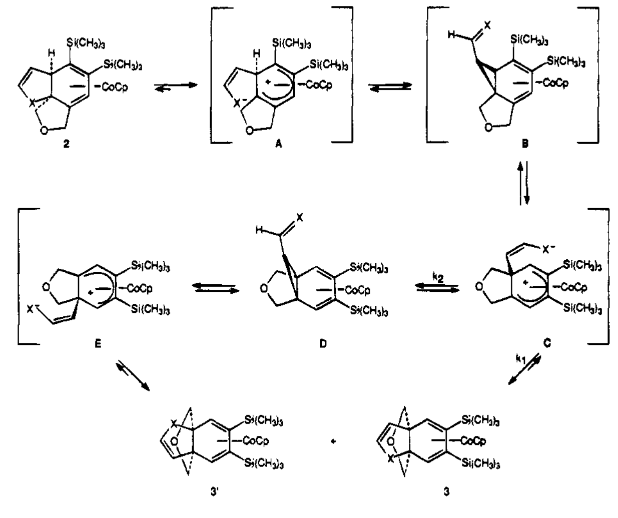
Scheme 4

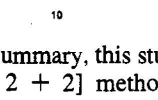


CpCo cyclohexadienyl cation.[12] Collapse of **A** by C–C bond formation would produce norcaradienecarbaldehyde **B**, which could reopen to zwitterion **C**. The latter can furnish **3** (Z_a = D) by direct closure at oxygen (k_1) or traverse (k_2) through another *but now symmetrical* norcaradienecarbaldehyde isomer **D** to **E** and then **3'** (Z_b = D and $k_1 \neq k_2$). The metamorphosis of **2** to **3** (and **6a** to **4a**) may also be rationalized by formulating a combination of 1,3- (the 2,3-dihydrofuran–cyclopropanecarbaldehyde equilibrium),[13] 3,5-,[14] and 1,5- (norcaradiene ringwalk)[15] sigmatropies, rendered less plausible by the insights gained with the thiophene analogs of **1a**.

Thus, **1c** underwent cycloaddition to BTMSA [5 equiv, toluene, 23 °C, CpCo $(C_2H_4)_2$], providing **2c** (8%) and **3c** (25%). Likewise, **1d** leads to **2d** only (43%), whereas **1e** and **1f** gave **3e** (3%) and **3f** (37%), respectively, as the only isolable materials (Scheme 1). The structural assignments of the entire series are cemented by X-ray analyses of **2d** and **3f**.[7] Surprisingly, **1c** and 3-hexyne converted to **7c** (38%) exclusively, the result of formal C_3–H activation, while **6b** mimicked **6a** (Scheme 3). The stereochemistry of the new diene unit in **7b,c** was corroborated by NOE experiments.

Mechanistically significant is that **2c**, **2d**, and **2e** (prepared from **2d**, 4-$CH_3C_6H_4SO_3H$, CH_3COCH_3, 23 °C, 58%) all underwent clean and essentially quantitative isomerization to **3c–e** above 80 °C (C_6H_6 or toluene). Specifically, **2c** followed first-order kinetics (C_6D_6 or THF-d_8) with $\Delta H^{\ddagger} = 27 \pm 1.5$ kcal mol^{-1} and $\Delta S^{\ddagger} = -7 \pm 4$ cal K^{-1}. The relative rates of conversion are in the order **2d**:**2c**:**2e** = 1:2.7:5.5. More instructive is the effect of solvent polarity in the reorganization of **2c** (95 °C): relative rates 1 (C_6D_{12}), 13 (C_6D_6), ~16 (THF-d_8), 258 (CD_3OD), ≫ 258 (CD_3CN), clearly consistent with rate-determining formation of zwitterions of the type **A** (Scheme 4).[16] A labeling experiment complementary to that using **1b** employed **1g**, cyclization of which produced **2g** and **3g** [D_b:D_a = 1.4:1 (23 °C)]. Independent isomerization of **2g** (>80 °C) ended in **3g** with D_b:D_a = 2.7:1 (unchanged by SiO_2 or heating to 130 °C for 56 h). Attempts to trap postulated intermediates **A–E** in the thermolysis of **2c** with hydride,[17] dienes,[18] and electrophiles[19] had no effect on the emergence of **3c**.

Oxidative demetalation ($CuCl_2 \cdot 2H_2O$, Et_3N, CH_3CN, 23 °C) of **2c–e** required added Et_3N to avoid decomposition and liberated the intact ligands **8** (~50%), which decomposed on heating (C_6D_6, 85 °C) or attempted recomplexation [C_6D_6, $CpCo(C_2H_4)_2$]. On the other hand, propellane complex **3c** released its ligand **9c** (63%) unchanged only in the *absence* of Et_3N, whereas the presence of the latter allowed isolation of the new isomer **10** (41%),[12c] in addition to **9c** (21%). Both isomers are stable at 80 °C (13 h) and to the oxidative demetalation mixture; **9c** is also inert to exposure to CpCo-$(C_2H_4)_2$ (3 days, 23 °C). In contrast, **10** is reconstituted rapidly to the more stable **9c** [MM2: $\Delta H^\circ_f(\mathbf{9c})$ = 27.81 kcal mol^{-1}, $\Delta H^\circ_f(\mathbf{10c})$ = 30.57 kcal mol^{-1}][7] with catalytic $CpCo(C_2H_4)_2$ (0.2 equiv, 15 min, 65%), presumably via a direct 1,5-shift mechanism perhaps mediated by a sulfur-complexed metal. Be that as it may, it is clear that the enol ether "walk" (Scheme 4) requires the presence of the η^4-diene CpCo unit. Finally, attempted decomplexation of **3f** (no Et_3N) effected chlorination[20] to complex **11** (34%), while hydrolysis unmasked ketone **12** (4-$CH_3C_6H_4SO_3H$, CH_3COCH_3, 23 °C, 21%).



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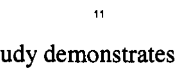

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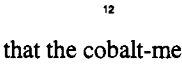

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In summary, this study demonstrates that the cobalt-mediated [2 + 2 + 2] methodology can be extended to furans and thiophenes but that in these, and possibly generally in related heteroalkenes, the generation of potential dienylic leaving groups in the resulting CpCo diene product may cause rearrangements and that formal C–H activations may complicate the outcome of the reaction. The observation that the relatively highly aromatic thiophene nucleus functions as a cocyclization partner points the way to a number of even more challenging substrates in this process.

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Supplementary Material Available: Experimental, spectral, analytical, and X-ray (for **2d**, **3f**) data for all new compounds (55 pages); observed and calculated structure factors for **2d** and **3f** (37 pages). This material is contained in many 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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