

Synthesis and some (4+3) -cycloaddition chemistry of a sulfur-substituted allylic acetal

Michael Harmata* and Kevin W. Carter

Department of Chemistry, University of Missouri-Columbia, Columbia, Missouri 65211

E-mail: harmatam@missouri.edu

Dedicated to Professor Albert Padwa on the occasion of his 65th birthday

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Abstract

The preparation of a sulfur-substituted allylic acetal is described and its application in 4+3 cycloaddition reactions with furan and cyclopentadiene is reported.

Keywords: Cycloaddition, Lewis acid, enol ether, acetal, furan, cyclopentadiene

Introduction

The (4+3)- cycloaddition reaction between allylic cations and dienes is a powerful method for the synthesis of seven-membered rings.¹ We have been interested in this area for some time and, in particular, in the application of heteroatom-stabilized allylic cations to the cycloaddition process.

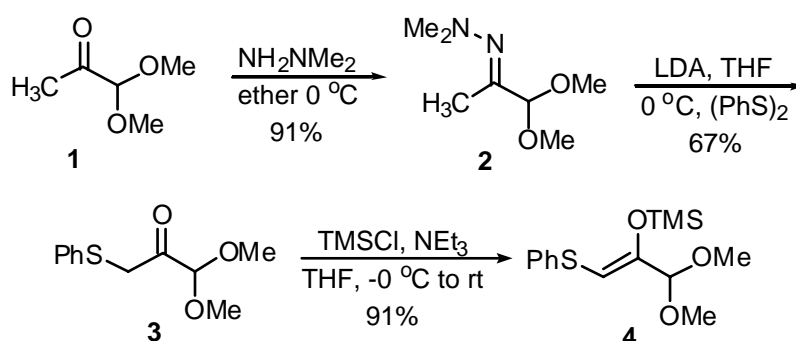
The use of heteroatom-stabilized cations in the 4+3 cycloaddition reaction is known.² This area is still of great interest as many possibilities remain for the development of (4+3)-dienophiles using this approach. Heteroatom stabilization offers the chance of controlling reactivity, regioselectivity and facial selectivity in the (4+3)- cycloaddition reaction.

Oxygen-stabilized allylic cations (vinyl oxocarbenium ions) can be produced in a number of ways. Allylic acetals were first used by Murray and Albizati as progenitors of such allylic cations for the (4+3) cycloaddition reaction.³ Both we and Hoffmann applied the basic approach to the development of chiral allylic cations capable of highly diastereoselective (4+3) cycloaddition reactions.^{4,5}

Sulfur-stabilized allylic cations have also been applied in (4+3) cycloaddition reaction chemistry by our group and by others.⁶ In the interest of extending the scope of the reaction and in understanding reactivity issues in (4+3) cycloaddition chemistry, we decided to begin a study of cations which were stabilized by both oxygen- and sulfur- electron donating groups. Our preliminary results are included in this report.

Results and Discussion

The synthesis of the target allylic cation precursor for our studies was relatively straightforward. The *N,N*-dimethylhydrazone of commercially available dimethoxyacetone (**1**) was prepared in 90% yield by reaction of the ketone with dimethylhydrazine in ether at 0 °C.⁷ Deprotonation of the hydrazone **2** with LDA and trapping with diphenyl disulfide afforded the ketosulfide **3** in 67% yield after hydrolysis of the hydrazone functionality.⁸ Reaction of this species with triethylamine and chlorotrimethylsilane afforded the enol ether **4** in 91% isolated yield (Scheme 1). The stereochemistry of **4** was established as shown (*Z*) by NOESY spectroscopic data, which showed a cross peak between the olefinic hydrogen (5.83 ppm), and the hydrogens of the methoxy group (3.36 ppm).



Scheme 1

With **4** in hand, cycloaddition experiments were begun. Treatment of a stirred solution of **4** and 10 equivalents of furan in CH_2Cl_2 (0.2 M) at -78 °C with 1 equivalent of TiCl_4 resulted only in the formation of the hydrolysis product **3**. Given this result, we set out to find conditions under which cycloaddition would occur. Table 1 shows the results of a small study involving TiCl_4 as Lewis acid, varying stoichiometry, temperature and solvent. The results were not spectacular, but two trends became apparent that would be useful later. First, the reaction improved when more than a stoichiometric amount of Lewis acid was present (Table 1, entries 2 and 3). The reaction also appeared to proceed better when the reaction mixture was allowed to warm (Table 1, entries 3 and 4).

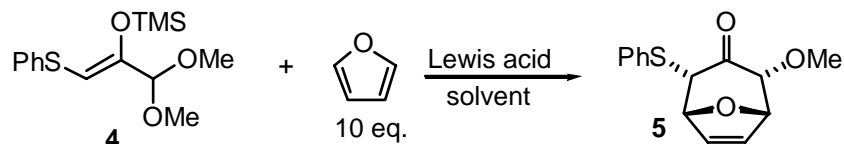


Table 1. Cycloaddition of **4** and furan using TiCl₄

Entry	Equiv. TiCl ₄	Solvent (0.2 M)	T / °C	Yield 5 (%)
1	1	CH ₂ Cl ₂	-78	0 ^b
2	1	CH ₂ Cl ₂	-78 to r.t.	4
3	2	CH ₂ Cl ₂	-78	12
4	2	CH ₂ Cl ₂	-78 to r.t.	28
5	1	EtNO ₂	-78	0 ^b
6	2	EtNO ₂	-78 to r.t.	8
7	2	CH ₂ Cl ₂ ^a	-78	13
8	2	EtNO ₂ ^a	-78	0 ^c

^a Inverse addition. Furan and **5** added to Lewis acid. ^b Compound **3** formed. ^c Compound **6** was formed in low yield.

We also examined other Lewis acids including TMSOTf, AlMe₃, AlClMe₂, AlMeCl₂, BF₃·Et₂O, SnCl₄, and Yb(OTf)₃. None of these offered any advantage over TiCl₄. In general, low yields of cycloadduct and hydrolysis product were obtained in attempted cycloaddition reactions with furan in CH₂Cl₂ at -78 °C.

In view of our earlier findings and in recognition of the possibility that **4** might serve as a bidentate ligand for titanium,^{6b} we examined the effect of variable amounts of TiCl₄ on the cycloaddition reaction. Having seen that higher temperatures affected the reaction favorably, we conducted these studies at 0 °C. The results are shown in Table 2. Note that the yield of cycloadduct did indeed increase as the number of equivalents of Lewis acid increased. The best yield was obtained when 4 equivalents of TiCl₄ were used. Additional Lewis acid caused a decrease in yield. At high TiCl₄ concentrations in CH₂Cl₂, or lower concentrations in EtNO₂, a compound assigned the structure of the hydrolysis product **6** was isolated in low yield, but this species was not rigorously characterized.

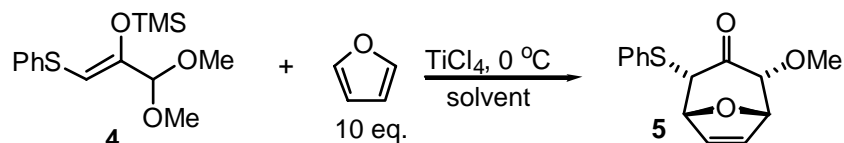
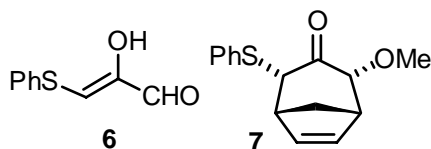


Table 2. Effect of Lewis acid stoichiometry on the reaction between **4** and furan

Entry	Equiv. TiCl ₄	Solvent (0.2 M)	Yield 5 (%)
1	1	CH ₂ Cl ₂	0 ^a
2	2	CH ₂ Cl ₂	35
3	4	CH ₂ Cl ₂	57
4	5	CH ₂ Cl ₂	33
5	6	CH ₂ Cl ₂	17
6	8	CH ₂ Cl ₂	0 ^b
7	2	EtNO ₂	0 ^b
8	4	EtNO ₂	29

^a Compound **3** formed. ^b Compound **6** was formed in low yield.



We observed that decomposition appeared to accompany the cycloaddition reaction, perhaps caused by destruction of both **4** and furan by the Lewis acid. We thus studied the use of milder Lewis acids in an attempt to improve the reaction; some success was achieved. The results are summarized in Table 3. As can be seen, the use of trichlorotitanium isopropoxide gave yields of cycloadduct **5** as high as 70%, when a fourfold excess of the Lewis acid was used in CH₂Cl₂ at 0 °C. We have also used these reaction conditions with cyclopentadiene and obtained a 50% yield of the cycloadduct **7**. It should be noted that the stereochemical assignments of both **5** and **7** are based at present on analogy with other alkoxy- and phenylthio-substituted cycloadducts we have prepared.^{4,6}

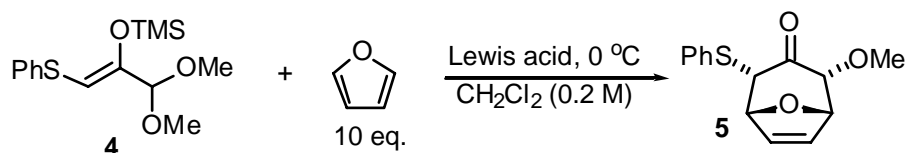


Table 3. Mixed Lewis acids and the reaction of **4** with furan

Entry	Lewis acid (equiv.)	Yield 5 (%)
1	TiCl ₄ , (2)	35
2	TiCl ₃ (OPr _i), (2)	56
3	TiCl ₂ (OPr _i) ₂ , (2)	0
4	TiCl(OPr _i) ₃ , (2)	0
5	Ti(OPr _i) ₄ , (2)	0
6	TiCl ₄ , (4)	57
7	TiCl ₃ (OPr _i), (4)	70
8	TiCl ₂ (OPr _i) ₂ , (4)	0
9	TiCl(OPr _i) ₃ , (4)	0
10	Ti(OPr _i) ₄ , (4)	0

In conclusion, we have developed a protocol for the generation of an allylic cation stabilized by both sulfur and oxygen atoms that is capable of undergoing a (4+3) cycloaddition reaction. Exploring the scope of this chemistry, particularly with respect to regiocontrol and stereocontrol, will be the subject of future investigations.

Experimental Section

General Procedures. All air- or moisture sensitive reaction were carried out in oven-dried (120 °C) or flame-dried glassware under a nitrogen atmosphere. Reactive liquids (*e.g.*, n-BuLi) were transferred by syringe or cannula and were added into reaction vessels through rubber septa. Ether and THF were freshly distilled from sodium benzophenone ketyl, and dichloromethane was distilled from CaH₂. Titanium tetrachloride was freshly distilled from copper dust immediately before use. Triethylamine was distilled from CaH₂ and stored over molecular sieves. Analytical thin layer chromatography was performed on silica gel plates with F254 indicator. Compounds were visualized under a UV lamp or by developing with iodine, vanillin or phosphomolybdic acid solution following by heating on a hotplate. Flash chromatography was performed on 230–400 mesh silica gel with technical grade solvents that were distilled prior to use. Medium pressure liquid chromatography (MPLC) was done using Merck Lobar columns. Gas chromatographic analyses were performed on a Shimadzu GC-9A instrument equipped with an SPB-5 fused silica capillary column (15m, i.d. 0.25 mm) and a flame ionization detector. Chromatograms were recorded on a Hewlett-Packard HP 3390A integrator. ¹H NMR spectra were recorded on Bruker AMX-250 or AMX-500 instruments at 250 MHz (62.9 MHz for ¹³C) or 500 MHz (125 MHz for ¹³C) as CDCl₃ solutions, with tetramethylsilane as the internal standard. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (0 ppm). Multiplicities are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), bs (broadened singlet), etc. Infrared

spectra were recorded on Nicolet 550 Magna FTIR- or Nicolet 20 DXB FTIR spectrometers, as neat liquids. Intensities are reported as s (strong, 67–100%), m (medium, 34–66%), and w (weak, 0–33%). Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona.

1,1-Dimethoxypropane dimethylhydrazone (2). To a flame-dried, 1 neck, round-bottomed flask equipped with a stir bar, septum, and N₂ balloon was added 1,1-dimethylhydrazine (14.7 mL, 193 mmol) and dry ether (8.8 mL). To this cooled (0 °C) solution was added 1.0 equiv. pyruvic aldehyde dimethyl acetal (**1**) (18.0 mL, 149 mmol). The colorless solution was allowed to gradually come to room temperature and stirred overnight. Anhydrous Na₂SO₄ was added and an hour later the mixture was filtered and concentrated under reduced pressure. Kugelrohr distillation of the oil gave the 21.3 g (91%) of the hydrazone. Purification of the oil by MPLC (15% EtOAc/hexanes) gave an analytically pure sample: ¹H NMR (500 MHz, CDCl₃) δ 4.49 (s, 1H), 3.39 (s, 6H), 2.53 (s, 6H), 1.92 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 162.1, 106.9, 54.7, 46.8, 11.5; IR (neat) 2996s, 2956s, 2865s, 2831s, 2780m, 1653w, 122m, 1431m, 1356s, 1192s, 1113s, 1078s, 1039s, 959s, 856w, 822w, 743m cm⁻¹; Anal. calcd. for C₇H₁₆O₂N₂: C, 52.43; H, 10.08. Found: C, 52.38; H, 10.01%.

1,1-Dimethoxy-3-phenylthioprop-2-one (3). To a flame-dried, 1 neck, round-bottomed flask equipped with a stir bar, septum, and N₂ balloon was added iPr₂NH (3.60 mL, 27.5 mmol) and dry THF (40.0 mL, 0.63 M). To the cooled (0 °C) solution were added 1.05 equivalents of 2.38 M n-BuLi (11.03 mL, 26.3 mmol). The slightly yellow solution was stirred for 15–30 min. at 0 °C, then 1.0 equiv. of **2** (4.00 g, 25.0 mmol) was added. The resulting brown solution was stirred for an additional 30 min. at 0 °C. After this time, the metallated hydrazone solution was directly added at 0 °C to a flask containing 1.0 equivalent of diphenyl disulfide (5.45 g, 25.0 mmol) and dry THF (10.0 mL, 2.5 M). Gradually coming to room temperature, the reaction was stirred overnight. The reaction was then poured into ether and washed with 2.0 M HCl (3x), saturated NaHCO₃ (1x), brine (1x), and dried over Na₂SO₄. Purification by flash chromatography (20% EtOAc/hexanes) gave **3** as a yellow oil in 71% yield. ¹H NMR (250 MHz, CDCl₃) δ 7.37–7.18 (m, 5H), 4.70 (s, 1H), 3.90 (s, 2H), 3.37 (s, 6H); ¹³C NMR (62.9 MHz, CDCl₃) δ 199.1, 134.6, 129.6, 128.8, 126.6, 102.5, 54.6, 54.5, 39.5; IR (neat) 3068w, 3006m, 2933w, 2831w, 1743m, 1593w, 1486m, 1441m, 1193w, 1075s, 991w, 738m, 700m cm⁻¹; Anal. calcd. for C₁₁H₁₄O₃S: C, 58.37; H, 6.25. Found: C, 58.16; H, 6.43%.

1,1-Dimethoxy-3-phenylthio-2-trimethylsilyloxy-2-(Z)-propene (4). To a flame-dried flask equipped with a septum, stir bar, and N₂ balloon was added **3** (1.00 g, 4.42 mmol) and dry THF (8.84 mL, 0.50 M). To the cooled (0 °C) solution was added 1.1 equiv. of triethylamine (0.68 mL, 4.86 mmol). After stirring for 10–15 min., 1.1 equiv. of chlorotrimethylsilane (0.617 mL, 4.86 mmol) was added. The yellow mixture was allowed to come gradually to room temperature and stirred for a minimum of 2–3 hours, diluted with pentane, and filtered through 545 Celite (2x). Concentration gave clean yellow oil in 91% yield. Kugelrohr distillation gave an analytically pure sample: ¹H NMR (500 MHz, CDCl₃) δ 7.35–7.16 (m, 5H), 5.83 (s, 1H), 4.61 (s, 1H), 3.36 (s, 6H), 0.27 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 147.5, 136.3, 128.8, 128.5,

125.9, 104.6, 102.1, 53.5, 0.60; IR (neat) 3066w, 2993w, 2964w, 2903w, 2814w, 1636w, 1579w, 1442w, 1354m, 1286w, 1252m, 1196w, 1171w, 1107s, 1078m, 1011m, 848s, 743m cm^{-1} ; Anal. Calcd. for $\text{C}_{14}\text{H}_{22}\text{O}_3\text{SiS}$: C, 56.32; H, 7.44. Found: C, 56.10; H, 7.28%.

Procedures for the (4+3) cycloaddition of **4** with dienes

Method 1. To a flame-dried, round-bottomed flask equipped with stir bar, septum, and N_2 balloon was added CH_2Cl_2 (0.20 M), 1.0 equiv. of **4**, and 10.0 equiv. of the diene. To this cooled (0°C), colorless solution was added 1–8 equiv. of freshly distilled TiCl_4 . The resulting dark solution was stirred at 0°C for 10–15 minutes, then quenched by the addition of $\text{CH}_3\text{OH}/\text{HCl}$ (1:1). The reaction mixture was poured into H_2O and extracted several times with CH_2Cl_2 , and the extracts washed with brine (1x) and dried over Na_2SO_4 . The filtrate was concentrated under reduced pressure to give a crude oil. The oil was purified by flash chromatography (EtOAc/hexanes).

Method 2. To a flame-dried, round-bottomed flask equipped with a stir bar, septum, and N_2 balloon was added CH_2Cl_2 (0.50 M) and 1.5 equiv. of freshly distilled TiCl_4 . To the colorless, cooled (0°C) solution was added 0.509 equiv. of distilled $\text{Ti}(\text{OiPr})_4$. The resulting colorless solution was stirred for 15 minutes at 0°C , then 1.0 equiv. of **4** and 10.0 equiv. of diene were added quickly. The resulting mixture was stirred for 10–15 minutes at 0°C and then quenched by the addition of $\text{CH}_3\text{OH}/\text{HCl}$ (1:1). The reaction was poured into H_2O and extracted several times with CH_2Cl_2 . The CH_2Cl_2 extracts were washed with brine (1x) and dried over Na_2SO_4 . The filtrate was concentrated under reduced pressure to give an oil. The oil was purified by flash chromatography (EtOAc/hexanes).

(**1S***, **2R***, **4S***, **5R***)-2-Methoxy-4-phenylthio-8-oxabicyclo[3.2.1]oct-6-en-3-one (**5**).

Method 1, using 1.0 equiv. of TiCl_4 (0.148 mL, 1.34 mmol), 10.0 eq of furan, 1.0 equiv. of **4** (0.100 g, 3.35 mmol), and CH_2Cl_2 (1.68 mL, 0.20 M). Purification of the crude product by flash chromatography (25% EtOAc/hexanes) gave 0.0425 g (48%) of **5** as an oil.

Method 2. using 3.0 equiv. of TiCl_4 (0.110 mL, 0.101 mmol), 1.0 equiv. of $\text{Ti}(\text{OPr}_i)_4$ (0.102 mL, 0.335 mmol), 1.0 equiv. of **4** (0.100 g, 0.34 mmol), 10.0 equiv. of furan (0.244 mL, 3.35 mmol), and CH_2Cl_2 (1.68 mL, 0.20 M). Purification of the crude product by flash chromatography (25% EtOAc/hexanes) gave 0.0612 g (70%) of **5** as an oil. Purification by MPLC (10% EtOAc/hexanes) gave an analytically pure sample: ^1H NMR (500 MHz, CDCl_3) δ 7.50–7.48 (m, 2H), 7.35–7.26 (m, 3H), 6.44 (dd, 1H, $J = 1.5, 6.1$ Hz), 6.38 (dd, 1H, $J = 1.7, 6.2$ Hz), 5.02 (dd, 1H, $J = 1.7, 5.0$ Hz), 4.91 (dd, 1H, $J = 1.6, 4.5$ Hz), 4.27 (d, 1H, $J = 4.4$ Hz), 4.08 (d, 1H, $J = 4.9$ Hz), 3.61 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 200.8, 133.4, 132.7, 129.3, 127.9, 87.0, 81.4, 80.4, 80.3, 61.4, 60.0; IR (neat) 3087w, 3057w, 2968w, 2928w, 2832w, 1808w, 1724s, 1569m, 1478m, 1469m, 1440m, 1337m, 1200m, 1194m, 1125m, 1084s, 993w, 981w, 924s, 866w, 841m, 812m, 747m, 737s, 694m, 668w cm^{-1} ; Anal. calcd. for $\text{C}_{14}\text{H}_{14}\text{O}_3\text{S}$: C, 64.08; H, 5.39. Found: C, 64.17; H, 5.34%.

(**1S**, **2R**, **4S***, **5R***)-2-Methoxy-4-phenylthiobicyclo[3.2.1]oct-6-en-3-one (**7**). **Method 2.** using 3.0 equiv. of TiCl_4 (0.221 mL, 2.01 mmol), 1.0 equiv. of $\text{Ti}(\text{OPr}_i)_4$ (0.204 mL, 0.671 mmol), 1.0

equivalent of **4** (0.200 g, 0.67 mmol), 10.0 equiv. of freshly distilled cyclopentadiene (0.444 g, 6.71 mmol), and CH_2Cl_2 (3.35 ml, 0.20 M). Purification of the crude product by flash chromatography (25% EtOAc/hexanes) gave 0.0865 g of **7** as a brown oil (50% yield). Further purification of the oil by MPLC (20% EtOAc/hexanes) gave an analytically pure sample: ^1H NMR (250 MHz, CDCl_3): δ 7.48–7.45 (m, 2H), 7.35–7.26 (m, 3H), 6.17 (br s, 2H), 4.13 (d, 1H, $J = 2.0$ Hz), 3.94 (d, 1H, $J = 3.4$ Hz), 3.55 (s, 3H), 3.13–3.10 (m, 1H), 2.99–2.97 (m, 1H), 2.20–2.13 (m, 1H), 1.85 (d, 1H, 11.8 Hz); ^{13}C NMR (62.9 MHz, CDCl_3) δ 203.1, 135.2, 133.9, 132.8, 129.0, 127.4, 63.0, 59.1, 45.4, 40.0, 41.0; IR (neat) 3056w, 2952m, 2869s, 2831w, 1719s, 1584w, 1474m, 1441m, 1352w, 1312w, 1280w, 1202w, 1124s, 1048m, 1029w, 1005w, 938w, 900w, 803w, 75 m, 695m cm^{-1} ; Anal. calcd. for $\text{C}_{15}\text{H}_{16}\text{O}_2\text{S}$: C, 69.20; H, 6.19. Found: C, 69.11; H, 6.39%.

Acknowledgments

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