JOC*Note*

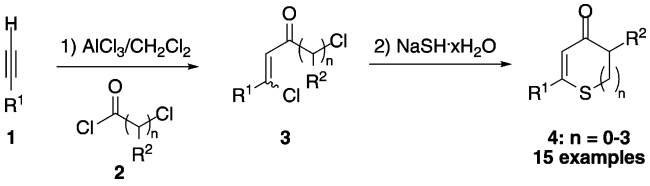
Synthesis of Cyclic Thioethers through Tandem C(sp^3)−S and C(sp^2)−S Bond Formations from α,β′-Dichloro Vinyl Ketones

Kyungsoo Oh,* Hyunjung Kim, Francesco Cardelli, Tamayi Bwititi, and Anna M. Martynow

Department of Chemistry and Chemical Biology, Indiana University Purdue University Indianapolis, Indianapolis, Indiana 46202

oh@chem.iupui.edu

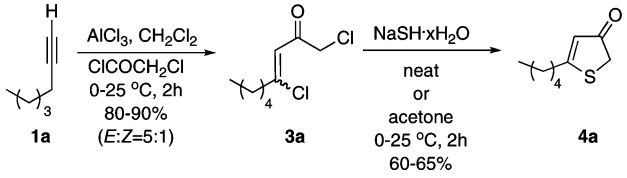
Received November 15, 2007



The synthesis of 5- to 8-memebered cyclic thioethers **4** has been achieved through a simple two-step sequence. The present methodology utilizes the facile Friedel−Crafts acylation of terminal alkynes **1** with acid chlorides **2** followed by tandem C(sp^3)−S and C(sp^2)−S bond formations with NaSH·xH$_2$O.

While the potential of sulfur heterocycles in synthetic strategies has been widely recognized, heterocycles containing a thioenol ether moiety have been a less-studied subject of investigation. Conjugated cyclic thioenol ethers have been proven as effective surrogates for unreactive cis-dienes in Diels−Alder reactions[1] as well as precursors for the synthesis of substituted cyclopentenones through Ramberg−Bäcklund reactions.[2] More recently, Vedejs reported an internal 1,4-addition of a tethered amine to dihydrothiopyran-4-one derivatives for the synthesis of the 8-membered-ring system of the pyrrolizidine alkaloid octonecine.[3] In the course of synthesis of biotin and its analogues, we utilized thiophen-3-one derivatives, cyclic β-keto thioenol ethers, to a biotin core.[4] Although Lebedev et al. have described a two-step sequence to thiophen-3-ones from a 2-(ethylsulfanyl)butanoyl fluoride·BF_3 complex with alkynes, the preparation of acid fluoride·BF_3 complexes is not trivial. Christoffers and Rosiak also recently reported the synthesis of 2,6-disubstituted 2,3-dihydrothiopyran-4-ones through double conjugation of sulfide to enynones; this approach, however, was confined to 6-membered heterocycles and substrates without a substituent at the C_6-position are low yielding (8−36%). Due to the shortage of synthetic routes to heterocycles containing a thioether,[5] we developed a facile synthesis of thiophen-3-ones through tandem C(sp^3)−S and C(sp^2)−S bond formations from the Friedel−Crafts acylation products, β-chloro vinyl ketones.[4] Herein, we report the extension of our methodology to the synthesis of 6- to 8-membered cyclic thioether derivatives.

SCHEME 1. Synthesis of Thiophen-3-one 4a[4]



From the outset of our synthesis, we reasoned that the "soft" and "hard" nucleophilic character of sulfur would facilitate the reaction with α,β′-dichloro vinyl ketones: via the intermolecular alkylation with a sulfur nucleophile followed by intramolecular Michael reaction/elimination, or intermolecular Michael reaction/elimination followed by intramolecuar alkylation of the pendent sulfur nucleophile.

Thus, in order to devise a unified synthetic pathway to access 5- to 8-membered heterocycles, we investigated double C−S bond formations using α,β′-dichloro vinyl ketones **3a** and a source of sulfur. The generation of the required substrate **3a** was initially investigated by using the Friedel−Crafts acylation of a chloroacetyl chloride−$AlCl_3$ complex with terminal alkynes **1a**.[6] The α,β′-dichloro vinyl ketones **3a** are routinely obtained in high yields as a mixture of cis- and trans-stereoisomers (*E:Z* = 1:1−20:1) depending on the reaction temperature.[7]

Next, we turned our attention to the identification of a suitable sulfur nucleophile to induce the C−S bond formations. Initially we screened a variety of sulfur nucleophiles (elemental sulfur S_8, thiourea, hydrogen sulfide, sodium sulfide, sodium hydrosulfide) in acidic and basic conditions with no success. After further experimentation, it was found that sodium hydrosulfide hydrate is the optimal source of sulfur to induce the desired double C−S bond formation in acetone or in neat form.

(1) (a) Ward, D. E.; Gai, Y. *Can. J. Chem.* **1997**, *75*, 681. (b) Ward, D. E.; Nixey, T. E.; Gai, Y.; Hrapchak, M.; Abaee, M. S. *Can. J. Chem.* **1996**, *74*, 1418. (c) Ward, D. E.; Nixey, T. E. *Tetrahedron Lett.* **1993**, *34*, 947.

(2) (a) Jeffrey, S. M.; Sutherland, A. G.; Pyke, S. M.; Powell, A. K.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2317. (b) Casy, G.; Taylor, R. J. K. *Tetrahedron* **1989**, *45*, 455.

(3) Vedejs, E.; Galante, R.; Goekjian, P. *J. Am. Chem. Soc.* **1998**, *120*, 3613.

(4) Oh, K. *Org. Lett.* **2007**, *9*, 2973.

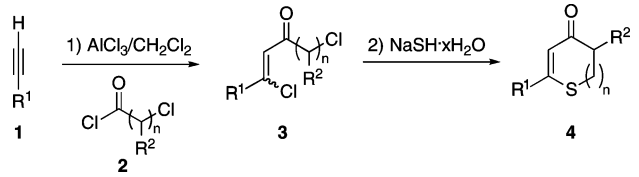
(5) For selected thiophen-3-one examples, see: (a) Lebedev, M. V.; Nenajdenko, V. G.; Balenkova, E. S. *Synthesis* **2001**, 2124. (b) Chuburu, F.; Lacombe, S.; Pfister-Guillouzo, G. *J. Org. Chem.* **1991**, *56*, 3445. (c) Hunter, G. A.; McNab, H. *J. Chem. Soc., Chem. Commun.* **1990**, 375. (d) Cheikh, A. B.; Dhimane, H.; Pommelet, J. C.; Chuche, J. *Tetrahedron Lett.* **1988**, *29*, 5919. (e) Camici, L.; Ricci, A.; Taddei, M. *Tetrahedron Lett.* **1986**, *27*, 5155. Selecteted thiopyran-4-one examples, see: (f) Rosiak, A.; Christoffers, J. *Tetrahedron Lett.* **2006**, *47*, 5095. (g) Bi, X.; Dong, D.; Li, Y.; Liu, Q.; Zhang, Q. *J. Org. Chem.* **2005**, *70*, 10886. (h) Samuel, R.; Nair, S.; Asokan, C. V. *Synlett* **2000**, 1804. (i) Rule, N. G.; Detty, M. R.; Kaeding, J. E.; Sinicropi, J. A. *J. Org. Chem.* **1995**, *60*, 1665. (j) Vedejs, E.; Eberlein, T. H.; Mazur, D. J.; McClure, C. K.; Perry, D. A.; Ruggeri, R.; Schwartz, E.; Stults, J. S.; Varie, D. L.; Wilde, R. G.; Wittenberger, S. *J. Org. Chem.* **1986**, *51*, 1556. (k) Vedejs, E.; Perry, D. A.; Wilde, R. G. *J. Am. Chem. Soc.* **1986**, *108*, 2985. (l) Kansal, V. K.; Taylor, R. J. K. *J. Chem. Soc. Perkin Trans. 1*, **1984**, 703. Selected benzo[*b*]thiepinone derivatives, see: (m) Bendorf, H. D.; Colella, C. M.; Dixon, E. C.; Marchetti, M.; Matukonis, A. N.; Musselman, J. D.; Tiley, T. A. *Tetrahedron Lett.* **2002**, *43*, 7031. (n) Tamura, Y.; Takebe, Y.; Mukai, C.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2978. (o) Kirby, N.; Reid, S. *J. Chem. Soc., Chem. Commun.* **1980**, 150.

(6) Benson, W. R.; Pohland, A. E. *J. Org. Chem.* **1964**, *29*, 385.

(7) Assignment of alkene geometry by NMR, see: Martens, H.; Hooranaert, G.; Toppet, S. *Tetrahedron* **1973**, *29*, 4241.

10.1021/jo702457t CCC: $40.75
Published on Web 02/16/2008

TABLE 1. Synthesis of Cyclic Thioethers



entry	R^1	R^2	*n*	% **3** (*Z*/*E*)[a]	% **4**[b]
1	pentyl	H	0	**3a**, 85 (1:5)	**4a**, 67
2	pentyl	Me	0	**3b**, 62 (1:3)	**4b**, 64[c]
3	pentyl	H	1	**3c**, 71 (1:2.3)	**4c**, 74[d]
4	pentyl	H	2	**3d**, 62 (1:1.3)	**4d**, 64
5	pentyl	H	3	**3e**, 77 (1:1.9)	**4e**, 55
6	c-Hex	H	0	**3f**, 64 (10:1)	**4f**, 47
7	c-Hex	Me	0	**3g**, 61 (2.7:1)	**4g**, 63[c]
8	c-Hex	H	1	**3h**, 62 (1:2)	**4h**, 66[d]
9	c-Hex	H	2	**3i**, 90 (1.2:1)	**4i**, 64
10	c-Hex	H	3	**3j**, 70 (1.1:1)	**4j**, 51
11	Ph	H	0	**3k**, 70 (>20:1)	**4k**, 50
12	Ph	Me	0	**3l**, 73 (2.6:1)	**4l**, 64[c]
13	Ph	H	1	**3m**, 80 (4.3:1)	**4m**, 98
14	Ph	H	2	**3n**, 73 (>20:1)	**4n**, 61
15	Ph	H	3	**3o**, 84 (>20:1)	**4o**, 30

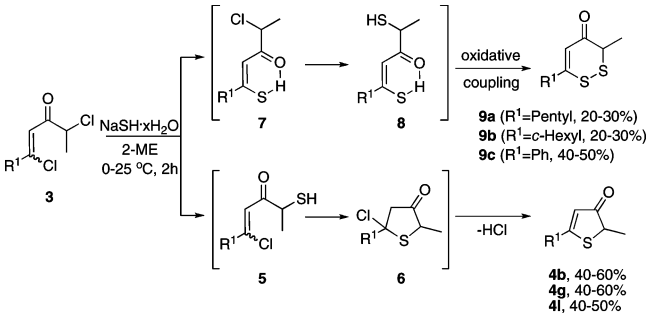
[a] Determined using ^{1}H NMR of crude mixture. [b] Isolated after silica gel chromatography. [c] Isolated yield after *O*-acetylation. [d] Reaction performed at 50 °C.

Having secured a concise synthesis for 5-membered cyclic β-keto thioenol ether **4a**, we explored the substrate and reagent scope and these results are summarized in Table 1. The reaction provided good to excellent yields with a wide range of aliphatic and aromatic alkynes as well as substituted acid chlorides (entries 2, 7, and 12). Thiophen-3-ones (**4a**, **4f**, **4k**) without a substituent at C_5 exist as a stable keto tautomer; however, the C_5-substituted 5-membered heterocycles (**4b**, **4g**, **4*l***) do not show the same stability as keto tautomers.[8] Although disubstituted alkyne, 2-octyne, failed to give the corresponding β-chloro vinyl ketone, the Friedel−Crafts acylation of terminal alkynes proceeded in modest to excellent yields. The subsequent tandem C(sp^3)−S and C(sp^2)−S bond formations was remarkably efficient and produced 5- to 8-membered cyclic thioethers **4** in 50−98% yield except **4o** (30%).[9] As expected the efficiency of ring formation diminished from 5- and 6-membered ring systems to 7- and 8-membered ring systems.

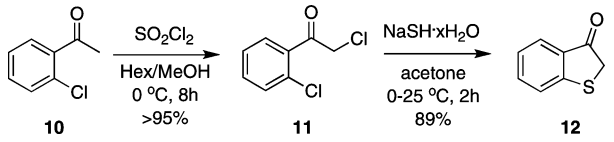
To gain insight into reaction pathways, we attempted to isolate two possible intermediates **5** and **6** with no success. Although the transient intermediates in the reaction have not been confirmed at the present time, we believe that the reaction proceeds via a sequence of intermolecular alkylation (C(sp^3)−S) with sodium hydrosulfide hydrate followed by intramolecular Michael reaction/elimination (C(sp^2)−S). We observed that the reaction in protic solvents (MeOH, EtOH, *t*-BuOH, and water) did not proceed to give the desired products, possibly due to the formation of hydrogen sulfide as well as the solvent cage surrounding the nucleophile.

During our investigation, we have also isolated an NMR quantity of byproducts, 1,2-dithiin-4(3*H*)-ones **9**, upon reactions

SCHEME 2. Synthesis of 1,2-Dithiin-4(3*H*)-ones



SCHEME 3. Synthesis of Benzo[*b*]thiophen-3(2*H*)-one



under protic solvents (MeOH and *i*-PrOH).[10] Hydrogen sulfide, a "soft" nucleophile, would have preferentially reacted in a Michael fashion rather than alkylation. The formation of **9** could be explained through an oxidative pathway (**7** to **8**) due to a facile isomerization of β-keto thioenol **7** to β-keto thioketone. Thus, the Michael addition product, (*Z*)-thioenol ether **7**, is prone to further reactions with either hydrogen sulfide or sodium hydrosulfide (Scheme 2). The formation of **4** from **7** is probably deterred due to the geometry of the alkene as a result of intramolecular H-bonding.[11] After some solvent screening, upon using 2-methoxyethanol[5f] coupled with sodium hydrosulfide hydrate we optimized reaction conditions to obtain 1,2-dithiin-4(3*H*)-ones **9**[12] (C(sp^2)−S to C(sp^3)−S) along with the 5-membered product, thiophen-3-ones **3** (C(sp^3)−S to C(sp^2)−S), in good to excellent yields.[13] On the basis of these above observations, we surmised that the alkylated intermediate **5** is the predominant species under aprotic solvents and subsequently undergoes faster intramolecular Michael reaction to give **6** than other oxidative pathways.

The scope and utility of the reaction mechanism was further extended toward the synthesis of benzo[*b*]thiophen-3(2*H*)-one **12** (Scheme 3).[14] Careful chlorination of 2′-chloroacetophenone **10** with use of sulfuryl chloride at 0 °C provided 2-chloro-1-(2-chlorophenyl)ethanone **11** in excellent yield.[15] The subsequent tandem C(sp^3)−S and C(sp^2)−S bond formations was effected smoothly with our optimized conditions via a sequence of intermolecular alkylation (C(sp^3)−S) with sodium hydrosulfide hydrate followed by intramolecular nucleophilic aryl substitution (C(sp^2)−S).[16]

(8) Capon, B.; Kwok, F-C. *J. Am. Chem. Soc.* **1989**, *111*, 5346. 2-Methyl thiophen-3-ones **4b**, **4g**, and **4l** rapidly decomposed at ambient temperature over 1−24 h, and thus are isolated as their *O*-acetyl thiophene derivatives, see the Supporting Information.

(9) *cis*- and *trans*-Chloro vinyl ketones **3a** undergo cyclization, respectively, thus a mixture of stereoisomers was employed in all other substrates **3b**−**o**.

(10) α′-Methyl-substituted β-chloro vinyl ketones **3b**, **3g**, and **3l** are expected to enhance the competition between Michael reaction and alkylation due to the steric hinderance of a methyl group.

(11) We are currently investigating the synthesis of β-keto thioketone of **7** to confirm the possibility of crossover between **5** and **8**, or **6** and **7**.

(12) Le Guillanton, G.; Do, Q. T.; Simonet, J. *Bull. Soc. Chim. Fr.* **1990**, *127*, 427.

(13) Oxidative S−S coupling of **7** followed by intramolecular alkylation to **9** cannot be ruled out.

(14) (a) Pradhan, T. K.; De, A.; Mortier, J. *Tetrahedron* **2005**, *61*, 9007. (b) Mukherjee, C.; Kamila, S.; De, A. *Tetrahedron* **2003**, *59*, 4767.

(15) Ikemoto, N.; Liu, J.; Brands, K. M. J.; McNamara, J. M.; Reider, P. *Tetrahedron* **2003**, *59*, 1317.

(16) Upon subjecting 2′-chloroacetophenone **10** to our NaSH·*x*H$_2$O conditions, no reaction was observed.

In conclusion, we have developed a facile synthesis of cyclic thioethers using iterative intermolecular *S*-alkylation followed by intramolecular Michael reaction/elimination. Furthermore, our methodology can be extended to the synthesis of benzo[*b*]-thiophen-3(2*H*)-one, a useful starting material for dyes.[17] We are currently investigating applications of our methodology as well as an asymmetric sulfoxidation of the sulfur heterocycles for the synthesis of biologically relevant compounds, and our result will be reported in due course.

Experimental Section

General Procedure for Double C−S Bond Formations. To a stirred sodium hydrosulfide hydrate (68−72% flakes, 89 mg, 1.06 mmol) at ambient temperature, was added the alkenes **3a** (200 mg, 0.90 mmol) in acetone (2 mL) dropwise. The reaction was complete in 5 min as evidenced by thin layer chromatography. The reaction mixture was diluted with diethyl ether (10 mL) and filtered through Celite. After solvent removal under reduced pressure, the residue was purified by flash chromatography on silica gel (eluent 90/10 hexanes/diethyl ether) to give thiophen-3-one **4a** as a yellowish oil (5.47 g, 67%).

4a: R_f 0.20 (1:4 Et_2O/Hex). IR (neat) 2957, 2928, 2857, 1656, 1564, 1460 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.00 (1H, s), 3.62 (2H, s), 2.61 (2H, t, 7.6 Hz), 1.65 (2H, m), 1.34 (4H, m), 0.89 (3H, t, 6.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.8, 185.7, 120.9, 40.8, 33.9, 31.2, 28.3, 22.4, 13.9. HRMS calcd for $C_9H_{14}O_1S_1$ 170.0765, found 170.0759 (M^+).

4c: R_f 0.66 (1:1 Et_2O/Hex). IR (neat) 2955, 2929, 2858, 1653, 1572 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.07 (1H, d, 1 Hz), 3.17 (2H, m), 2.65 (2H, m), 2.37 (2H, td, 7.5 Hz, 0.5 Hz), 1.62 (2H, m), 1.35 (4H, m), 0.90 (3H, t, 7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.4, 165.1, 121.7, 38.3, 36.8, 31.1, 28.4, 27.4, 22.3, 13.8. HRMS calcd for $C_{10}H_{16}OS$ 184.0916, found 184.0903 (M^+).

4d: R_f 0.17 (1:5 Et_2O/Hex). IR (neat) 2956, 2927, 2857, 1655, 1578 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.04 (1H, s), 2.93 (2H, t, 6.5 Hz), 2.82 (2H, td, 7 Hz, 0.5 Hz), 2.37 (2H, td, 8 Hz, 0.5 Hz), 2.23 (2H, quintet, 10 Hz), 1.60 (2H, quintet, 7.5 Hz), 1.34 (4H, m), 0.89 (3H, t, 4.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.1, 166.6, 127.5, 41.6, 40.1, 37.6, 31.1, 30.7, 28.8, 22.3, 13.9. HRMS calcd for $C_{11}H_{18}OS$ 198.1073, found 198.1081 (M^+).

4e: R_f 0.24 (1:5 Et_2O/Hex). IR (neat) 2929, 2857, 1659, 1645, 1633, 1592 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 5.93 (1H, s), 2.87 (2H, t, 5.5 Hz), 2.70 (2H, t, 6 Hz, 0.5 Hz), 2.27 (2H, t, 8 Hz, 7.5 Hz), 2.03 (2H, m), 1.90 (2H, m), 1.62 (2H, m), 1.32 (4H, m), 0.90 (3H, t, 6.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.7, 154.5, 123.1, 42.1, 40.3, 32.8, 31.1, 30.3, 29.1, 22.3, 21.5, 13.9. HRMS calcd for $C_{12}H_{20}OS$ 212.1229, found 212.1239 (M^+).

Acknowledgment. The School of Science (IUPUI) is acknowledged for start-up funding. This investigation was supported through a Research Support Funds Grant (RSFG-IUPUI). The Bruker 500 MHz NMR was purchased via a NSF-MRI award (CHE-0619254). The authors thank the IUPUI Undergraduate Research Opportunities Program for fellowships (A.M.M. and T.B.). A.M.M. and T.B. are recipients of the 2007 Eli Lilly Undergraduate Research Award and the IUPUI Summer Research Opportunity Program Fellowships, respectively.

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702457T

(17) Sulfone analogues for cell imaging application, see: Toutchkine, A.; Nguyen, D.; Hahn, K. M. *Org. Lett.* **2007**, *9*, 2775 and references cited therein.