ORGANIC
LETTERS

2011
Vol. 13, No. 4
776–779

An Approach to α-Keto Vinyl Carbinols

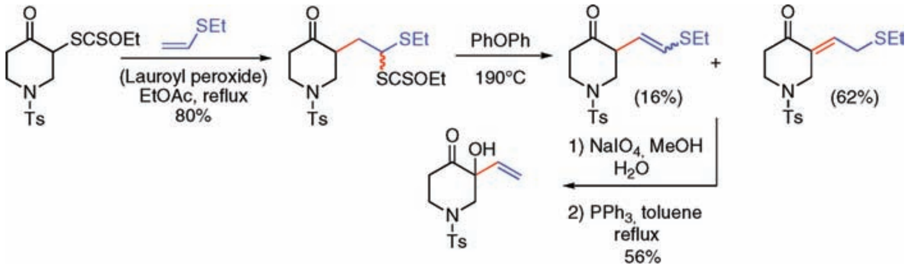
Marie-Gabrielle Braun and Samir Z. Zard*

Laboratoire de Synthèse Organique, CNRS UMR 7652 Ecole Polytechnique, 91128 Palaiseau Cedex, France

zard@poly.polytechnique.fr

Received December 16, 2010

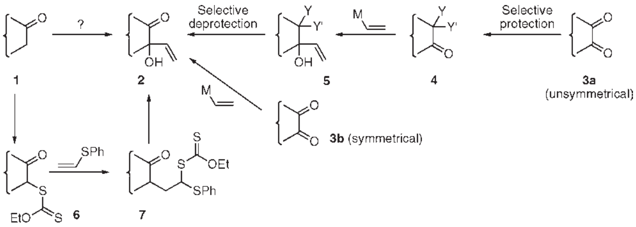
ABSTRACT



Adducts from the radical addition of xanthates to ethyl vinyl sulfide readily undergo elimination of the xanthate group upon thermolysis to give vinylic and/or allylic sulfides, depending on the structure. In the case of α-xanthyl ketones, the adducts are converted into α-keto vinyl carbinols by rearrangement of the sulfoxides derived from the vinylic and allylic sulfides.

As part of a synthetic project, we needed to develop a simple route to α-keto vinyl carbinols of structure **2** starting from monoketones **1** (Scheme 1). α-Keto vinyl carbinols motifs are relatively rare, and usually require reacting α-diketones **3a**,**b** with vinylmetal reagents.[1] In the case of unsymmetrical α-diketones where no steric or electronic bias exists to direct the addition of the vinylmetal, a monoprotected substrate **4** has to be used. While this approach is efficient, it is severely limited by the dearth of available α-diketones and the problems of regioselectivity when dealing with unsymmetrical substrates.[2]

Scheme 1



Toward this end, we contemplated the possibility of obtaining such derivatives through the radical addition of an α-keto-xanthate **6** to commercially available phenyl vinyl sulfide and elaborating the corresponding adduct **7** into the desired vinyl carbinol **2** (Scheme 1). The addition of a xanthate to a vinyl sulfide had not hitherto been accomplished, but appeared reasonably facile in view of the mildness of the reaction conditions and the compatibility of the radical process with numerous functional groups.[3] Xanthate **6a** was therefore reacted with phenyl

---

(1) (a) Runcie, K. A.; Taylor, R. J. K. *Org. Lett.* **2001**, *3*, 3237. (b) Rodriguez, J. R.; Castedo, L.; Mascarenas, J. L. *Org. Lett.* **2001**, *3*, 1181. (c) Brown, M. J.; Harrison, T.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5378. (d) Fang, J.-M.; Chen, M.-Y.; Yang, W.-J. *Tetrahedron Lett.* **1988**, *29*, 5937. (e) Fugisawa, T.; Watanabe, M.; Sato, T. *Chem. Lett.* **1984**, 2055. (f) Trost, B. M.; Keinan, E. *J. Org. Chem.* **1980**, *45*, 2741. (g) Maignan, C.; Rouessac, M. *Bull. Soc. Chim. Fr.* **1973**, 1454. (h) Leriverend, P.; Conia, J.-M. *Bull. Soc. Chim. Fr.* **1970**, 1040.

(2) For other routes, see: (a) Nagao, Y.; Tanaka, S.; Ueki, A.; Kumazawa, M.; Goto, S.; Ooi, S.; Sano, S.; Shiro, M. *Org. Lett.* **2004**, *6*, 2133. (b) Stone, G. B.; Liebskind, L. S. *J. Org. Chem.* **1990**, *55*, 4614. (c) Mauze, B.; Doucoure, A.; Miginiac, I. *J. Organomet. Chem.* **1981**, *215*, 1.

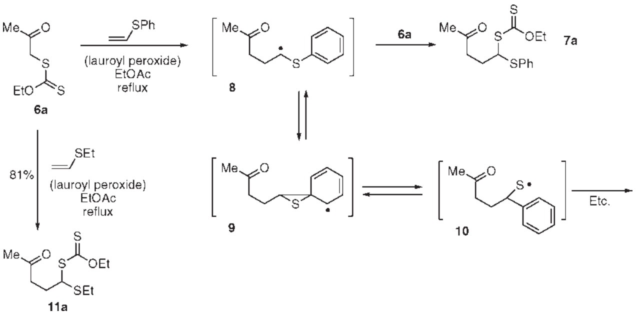
(3) For reviews of the xanthate transfer chemistry, see: (a) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672. (b) Zard, S. Z. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, p 90. (c) Quiclet-Sire, B.; Zard, S. Z. *Chem.—Eur. J.* **2006**, *12*, 6002. (d) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (e) Zard, S. Z. *Aust. J. Chem.* **2006**, *59*, 663. (f) Zard, S. Z. *Org. Biomol. Chem.* **2007**, *5*, 205. (g) Quiclet-Sire, B.; Zard, S. Z. *Pure Appl. Chem.* DOI:10.1351/PAC-CON-10-08-07. Published Online: Oct 15, 2010.

10.1021/ol103044x

vinyl sulfide in the presence of lauroyl peroxide as the initiator. Surprisingly, the reaction was abnormally slow and required near stoichiometric amounts of the peroxide. The expected adduct **7a** could be observed in the crude NMR of what was clearly a complex mixture. One possible side reaction accounting for this failure is an undesired radical neophilic rearrangement of intermediate radical **8**,[4] resulting in the formation of thiyl radical **10** through the temporary epi-sulfide **9**. Thiyl radical **10** is unable to propagate the chain and can evolve in a myriad of ways. It is worth mentioning that we have used phenyl vinyl sulfone as a radical trap in conjunction with xanthates on several occasions without encountering such problems.[5]

To test whether our hardships were indeed caused by a neophilic rearrangement due to the presence of the phenyl ring or to an inherent instability of radical adduct **8** under the reaction conditions, we repeated the addition using ethyl vinyl sulfide, and conveniently a commercially available compound. We were pleased to find that the desired addition proceeded to give the expected adduct **11a** in good yield (81%) (Scheme 2). One practical advantage of ethyl vinyl sulfide is its volatility so any unreacted material is simply removed by evaporation.

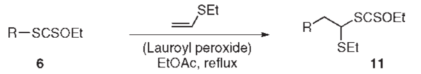
Scheme 2

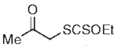
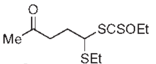
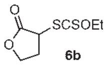
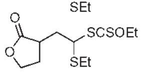
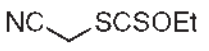
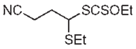
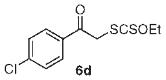
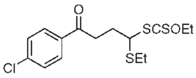
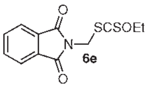
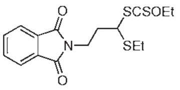
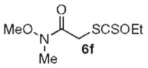
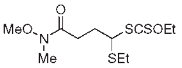
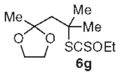
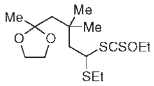
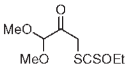
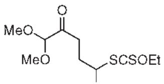
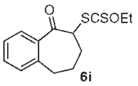
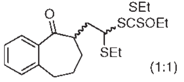
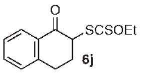
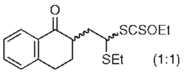
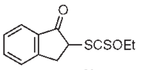
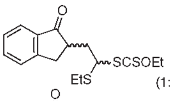
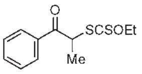
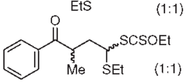
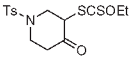
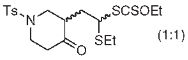


In a similar fashion, various α-keto-xanthates were made to add to ethyl vinyl sulfide. The results, collected in Table 1, testify to the broad generality of the process, its efficiency, and its tolerance. Yields are generally greater than 80% and numerous functional groups can be present on the starting xanthate. The problems initially encountered with additions to phenyl vinyl sulfide are not therefore related to the stability of the adduct, but lie presumably in the existence of a competing neophilic rearrangement.

More complex derivatives could be prepared by cumulating two sequential radical additions, as shown in Scheme 3. Thus, reaction of xanthate **6c** with *N*-vinyl phthalimide furnished adduct **6n**, which in turn could be made to add to ethyl vinyl sulfide to give **11n** as a (1:1) mixture of two diastereoisomers in good yield. Similarly, addition of xanthate **6e** to *N*-phenyl maleimide followed by reaction of the resulting adduct **6o** with ethyl vinyl sulfide afforded **11o**, also as a (1:1) mixture of two diastereoisomers.

Table 1. Radical Addition of Xanthate **6** to Ethyl Vinyl Sulfide



entry	xanthate **6**	radical adduct **11**	**11** (yield)[a]
1	 **6a**		**11a** (81%)
2	 **6b**		**11b** (88%)
3	 **6c**		**11c** (87%)
4	 **6d**		**11d** (90%)
5	 **6e**		**11e** (81%)
6	 **6f**		**11f** (85%)
7	 **6g**		**11g** (52%) (74%)[b]
8	 **6h**		**11h** (76%)
9	 **6i**		**11i** (88%)
10	 **6j**		**11j** (91%)
11	 **6k**		**11k** (89%)
12	 **6l**		**11l** (94%)
13	 **6m**		**11m** (80%)

[a] Yields refer to reactions of xanthate **7** with 2 equiv of ethyl vinyl sulfide in refluxing ethyl acetate at 1 M concentration. [b] Yield based on recovered starting material.

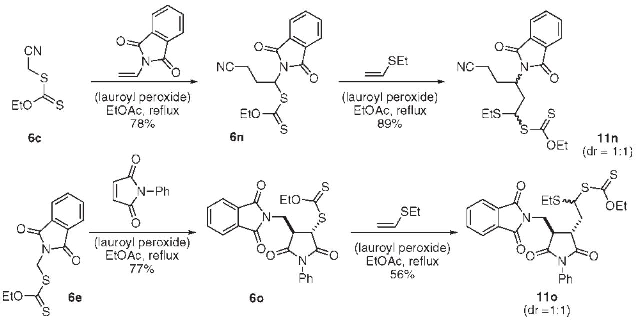
With an efficient, flexible, and convergent route to the desired intermediates in hand, our next task was to convert these adducts into vinyl sulfides. We found some years ago that xanthate addition products to *N*-vinyl pyrrolidone such as **12** (Scheme 4) underwent smooth elimination to give the unsaturated product **13** when heated at moderate temperatures (> 100 °C).[6] The presence of a geminal nitrogen substituent on the carbon bearing the xanthate

---

(4) (a) Studer, A. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, pp 62−80. (b) Studer, A.; Bossart, M. *Tetrahedon* **2001**, *57*, 9649.

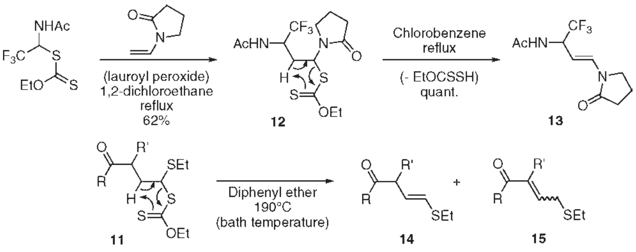
(5) (a) Bertrand, F.; Pevere, V.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2001**, *3*, 1069. (b) Denieul, M.-P.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 5495. (c) Delduc, P.; Tailhan, C.; Zard, S. Z. *J. Chem. Soc., Chem. Commun.* **1988**, 308.

Scheme 3



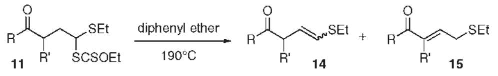
group weakens the carbon−sulfur bond through an anomeric type effect involving the interaction of the lone electron pair on the nitrogen atom with the antibonding σ^* orbital of the carbon−sulfur bond. Tertiary[7] and benzylic type xanthates and related dithiocarbonyl derivatives containing a moderately weak carbon−sulfur bond also undergo elimination but the temperatures required are generally higher (> 150 °C).[8]

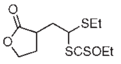
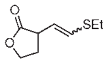
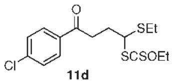
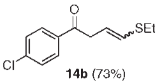
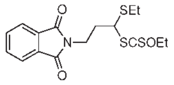
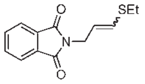
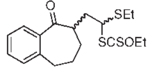
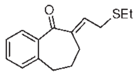
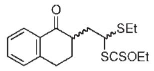
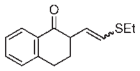
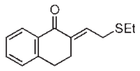
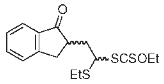
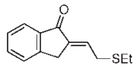
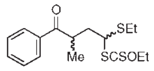
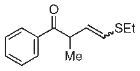
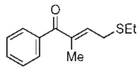
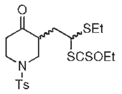
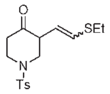
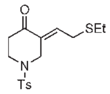
Scheme 4



We anticipated that thermolysis of adducts **11** should also be possible, even if anomeric-type weakening exerted by the sulfide sulfur would be much less powerful than that with the nitrogen of the pyrrolidone. Ultimately, we found that heating in diphenyl ether at around 190 °C (bath temperature) accomplished the desired elimination cleanly to give the desired unsaturated sulfide, in a few cases as a mixture of regioisomers **14** and **15** (Scheme 4). The former is the kinetic product which, depending on the structure and reaction time, is partially or totally converted into the more stable conjugated isomer. The results of the thermolyses are compiled in Table 2.

Table 2. Formation of Vinyl and Allyl Sulfides



entry	xanthate 11	vinyl sulfide 14 (yield)	allyl sulfide 15 (yield)
1	 **11b**	 **14a** (75%) (*E*/*Z* = 1:1)	-
2	 **11d**	 **14b** (73%) (*E*/*Z* = 1:1)	-
3	 **11e**	 **14c** (85%) (*E*/*Z* = 1:1)	-
4	 **11i**	-	 **15d** (67%)
5	 **11j**	 **14e** (18%) (*E*/*Z* = 1:1)	 **15e** (67%)
6	 **11k**	-	 **15f** (67%)
7	 **11l**	 **14g** (49%) (*E*/*Z* = 1:1)	 **15g** (39%)
8	 **11m**	 **14h** (16%) (*E*/*Z* = 1:1)	 **15h** (62%)

In the case of lactone **11b**, unbranched ketone **11d**, and imide **11e**, the elimination was not followed by migration of the alkene, and the corresponding vinyl sulfides **14a**−**c** were obtained exclusively as mixtures of geometrical isomers, which could be separated. In contrast, thermolysis of benzosuberone and indanone derivatives **11i** and **11k** afforded only the conjugated allylic sulfides **15d** and **15f**, as the *E* isomers. Finally, in the case of 6-membered-ring ketone xanthates **11j** and **11m**, and branched ketone xanthate **11*l***, the elimination produced a mixture of the respective vinylic and allylic sulfides **14e** and **15e**, **14g** and **15g**, and **14h** and **15h**. The latter two mixtures could be separated into the constituents by chromatography. In all cases, vinylic sulfides **14e**,**g**,**h** were again 1:1 mixtures of geometrical isomers, which were not separated.

Having established an efficient and short route to vinylic and allylic sulfides, the final operation that remained was to convert these adducts into the target vinyl carbinols through their respective sulfoxides, as detailed in Scheme 5.

Selective oxidation of both vinylic and allylic sulfides **14** and **15** into the corresponding sulfoxides **16** and **17** was accomplished with sodium periodate in a mixture of methanol and water. Heating the crude mixture of sulfoxides with triphenyl phosphine leads to the desired vinyl

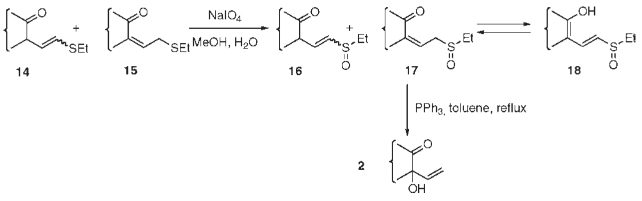
---

(6) Gagosz, F.; Zard, S. Z. *Org. Lett.* **2003**, *5*, 2655.

(7) Bingham, M. J.; Zard, S. Z. Unpublished observations.

(8) (a) Ahmed, S.; Baker, L. A.; Grainger, R. S.; Innocenti, P.; Quevedo, C. E. *J. Org. Chem.* **2008**, *73*, 8116. (b) Postma, A.; Davis, T. P.; Moad, G.; O'Shea, M. S. *Macromolecules* **2005**, *38*, 5371. (c) Xu, J.; He, J.; Fan, D.; Tang, W.; Yang, Y. *Macromolecules* **2006**, *39*, 3753. (d) Liu, Y.; He, J.; Xu, J.; Fan, D.; Tang, W.; Yang, Y. *Macromolecules* **2005**, *38*, 10332.

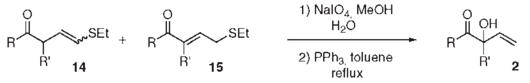
Scheme 5

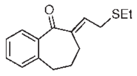
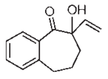
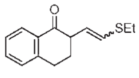
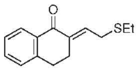
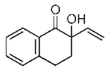
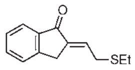
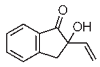
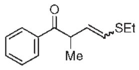
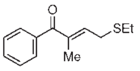
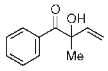
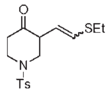
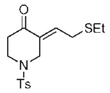
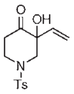


carbinol **2** through the well-known Mislow−Braverman−Evans reaction.[9] Separation of the complex mixture of sulfoxides is neither necessary nor desirable since, under the reaction conditions, both vinyl and allyl sulfoxides **16** and **17** are in equilibrium via their common enol **18** but only the latter can undergo the sigmatropic rearrangement followed by the *irreversible* reduction of the intermediate sulfenate by the phosphine.[10] The enolate corresponding to **18** is stabilized by two electron-withdrawing groups, the ketone and the sulfoxide, and phosphine is sufficiently basic to mediate its formation.

Examples of the vinyl carbinols obtained by this route are collected in Table 3. The unoptimized overall yields from the corresponding sulfides are synthetically useful. It is worth emphasizing that some of these compounds would be difficult to access by more conventional approaches.

Table 3. Formation of Vinyl Carbinols



entry	vinyl sulfide **14**	allyl sulfide **15**	vinyl carbinol **2** (yield %)
1	-	 **15d**	 **2a** (51%)
2	 **14e**	 **15e**	 **2b** (65%)
3	 **15f**	-	 **2c** (71%)
4	 **14g**	 **15g**	 **2d** (67%)
5	 **14h**	 **15h**	 **2e** (56%)

In summary, we have devised a convergent, flexible route to α-keto vinyl carbinols. These densely functionalized structures can serve as starting points for numerous subsequent transformations. More generally, the combination of the radical addition of a xanthate to ethyl vinyl sulfide and thermolysis represents a simple access to variously substituted vinyl sulfides, a class of compounds with a very rich yet surprisingly underused chemistry.[11] Hopefully, the present work will contribute to reviving interest in this area by providing a practical and versatile synthetic protocol.

Acknowledgment. We dedicate this paper with respect to Professor Koichi Narasaka (Nanyang Technological University, Singapore). M.-G.B. thanks Ecole Polytechnique for a scholarship.

Supporting Information Available. Experimental procedures, full spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

---

(9) (a) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147. (b) Bickart, P.; Carson, F. W.; Jacobus, J.; Miller, E. G.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4869. (c) Braverman, S.; Stabinsky, Y. *J. Chem. Soc., Chem. Commun* **1967**, 270. (d) For a review, see: Brückner, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, UK, 1991; Vol. 6, p 873.

(10) (a) Miura, M.; Toriyama, M.; Kawakubo, T.; Yasukawa, K.; Takido, T.; Motohashi, S. *Org. Lett.* **2010**, *12*, 3882. (b) Giardinà, A.; Marcantoni, E.; Mecozzi, T.; Petrini, M. *Eur. J. Org. Chem.* **2001**, *4*, 713. (c) Nokami, J.; Kataoka, K.; Shiraishi, K.; Osafune, M.; Hussain, I.; Sumida, S. *J. Org. Chem.* **2001**, *66*, 1228. (d) Nokami, J.; Osafune, M.; Shiraishi, K.; Sumida, S.; Imai, N. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2947. (e) Nokami, J.; Taniguchi, T.; Ogawa, Y. *Chem. Lett.* **1994**, 43. (f) Boivin, J.; Chauvet, C.; Zard, S. Z. *Tetrahedron Lett.* **1992**, *33*, 4913. (g) Nokami, J.; Nishimura, A.; Sunami, M.; Wakabayashi, S. *Tetrahedron Lett.* **1987**, *28*, 649.

(11) (a) Yang, J.; Sabarre, A.; Fraser, L. R.; Patrick, B. O.; Love, J. A. *J. Org. Chem.* **2009**, *74*, 182. (b) Wang, Z.-L.; Tang, R.-I.; Luo, P.-S.; Deng, C.-L.; Zhong, P.; Li, J.-H. *Tetrahedron* **2008**, *64*, 10670. (c) Sasmal, P. K.; Maier, M. E. *Org. Lett.* **2002**, *4*, 1271. (d) Ogawa, A.; Ikeda, T.; Kimura, K.; Hirao, T. *J. Am. Chem. Soc.* **1999**, *121*, 5108. (e) Paquette, L. A.; Sun, L.-Q.; Watson, T. J. N.; Friedrich, D.; Freeman, B. T. *J. Org. Chem.* **1997**, *62*, 8155. (f) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958. (g) Blumenkopf, T. A.; Bratz, M.; Castafieda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386. (h) Trost, B. M.; Lavoie, A. C. *J. Am. Chem. Soc.* **1983**, *105*, 5075.