ORGANIC LETTERS

2012
Vol. 14, No. 4
1020–1023

A Convenient Conversion of Terminal Alkenes into Homologous Unsaturated and Doubly Unsaturated Esters

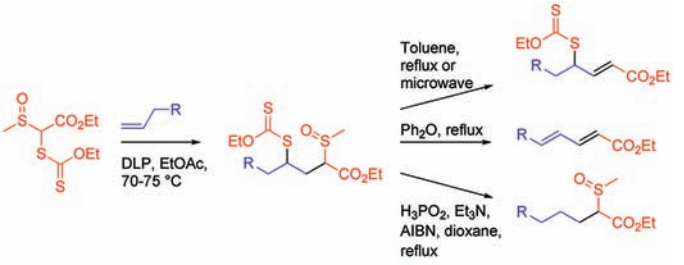
Bill Hawkins, Victoria L. Paddock, Nina Tölle, and Samir Z. Zard*

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

zard@poly.polytechnique.fr

Received December 19, 2011

ABSTRACT



Unsaturated and doubly unsaturated esters have been synthesized in two steps by the application of a radical xanthate transfer process of a simple methylsulfoxide starting material to a range of terminal alkenes. *syn*-Elimination of the sulfoxide gives α,β-unsaturated esters, which coupled with a xanthate elimination yields α,β,γ,δ-unsaturated esters.

The creation of C−C bonds in an *intermolecular* fashion starting with unactivated alkenes is a longstanding problem in organic synthesis that has in part been addressed by the cross-metathesis reaction. This explains the large impact of this remarkable process on the design of synthetic strategies, especially with the emergence of later generations of catalysts and the design of experimental set-ups that circumvent the inherent problem of competing self-metathesis.[1] Thus, the conversion of an alkene **1** into an unsaturated ester **2** can be accomplished directly through cross-metathesis (Scheme 1), whereas a more traditional approach would have required oxidative cleavage of the alkene to the aldehyde followed by a Wittig or a Horner−Wadsworth−Emmons condensation.

In contrast, the conversion of the same alkene **1** into the homologous unsaturated ester **3** or dienyl ester **4** cannot thus far be directly accomplished through a metathesis process. In view of its potential synthetic utility, and in connection with an ongoing total synthesis project, we explored the possibility of effecting this transformation by a radical based route. Our strategy relied on combining the radical xanthate addition we have uncovered with the well-known *syn*-elimination of sulfoxides.[2]

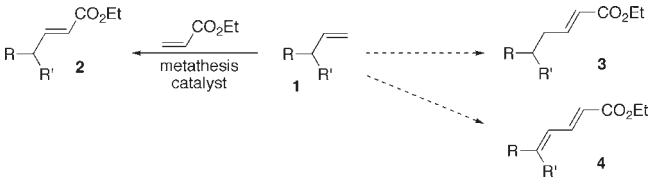
The seemingly straightforward approach displayed in Scheme 2 could not, however, be readily implemented. When we attempted the radical addition of sulfoxide **5** to terminal alkenes under the usual conditions, the reactions were disappointingly sluggish and low yielding. There was no obvious reason to imagine that the radical addition was the inefficient step or that the xanthate transfer process was, which should also proceed normally. The untoward generation of radical inhibitors in the medium is a more plausible explanation. While sulfoxide elimination cannot take place in the starting reagent **5**, it could happen at the

(1) For a review on cross-metathesis, see: (a) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. For recent, more general reviews of the metathesis reaction, see: (b) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746. (c) Samojlowicz, C.; Bieniek, M.; Grela, K. *Chem. Rev.* **2009**, *109*, 3708. The hydroformylation and hydrocyanation reactions, while less broadly used in academia, are industrially important processes. See:(d) Maitlis, P.; Haynes, A. *Metal-catalysis in Industrial Organic Processes*; Royal Society of Chemistry: Cambridge, 2008.

(2) For reviews on xanthate radical addition-transfer reaction, see: (a) Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 672. (b) Quiclet-Sire, B.; Zard, S. Z. *Chem.—Eur. J.* **2006**, *12*, 6002. (c) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (d) Zard, S. Z. *Aust. J. Chem.* **2006**, *59*, 663. (e) Zard, S. Z. *Org. Biomol. Chem.* **2007**, *5*, 205. (f) Quiclet-Sire, B.; Zard, S. Z. *Pure Appl. Chem.* **2011**, *83*, 519.

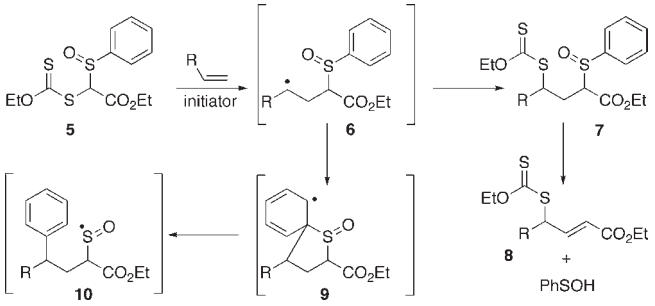
10.1021/ol203387r
Published on Web 02/01/2012

Scheme 1. Conversion of Alkenes to Unsaturated Esters



level of the addition product **6**. The decomposition need not be extensive: even a small amount of phenylsulfenic acid in the medium would be sufficient to inhibit the chain process. Another, less obvious side reaction leading to potential inhibitors arises from a radical Smiles rearrangement leading to an aryl shift and the formation of sulfur-centered and chain-terminating sulfenyl radical **10**.[3]

Scheme 2. Attempted Radical Addition of Sulfoxide **5** to an Alkene



One possible way of circumventing these difficulties would consist of operating at a much lower temperature than that of the usual refluxing ethyl acetate, for example by initiating the system photochemically or by using a combination of triethylborane and oxygen.[4] Both of these experimental variations were not appealing, because of problems of scale up with the former and because of the capriciousness of the latter.[5]

A better solution was found in an early work by Trost and co-workers, who noted that *phenyl*sulfoxides underwent elimination at about 70 °C *below* the temperature needed to cause the elimination of the analogous *methyl*-sulfoxides.[6] The phenyl group weakens the carbon−sulfur bond and stabilizes the partial negative charge that apparently builds up on the sulfur atom in the transition state. Thus, replacing the phenyl with a methyl group should hopefully sufficiently raise the temperature needed for the onset of the *syn*-elimination to allow the normal radical chain to proceed under practical conditions. A methyl group would also obviate any complications from a Smiles-type rearrangement of the intermediate adduct radical.

The desired methylsulfoxide was synthesized from the commercially available ethylmethylthio-acetate, which was monochlorinated following literature precedent.[7] The chlorinated product was then transformed into the xanthate upon treatment with potassium *O*-ethyl xanthate and finally oxidation of the thioether with *m*-CPBA gave the sulfoxide in good yield, without affecting the xanthate group.

With methylsulfoxide **11** in hand it was pleasing to find that when the xanthate transfer reaction was conducted strictly between 70 and 75 °C with dilauryl peroxide (DLP, 0.8−1.8 equiv)[8] in ethyl acetate, the desired addition product, xanthate **12**, could be isolated in a high yield without any trace of the *syn*-eliminated product being observed. With optimal reaction conditions developed the radical addition of methylsulfoxide **11** to a range of terminal alkenes was successfully carried out (Table 1). In all cases, either microwave irradiation or refluxing a toluene solution of the isolated or crude addition products, xanthates **12a**−**q**, induced the *syn*-elimination of the sulfoxide to yield the desired α,β-unsaturated esters **8a**−**q** in good to excellent yields (Table 1). Aryl allylic alkenes bearing both electron-withdrawing and -donating groups were successfully transformed (entry 1), as well as allyl and homoallyl amine derivatives with various substituents on the nitrogen (entries 2, 3, and 6). Alkyl alkenes containing common functionalities such as acetates, esters, ethers (entries 4, 5, and 7−11), or cyclic ketones (entries 12−14) were useful substrates. Finally, the complex, highly substituted tetrahydrofuran derivative **12q** was isolated in a good yield over the two steps (entry 15).

It is known that xanthates can undergo intramolecular cyclization onto aromatic rings in the presence of stoichiometric amounts of DLP, which acts as both the radical initiator and the oxidant for the final rearomatization.[9] Therefore, it was not surprising to find that adducts derived from allyl and homoallyl amines with an aromatic group on the nitrogen, such as xanthates **12d** and **12e**, could undergo further addition onto the aromatic ring to

(3) For a review on radical aryl migrations, see: (a) Studer, A.; Bossart, M. *Tetrahedron* **2001**, *57*, 9649. (b) Studer, A.; Bossart, M. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, p 62.

(4) (a) Briggs, M. E.; Zard, S. Z. *Synlett* **2005**, 334. (b) Jean-Baptiste, L.; Yemets, S.; Legay, R.; Lequeux, T. *J. Org. Chem.* **2006**, *71*, 2352. (c) Charrier, N.; Gravestock, D.; Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **2006**, *45*, 6520. (d) García-Merinos, J. P.; Hernández-Pérez, J. P.; Martínez-García, L.; Rojas-Lima, S.; López-Ruiz, H. *J. Mex. Chem. Soc.* **2007**, *51*, 209. (e) Boivin, J.; Nguyen, V. T. *Beilstein J. Org. Chem.* **2007**, *3*, 45–47. For the capricious nature of the process, see footnote 6 in ref 4c and Legrand, N. PhD Thesis, Ecole Polytechnique, France, 2001.

(5) Another potential solution would be to start with the sulfide of **5** and oxidize to the corresponding sulfoxide after the radical addition. The problem is that the derived radical $PhSC^{\bullet}HCO_2Et$ is a captodative radical and therefore stabilized and rather unreactive towards unactivated alkenes.

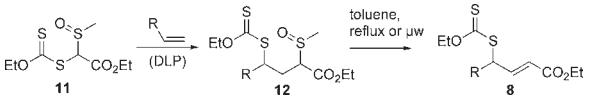
(6) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

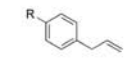
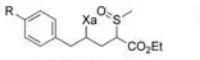
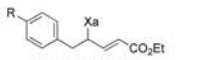
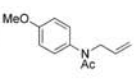
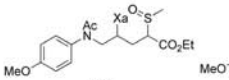
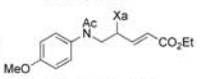
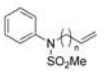
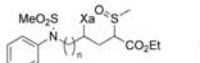
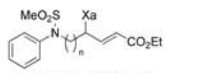
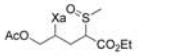
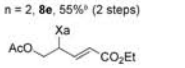
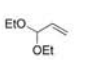
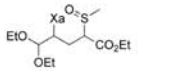
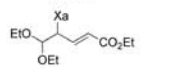
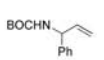
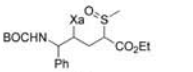
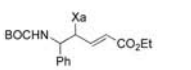
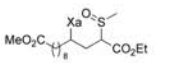
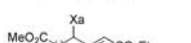
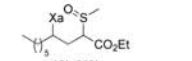
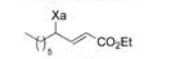
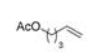
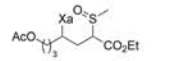
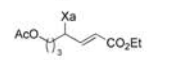
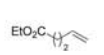
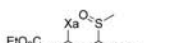
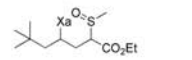
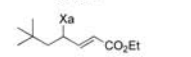
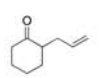
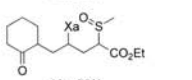
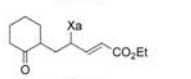
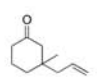
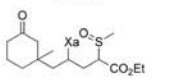
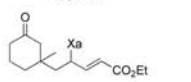
(7) Bass, J. Y.; Deaton, D. N.; McFadyen, R. B.; Mills, W. Y.; Navas, F., III; Smalley, T. L., Jr; Spearing, P. K.; Cavavella, J. A.; Madauss, K. P.; Miller, A. B.; Williams, S. P.; Chen, L.; Creech, K. L.; Marr, H. B.; Parks, D. J.; Wisley, G. B.; Todd, D. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1206.

(8) Because the half-life of the peroxide is much longer at this lower temperature, a greater amount is required to keep a useful flux of initiating radicals. Most of the peroxide in fact remains unconsumed at the end of the reaction.

(9) de Greef, M; Zard, S. Z. *Tetrahedron* **2004**, *60*, 7781.

Table 1. Xanthate Transfer with Methylsulfoxide **11** and Terminal Alkenes Followed by *syn*-Elimination



entry	alkene	radical adduct **12**[a]	eliminated product **8**
1		 R = OMe **12a**, 63% R = F **12b**, 51%	 R = OMe **8a**, 80%[b] R = F **8b**, 80%[b]
2		 **12c**[c]	 **8c**, 62%[b] (2 steps)
3		 n = 1, **12d**[c] n = 2, **12e**[c]	 n = 1, **8d**, 74%[b] (2 steps) n = 2, **8e**, 55%[b] (2 steps)
4		 **12f**, 63%	 **8f**, 98%[b]
5		 **12g**[c]	 **8g**, 69%[b] (2 steps)
6		 **12h**[c]	 **8h**, 73%[b] (2 steps)
7		 **12i**[c]	 **8i**, 62%[b] (2 steps)
8		 **12j**, 68%	 **8j**, 89%[b]
9		 **12k**, 69%	 **8k**, 71%[d]
10		 **12l**, 57%	 **8l**, 80%[d]
11		 **12m**, 66%	 **8m**, 71%[d]
12		 **12n**, 73%	 **8n**, 57%[d]
13		 **12o**, 62%	 **8o**, 66%[b]
14		**12p**[c]	**8p**, 56%[b] (2 steps)
15		**12q**[c]	**8q**, 55%[b] (2 steps)

[a] Radical adducts **12a**–**12q** were not fully characterised due to the high number of possible diastereoisomers and instead full characterisation of *syn*-eliminated products **8a**–**8q** was carried out. Xa = SCSOEt. [b] Reflux in toluene. [c] Addition product not isolated. [d] Microwave irradiation.

give indoline **13a** and, more remarkably, tetrahydroquinoline **13b** in good yields (Scheme 3). The *syn*-elimination of the sulfoxide could then also be carried out to give the unsaturated esters **14a** and **14b** (Scheme 3).

Scheme 3. Intramolecular Radical Cyclizations

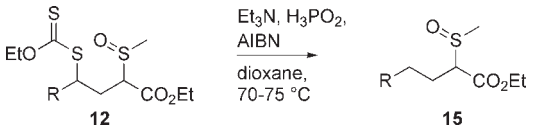
In addition to the *syn*-elimination of the sulfoxide, the versatility of adducts **12** was demonstrated by reduction of the xanthate in the presence of the sulfoxide. Treatment of xanthate **12** with triethylammonium hypophosphite and a small amount of AIBN[10] at 70–75 °C allowed the isolation of sulfoxide **15** in good to excellent yields (Table 2). Substrates containing aromatic groups (entry 1), amines (entry 2), and cyclic ketones (entry 3) could be successfully converted into sulfoxides **15a**–**c**. *syn*-Elimination of these products would then give access to α,*β*-unsaturated esters free of the xanthate group.

It has previously been shown that xanthates can be eliminated by thermolysis to yield unsaturated compounds, when the carbon bearing the xanthate is substituted with a nitrogen or a sulfur, weakening the carbon sulfur bond.[11] We envisaged that *syn*-elimination of the sulfoxide with a simultaneous elimination of the xanthate would give us access to the extremely useful and versatile α,*β*,*γ*,*δ*-unsaturated esters. Although our addition products, xanthates **12a**–**q**, do not possess any substituents that weaken the carbon sulfur bond, we were reasonably confident that thermolysis would be successful. The reaction was therefore attempted and a solution of xanthate **12a** in diphenyl ether was heated to 190 °C for 2 h. We were pleased find that after this time complete conversion of the starting material had occurred and we could isolate the desired doubly unsaturated ester **16a** in 54%. However, when we attempted the reaction with xanthate **12b** the reaction was sluggish and a reaction time of over 3 h was required for complete conversion. In order to allow for the reaction to be run at higher temperatures the elimination was attempted using microwave irradiation.

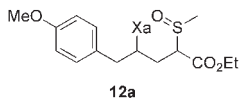
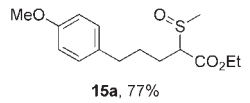
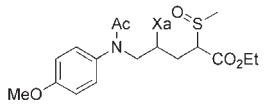
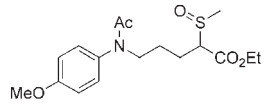
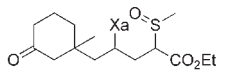
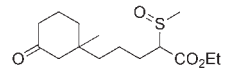
(10) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. Cs. *Tetrahedron Lett.* **1992**, *33*, 5709. (b) Boivin, J.; Jrad, R.; Juge, S.; Nguyen, V. T. *Org. Lett.* **2003**, *5*, 1645.

(11) Gagosz, F.; Zard, S. Z. *Org. Lett.* **2003**, *5*, 2655. (b) Braun, M.-G.; Zard, S. Z. *Org. Lett.* **2011**, *13*, 776.

Table 2. Xanthate Reduction in the Presence of the Sulfoxide[a]

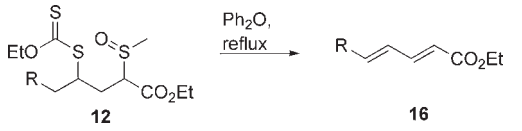


12 15

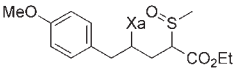
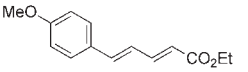
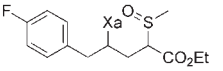
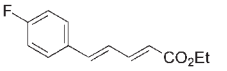
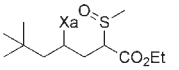
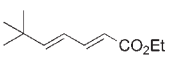
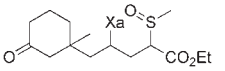
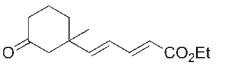
entry	xanthate	product
1	 **12a**	 **15a**, 77%
2	 **12c**	 **15b**, 83%
3	 **12o**	 **15c**, 53%

[a] Xa = SCSOEt.

Table 3. Simultaneous Elimination of the Sulfoxide and the Xanthate[a]



12 16

entry	xanthate	product
1	 **12a**	 **16a**, 57%
2	 **12b**	 **16b**, 53%
3	 **12m**	 **16c**, 38%
4	 **12o**	 **16d**, 68%

[a] Xa = SCSOEt.

Unfortunately, after much experimentation, no improvement on the yield was achieved. Finally, we found that by intensely heating a solution of xanthate **12a** in Ph_2O to reflux (~ 260 °C) for 4−10 min our desired product could be isolated in a slightly improved yield of 57% (Table 3, entry 1). Additionally the reaction of **12b** could now be carried out on the same time scale to yield ester **16b** in 53% yield (Table 3, entry 2). Using our optimized reaction conditions, alkyl xanthates **12m** and **12o**, containing a quaternary center at the β-position to the xanthate, were used and yielded the desired esters **16c** and **16d** in moderate to good yields (Table 3, entries 3 and 4).

Although the reaction was successful, to a certain extent, with other alkyl substrates, such as xanthates **12j** and **12k**, without a quaternary center at the β-position, the reaction times were longer (10−15 min) and the products were only isolated in low yields (< 20%, not reported). Furthermore, the products were hard to isolate from other alkene side products, presumably formed due to the prolonged reaction times required, which ultimately caused decomposition of the highly reactive diene products. It was also noted that with xanthates such as **12l** and **12n**, where the resulting dienes are in conjugation with the ester or ketone functionality, a complex mixture of products was formed under the reaction conditions, with none of the desired products being isolated. Even though this reaction may be limited to substrates with bulky substituents, it provides products that may not be easily accessible *via* more conventional methods due to this steric hindrance.

In conclusion, we have developed the synthesis of unsaturated and doubly unsaturated esters in only two steps from easily accessible and commercially available starting materials, methylsulfoxide **11** and terminal alkenes. The α-β-unsaturated esters can be synthesized simply by affecting the *syn*-elimination by subjecting the xanthate addition products to refluxing toluene or microwave irradiation. Additionally we have shown that the xanthate can be removed before *syn*-elimination widening the scope of this reaction. A double elimination of both the sulfoxide and the xanthate demonstrates the synthesis of the nontrivial α,β,γ,δ-unsaturated esters. The rapid assembly of diene **16d** is remarkable in this respect, as such a compound would be tedious to make by classical routes.

Acknowledgment. We dedicate this paper to the memory of Professor Hans Wijnberg (University of Groningen). Some of us (B.H., V.L.P., and N.T.) thank Ecole Polytechnique for scholarships.

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

The authors declare no competing financial interest.