

Highly selective anti-Markovnikov addition of thiols to vinyl ethers under solvent- and catalyst-free conditions

Feng-Wen Lou, Jian-Ming Xu, Bo-Kai Liu, Qi Wu, Qian Pan and Xian-Fu Lin*

Department of Chemistry, Zhejiang University, Hangzhou 310027, People's Republic of China

Received 8 August 2007; revised 11 October 2007; accepted 16 October 2007

Available online 22 October 2007

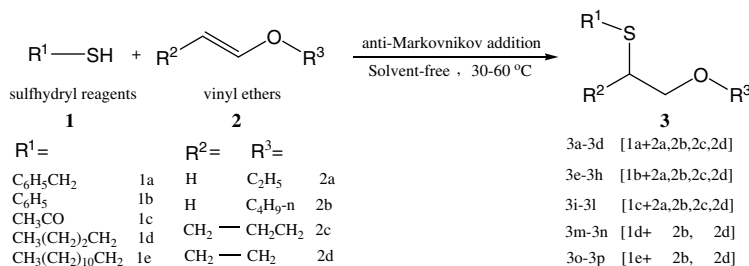
Abstract—A simple and efficient protocol for the anti-Markovnikov addition of thiols to vinyl ethers under solvent- and catalyst-free conditions has been established. A series of thiol ethers containing oxygen atom were obtained with good to excellent yields. © 2007 Elsevier Ltd. All rights reserved.

Thiol ether moiety has been found in a quite number of natural products and some pharmaceutically active substances.¹ Some sulfide constitutes an interesting family of natural compounds in the field of flavour and fragrance chemistry. Over the past few decades, a great number of alternative procedures have been developed to synthesize these potentially bioactive sulfur-containing compounds.² A radical initiator such as peroxide, AIBN, UV irradiation, or an oxidising agent was used to promote the formation of sulfur centered radicals and anti-Markovnikov-type adducts.³ However, the by-product such as disulfides was generated. Other procedures generally employ transition metal catalysts⁴ including Pd(OAc)₂,⁵ RhCl(PPh₃)₃,⁶ K₂PtCl₄,⁶ and NiCl₂.⁷ Considering the substantial high cost and high toxicity associated with these metal complex catalysts, chemists are investigating alternative procedure. Solvent- and catalyst-free reactions have attracted increasing interest due to the highly facile, efficient, and environmentally benign process.⁸ High selectivity

of anti-Markovnikov products from thiols, thiobenzoic acids and olefins was realized in benzene without any catalyst.⁹ Later, Ranu and Mandal developed a simple protocol for the anti-Markovnikov addition of thiol to alkenes in water.¹⁰

Although the anti-Markovnikov addition of thiols to carbon–carbon double bonds is well known, the formation of thiol ether containing other heteroatoms has been rarely reported.¹¹ In this Letter, we wish to report a convenient and practical synthesis of the anti-Markovnikov product by addition of thiols to vinyl ethers in solvent-free conditions without the use of a catalyst. A series of thiol ethers containing oxygen atom were obtained with good to excellent yields under mild conditions (Scheme 1).

An initial experiment on the anti-Markovnikov addition of benzyl thiol to vinyl butyl ether was carried out in different conditions, shown in Table 1. We examined



Scheme 1.

* Corresponding author. E-mail: llc123@zju.edu.cn

Table 1. Anti-Markovnikov addition between benzyl thiol and vinyl ether under different solvents^a

Entry	Solvent	Equiv (2a)	Temp (°C)	Time (h)	Yield (%)
1	<i>n</i> -Hexane	1.2	25	15	13 ^{b,d}
2	Toluene	1.2	25	15	17 ^{b,d}
3	Chloroform	1.2	25	15	31 ^{b,d}
4	Ethanol	1.2	25	15	35 ^{b,d}
5	Tetrahydrofuran	1.2	25	15	56 ^{b,d}
6	[bmim]OH	1.2	25	8	8 ^{b,c}
7	[bmim]BF ₄	1.2	25	8	67 ^{b,c}
8	[bmim]PF ₆	1.2	25	8	82 ^{b,c}
9	Solvent-free	1.2	25	5	88 ^{b,c}
10	Solvent-free	1.2	15	5	67 ^d
11	Solvent-free	1.2	30	5	90 ^d
12	Solvent-free	1.2	40	5	95 ^d
13	Solvent-free	1.2	50	5	92 ^d
14	Solvent-free	1.2	60	5	91 ^d

^a All reactions were run on a 1.0 mmol scale of benzyl thiol with 1.2 equiv of vinyl butyl ether.

^b In 1 mL of organic media or ionic liquid.

^c Isolated yields.

^d Conversion was calculated from the GC results.

the anti-Markovnikov addition reaction in several organic media or ionic liquids. The reaction was very sluggish in common organic solvents. Poor yields were obtained after 15 h (Table 1, entries 1–5). Two neutral ionic liquids, [bmim]BF₄ and [bmim]PF₆, could catalyze the reaction with moderate yields after 8 h (Table 1, entries 7 and 8). The reaction catalyzed by basic ionic liquid gave only 8% anti-Markovnikov adduct (Table 1, entry 6). To our surprise, under the solvent-free conditions, the reaction proceeded smoothly and could obtain good yields in 5 h (Table 1, entry 9). Then we examined the influence of reaction temperature on this reaction. When the reaction was performed at 15 °C, only 67% yield was obtained after 5 h (Table 1, entry 10). The reaction yield increased as the increase of reaction temperature (Table 1, entries 9–11). When the temperature was higher than 40 °C, the reaction yield decreased slightly (Table 1, entries 12–14).

With optimal conditions in hand, we then examined the scope of the substrates of this reaction. The protocol was proved to be effective for a variety of structurally

Table 2. Anti-Markovnikov addition of thiols to vinyl ethers^a

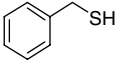

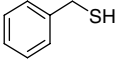
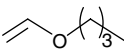
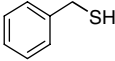

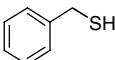




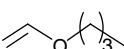







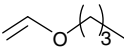




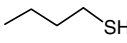
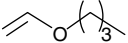
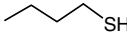

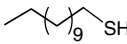
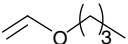
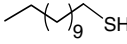

Entry	Nu-H	Substrate	Temp (°C)/time (h)	<i>M</i> / <i>anti-M</i>	Yield ^b (%)
1			30/5	0.7/99.3	3a 93
2			40/5	0/100	3b 91
3			40/7	3.2/96.8	3c 85
4			40/5	0/100	3d 95
5			30/5	1.6/98.4	3e 86
6			50/5	0.8/99.2	3f 83
7			50/7	2.7/97.3	3g 72
8			50/5	4.3/95.7	3h 91
9			30/3	1.8./98.2	3i 96
10			30/3	5.9/94.1	3j 93
11			30/3	1.0/99.0	3k 91

Table 2 (continued)

Entry	Nu-H	Substrate	Temp (°C)/time (h)	M/anti-M	Yield ^b (%)
12			30/3	1.0/99.0	3l 95
13			50/5	1.2/98.8	3m 82
14			50/5	— ^c	3n 86
15			60/5	4.7/95.3	3o 76
16			60/5	— ^c	3p 78

^a Reactions were carried out on 1.0 mmol scale of thiol with 1.2 equiv of vinyl ethers in solvent-free.

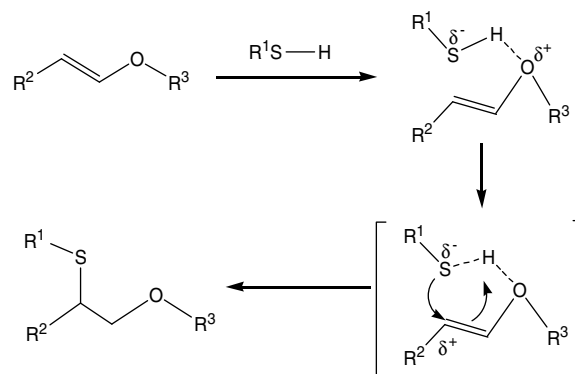
^b Yields refer to those of pure isolated anti-Markovnikov product characterized by IR, ¹H and ¹³C NMR spectroscopic data.

^c Not determined.

diverse thiols and vinyl ethers. The anti-Markovnikov addition of benzyl thiol to vinyl ethyl ether, vinyl butyl ether proceeded smoothly and provided good yields (Table 2, entries 1 and 2). Compared with vinyl ethyl ether, the reaction rate of vinyl butyl ether was slightly slower. Accordingly, higher reaction temperature was required to obtain good yield. Apart from the chain-like vinyl ether, cyclic vinyl ether such as dihydropyran and dihydrofuran also underwent anti-Markovnikov addition with benzyl thiol leading to the corresponding adducts with good yields (Table 2, entries 3 and 4). As seen from the result, dihydropyran showed lower reactivity than dihydrofuran. Aromatic thiols such as thiophenol could also be employed as substrates for the anti-Markovnikov addition reaction. The expected products were formed in good yields (Table 2, entries 5–8). In the case of the anti-Markovnikov addition between thioacetic *S*-acid and acyclic vinyl ethers or cyclic vinyl ethers, excellent yields were achieved (Table 2, entries 9–12). In addition, some aliphatic thiols with long carbon chain were tested as the substrate. The reactions of butyl thiol, dodecyl mercaptan with the vinyl butyl ether, dihydrofuran were furnished in good yields (Table 2, entries 13–16).

In general, the reaction was highly selective and high-yielding. The Markovnikov addition by-products were less than 6%. The work-up procedure was very simple and suitable for large scale production (see Supplementary data). All the novel compounds were characterized by IR, NMR and HR-MS. For the known compounds, the data are in good agreement with those have been previously reported.

Based on the experimental results, we proposed a mechanism for the anti-Markovnikov addition reaction under solvent-free conditions as shown in Scheme 2. The interaction between oxygen in vinyl ether and hydrogen in



Scheme 2.

thiol could activate the C–C double bond. The beta carbon might become partially positive charged and could be attracted by sulfur. Then the bond between sulfur and hydrogen would be broken. The alpha carbon could abstract the proton from oxygen subsequently and give the anti-Markovnikov addition products.

In summary, we have developed an efficient protocol for the anti-Markovnikov addition of thiols to vinyl ethers under solvent- and catalyst-free conditions. This new methodology constituted the ease of reaction, short reaction time, high regioselectivity, high yields and green synthesis of thiol ester containing oxygen atom.

Acknowledgments

This investigation has enjoyed financial support from the Natural Science Foundation of China (No. 20572099), the Zhejiang Provincial Science and Technology Council (No. 2006C11197) and Ph.D. Programs Foundation of Ministry of Education of China (20060335031).

References and notes

- (a) Bur, S. K.; Padwa, A. *Chem. Rev.* **2004**, *104*, 2401–2432; (b) Pachamuthu, K.; Schmidt, R. R. *Chem. Rev.* **2006**, *106*, 160–187; (c) Jones, D. P.; Go, Y. M.; Anderson, C. L.; Ziegler, T. R.; Kinkade, J. M.; Kirilin, W. G. *FASEB J.* **2004**, *18*, 1246–1248; (d) Suzuki, T.; Kouketsu, A.; Matsuura, A.; Kohara, A.; Ninomiya, S.; Kohda, K.; Miyata, N. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3313–3317.
- (a) Smith, R. L.; Cohen, S. M.; Doull, J.; Feron, V. J.; Goodman, J. I.; Marnett, L. J.; Portoghese, P. S.; Waddell, W. J.; Wagner, B. M.; Adams, T. B. *Food Technol.* **2003**, *57*, 46–59; (b) Sarrazin, E.; Shinkaruk, S.; Tominaga, T.; Bennetau, B.; Frerot, E.; Dubourdiou, D. *J. Agric. Food Chem.* **2007**, *55*, 1437–1444.
- (a) Ipatieff, V. N.; Pines, H.; Friedman, B. S. *J. Am. Chem. Soc.* **1938**, *60*, 2731–2734; (b) Bordwe, F. G.; Hewett, W. A. *J. Am. Chem. Soc.* **1957**, *79*, 3493–3496; (c) Jenner, E. L.; Lindsey, R. V. *J. Am. Chem. Soc.* **1961**, *83*, 1911–1915; (d) Missakian, M. G.; Ketcham, R.; Martin, A. R. R. *J. Org. Chem.* **1974**, *39*, 2010–2012; (e) Kannan, P.; Pitchumani, K. *Catal. Lett.* **1997**, *45*, 271–273; (f) Ranu, B. C.; Mandal, T. *Tetrahedron Lett.* **2006**, *47*, 6911–6914.
- (a) Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205–3220; (b) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368–3398.
- Kuniyasu, H.; Ogawa, A.; Sato, K. I.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 5902–5903.
- Ogawa, A.; Ikeda, T.; Kimura, K.; Hirao, T. *J. Am. Chem. Soc.* **1999**, *121*, 5108–5114.
- Ananikov, V. P.; Malyshev, D. A.; Beletskaya, I. P.; Aleksandrov, G. G.; Eremenko, I. L. *Adv. Synth. Catal.* **2005**, *347*, 1993–2001.
- (a) Metzger, J. O. *Angew. Chem., Int. Ed.* **1998**, *37*, 2975–2978; (b) Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Zuccaccia, C.; Vaccaro, L. *Green Chem.* **2006**, *8*, 19–196; (c) Rodriguez, B.; Rantanen, T.; Bolm, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 6924–6926; (d) Fringuelli, F.; Pizzo, F.; Tortoioli, S.; Vaccaro, L. *Tetrahedron Lett.* **2003**, *44*, 6785–6787; (e) Nuchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.* **2004**, *6*, 128–141; (f) Varma, R. S. *Green Chem.* **1999**, *1*, 43–55.
- Kanagasabapathy, S.; Sudalai, A.; Benicewicz, B. C. *Tetrahedron Lett.* **2001**, *42*, 3791–3794.
- Ranu, B. C.; Mandal, T. *Synlett* **2007**, *6*, 925–928.
- (a) Ruano, J. L. G.; Rodriguez, J.; Alcudia, F.; Llera, J. M.; Olefirowicz, E. M.; Eliel, E. L. *J. Org. Chem.* **1987**, *52*, 4099–4107; (b) Jessop, C. M.; Parsons, A. F.; Routledge, A.; Irvine, D. J. *Tetrahedron Lett.* **2004**, *45*, 5095–5098.