Addition of Thiols to Styrenes: Formation of Benzylic Thioethers

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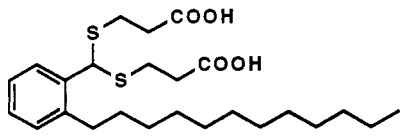
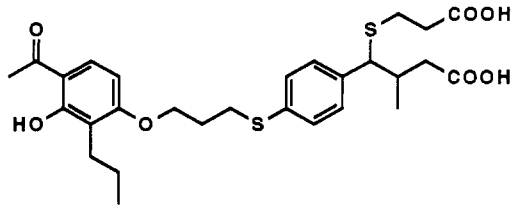
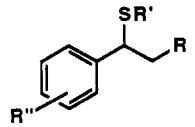
As part of our program to find new LTD_4 antagonists, we were interested in synthesizing the analogues **3** of the dithioacetal **1** (SK&F no. 102,081)[1] and of the benzylic thioether **2** (L-655,278).[2] A simple and versatile approach to this class of compounds would be the addition of a thiol to a styrene, which in turn could be obtained easily from a Wittig reaction on substituted benzaldehydes.[3]



1



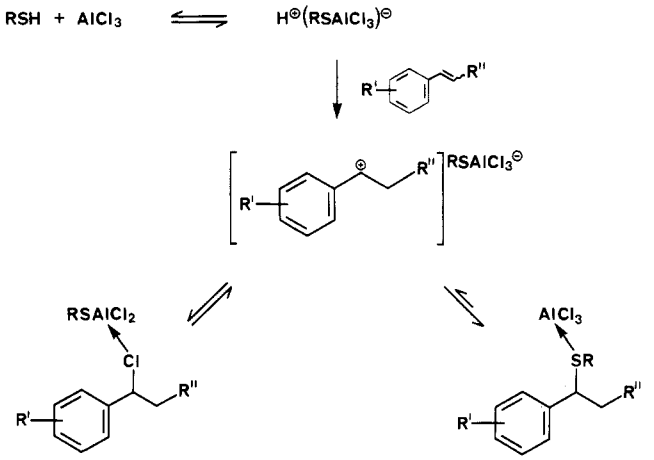
2



3

Although the Markovnikoff addition of a thiol to a double bond is a known reaction,[4] there is an obvious lack of literature precedent when it comes to styrene substrates, probably because they polymerize so easily under acidic conditions. Only three papers report this reaction. First, in 1972, Wolf and Finke reported the use of *p*-TsOH as a catalyst in the addition of acidic thiols to an activated styrene, *p*-isopropenylphenol. Their conditions, however, failed with H_2S and alkylthiols, while thiophenol gave Friedel–Crafts addition products.[5] Then, in 1973, Mukaiyama et al. used $TiCl_4$ as the catalyst in the addition of ethanethiol to styrene and α-methylstyrene[6] in cyclohexane solvent. Finally, in 1979, Screttas and Micha-Screttas reported the addition of thiophenol to unfunctionalized styrenes in the presence of perchloric acid.[7]

Scheme I



Using the method of Mukaiyama with functionalized styrenes and thiols, we at first obtained only polymers of styrene. However, modification of the procedure, namely, addition of $TiCl_4$ dropwise to a cyclohexane solution containing the styrene and the thiol, gave some addition product (Table I). The reaction was heterogeneous and gave only poor to modest yield. In cases where the styrene moiety was not activated by a methoxyl group (entries 5, 6) and where one amide or acid function was present (entries 2–4), the rate and the yield of the reaction dropped dramatically.

Unsatisfied with these reaction conditions, we discovered, much to our surprise, that $AlCl_3$ is a very good catalyst for this addition reaction. Thus, the use of 1 equiv of $AlCl_3$ for each potential complexation site, plus 1 equiv in excess, afforded the Markovnikoff addition products in good yield (Table II). Methyl esters and aromatic methyl ethers are stable under the reaction conditions, although their hydrolysis by RSH·$AlCl_3$ has been reported.[8] Amides and acids did not inhibit the reaction (entries 5, 7, 10–13), as was the case with $TiCl_4$. Aromatic thiols can also be used (entries 4 and 14).

The presence of activating or deactivating substituents on the styrene influences the rate of the reaction. In the presence of a methoxy substituent, the reaction can be run at −10 °C with only 1.3 equiv of thiol.[9] Conversely, a cyano-substituted styrene requires higher temperature and longer reaction time.

Another peculiarity of this reaction was noticed in some cases, where radical processes interfered. This problem can be overcome by running these reactions in the dark and in the presence of 1,6-di-*tert*-butyl-4-methylphenol (BHT) as a radical scavenger.

Although the actual mechanism of the reaction was not studied, a plausible one is that a complex is first formed

(1) Perchonock, C. D.; McCarthy, M. E.; Erhard, K. F.; Gleason, J. G.; Wasserman, M. A.; Muccitelli, R. M.; DeVan, J. F; Tucker, S. S.; Vickery, L. M.; Kirchner, T.; Weichman, B. M.; Mong, S.; Crooke, S. T.; Newton, J. F. *J. Med. Chem.* **1985**, *28*, 1145.

(2) Young, R. N.; Gauthier, J. Y.; Frenette, R. European Patent Application 206,741, Dec 30, 1986.

(3) For other methods of formation of the C–S bond, see: Young, R. N.; Coombs, W.; Guindon, Y.; Rokach, J.; Ethier, D.; Hall, R. *Tetrahedron Lett.* **1981**, *22*, 4933. Guindon, Y.; Young, R. N.; Frenette, R. *Synth. Commun.* **1981**, *11*, 391. Guindon, Y.; Frenette, R.; Fortin, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 1357. Gauthier, J. Y.; Bourdon, F.; Young, R. N. *Tetrahedron Lett.* **1986**, *27*, 15.

(4) For a review on the subject, see: Prilezhaeva, E. N.; Shostakovskii, M. F. *Russ. Chem. Rev. (Engl. Transl.)* **1963**, *32*, 399. For the addition reaction of thiol to olefins with $AlCl_3$, see: Bell, R. T. U.S. Patent 2,535,831, Dec 26, 1950. For recent work, see: Tolstikov, G. A.; Kanzafarov, F. Ya.; Sangalov, Yu. A.; Dzemilev, U. M. *Pet. Chem. USSR (Engl. Transl.)* **1979**, *19*, 425.

(5) Wolf, F.; Finke, H. *Z. Chem.* **1972**, *12*, 180.

(6) Mukaiyama, T.; Izawa, T.; Saigo, K.; Takei, H. *Chem. Lett.* **1973**, 335.

(7) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1979**, *44*, 713.

(8) Node, M.; Nishide, K.; Sai, M.; Ichikawa, K.; Fuji, K.; Fujita, E. *Chem. Lett.* **1979**, 97. Node, M.; Nishide, K.; Sai, M.; Fujita, E. *Tetrahedron Lett.* **1978**, 5211.

(9) Higher temperature and excess thiol resulted in the cleavage of the methoxy substituent. For examples of this reaction, see ref 8.

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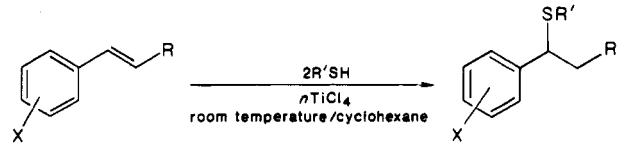
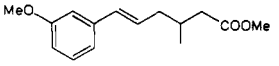
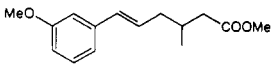
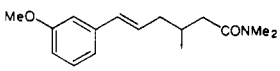
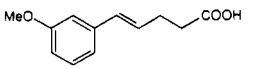
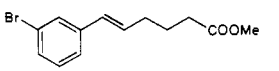
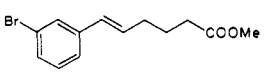
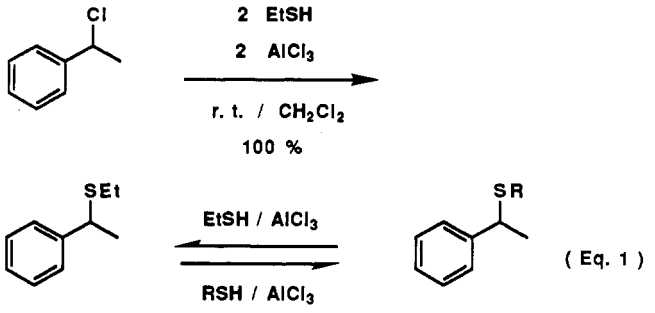
Table I. Addition of Thiols to Styrenes under $TiCl_4$ Catalysis



entry	styrene	thiol	n	time, h	yield,[a] %
1		$HS(CH_2)_2COOMe$	5	4	54
2		$HS(CH_2)_2CONHBu^t$	3.3	20	10
3		$HS(CH_2)_2COOMe$	8	100	57[b]
4		$HS(CH_2)_2COOMe$	4	20	0[c]
5		$HS(CH_2)_2COOMe$	5	72	35
6		$HSC(=O)CH_3$	6	20	45[d]

[a] Most of the products are oils. ^1H NMR spectra showed a triplet at ~3.7 ppm, which is characteristic for ArC*H*SR. Some of the mass spectra showed a peak corresponding to $[ArCH{=}SR]^+$. [b] Four equivalents of R'SH. [c] No reaction. [d] Three equivalents of MeCOSH.

between the thiol and $AlCl_3$ (Scheme I).[10] The acidic proton then adds to the styrene to form a carbocation, which reacts with the aluminum species to yield the thioether or the chloride (see Table II, note *b*). This mechanistic scheme is compatible with the fact that all these products are in equilibrium. Indeed, α-chloroethylbenzene can be converted quantitatively to α-(ethylthio)ethylbenzene (eq 1), and benzylic sulfides can be displaced by RSH·$AlCl_3$ to give a mixture of the two sulfides.



(Eq. 1)

In summary, the addition of thiols to styrenes in the presence of $AlCl_3$ represents an easy and versatile approach to the synthesis of benzylic thioethers. The use of this reaction for the preparation of potent LTD_4 antagonists will be described in due course.

Experimental Section

General Procedures. Nuclear magnetic resonance spectra were recorded on a Bruker AM 250 or 300-MHz FT spectrometer. Infrared spectra were obtained on a Perkin-Elmer Model 681 instrument. High-resolution mass spectra were obtained at the McGill University mass spectrometry unit on a ZAB-HS spectrometer (chemical ionization with NH_3). Purifications by flash chromatography employed 200–400-mesh silica gel supplied by E. Merck.

Methyl 6-((2-(Methoxycarbonyl)ethyl)thio)-6-(3-methoxyphenyl)-3-methylhexanoate (Table I, Entry 1). To methyl 6-(3-methoxyphenyl)-3-methyl-5-hexenoate (835 mg, 3.36 mmol) and methyl 3-mercaptopropanoate (750 μL, 2 equiv) in cyclohexane (17 mL) was added $TiCl_4$ (1.9 mL, 5 equiv) dropwise. The gummy reaction mixture was stirred in the dark for 4.25 h. At 0 °C, 25% aqueous NH_4OAc and EtOAc were added[12] and the mixture was extracted with EtOAc. The title compound was purified by flash chromatography on silica with EtOAc–toluene, 2.5:97.5: IR (neat) 2920, 1733, 1598, 1431 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (2 d, 3 H), 1.00–1.45 (m, 2 H), 1.70–2.00 (m, 3 H), 2.09 (m, 1 H), 2.27 (m, 1 H), 2.45 (m, 2 H), 2.55 (m, 2 H), 3.64 (s, 3 H), 3.67 (s, 3 H), 3.69 (t, 1 H), 3.82 (s, 3 H), 6.78 (dd, 1 H), 6.85 (s, 1 H), 6.88 (d, 1 H), 7.23 (dd, 1 H); MS, *m/e* 369 (M + H), 368 (M^+), 249 (M – $SCH_2CH_2CO_2Me$); exact mass calcd for $C_{19}H_{29}O_5S$ 369.1736, found 369.1734.

Methyl 6-(3-Bromophenyl)-6-((2-(methoxycarbonyl)ethyl)thio)hexanoate (Table II, Entry 6). To methyl 6-(3-bromophenyl)-5-hexenoate (28 mg, 99 μmol) and methyl 3-mercaptopropanoate (22 μL, 2 equiv) in CH_2Cl_2 (1 mL) was added $AlCl_3$ (66 mg, 5 equiv) at −10 °C, and the mixture was stirred at room temperature for 45 min. At 0 °C, 25% aqueous NH_4OAc was added.[12] Extraction with EtOAc and flash chromatography of the residue on silica with EtOAc–hexane, 15:85, yielded the title thioether: IR (neat) 2920, 1737, 1590, 1565, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (m, 2 H), 1.61 (m, 2 H), 1.83 (m, 2 H), 2.27 (t, 2 H), 2.48 (m, 2 H), 2.54 (m, 2 H), 3.67 (s, 3 H), 3.69 (s, 3 H), 3.74 (t, 1 H), 7.20 (m, 2 H), 7.37 (dt, 1 H), 7.47 (s, 1 H); MS, *m/e* (relative intensity) 423 (20), 422 (98), 421 (19), 420 (100, M + NH_4), 405 (34), 403 (30, M + H), 302 (23), 300 (21, M – $(CH_2)_3CO_2Me$ – H), 285 (81), 283 (82, M – $S(CH_2)_2CO_2Me$); exact mass calcd for $C_{17}H_{24}O_4SBr$ 403.0579, found 403.0583.

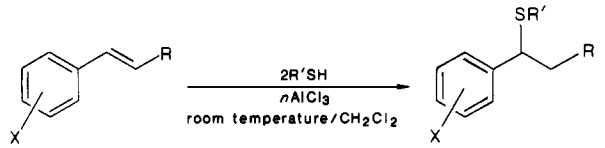
3-((1-(3-Cyanophenyl)-5-(methoxycarbonyl)-4-methyl-1-pentyl)thio)propanoic Acid (Table II, Entry 13). To a stirred

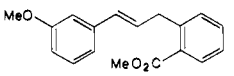
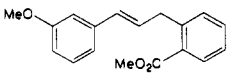
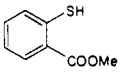
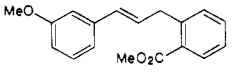
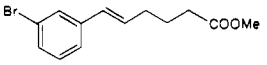
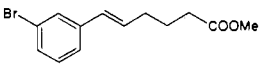
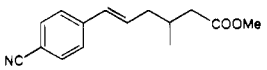
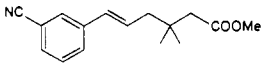
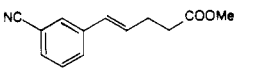
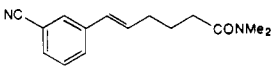
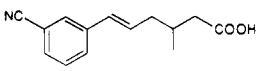
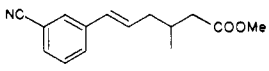
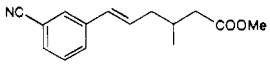
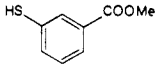
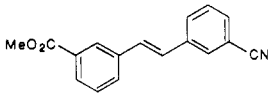
(10) These complexes, where the aluminum is sp^3 hybridized and the acidic proton is not attached to the sulfur atom, have been described by Hoffmann.[11] We have recorded low-temperature ^1H NMR spectra of the EtSH·$AlCl_3$ complex in CD_2Cl_2, and our observations are in agreement with those of Hoffmann for the benzene solution.

(11) Hoffmann, G. G. *Chem. Ber.* **1985**, *118*, 3320.

(12) In some cases, addition of THF facilitates the hydrolysis step. Filtration of this mixture through Celite is recommended when emulsions occur or when there are excessive quantities of insoluble aluminum salts.

Table II. Addition of Thiols to Styrenes under $AlCl_3$ Catalysis



entry	styrene	thiol	n	time, h	yield,[a] %
1		EtSH	2	2	61[b]
2		EtSH	2	3	57
3		$HS(CH_2)_2COOMe$	5	0.3	59[c]
4			6	2	74[c-e]
5		$HS(CH_2)_2CONMe_2$	6	2	77[c-e]
6		$HS(CH_2)_2COOMe$	5	0.8	70[f]
7		$HS(CH_2)_2CONMe_2$	5	0.8	80[f]
8		$HS(CH_2)_2COOMe$	6	44	45[g]
9		$HS(CH_2)_2COOMe$	5	18	62[g]
10		$HS(CH_2)_2CONMe_2$	5	6	79[d,g]
11		$HS(CH_2)_2COOMe$	5	3.5	70[d,g]
12		$HS(CH_2)_2COOMe$	6	6.5	75
13		$HS(CH_2)_2COOH$	6	25	83
14			4	1.5	79[d]
15		$HS(CH_2)_2COOMe$	6	1.8	84[d,h]

[a] See Table I, footnote *a*. [b] α-Chloroethylbenzene (14%) was also found. [c] Reaction at −10 °C. [d] 1.3 equiv of R'SH. [e] Addition of 0.2 equiv of BHT to the reaction mixture. [f] Addition of $AlCl_3$ at −10 °C. [g] Addition of $AlCl_3$ at 0 °C. [h] Mixture of two isomers, 9:1; the major one contains the thioether at the benzylic position of the (methoxycarbonyl)phenyl group.

solution of methyl 6-(3-cyanophenyl)-3-methyl-5-hexenoate (2.006 g, 8.25 mmol) and 3-mercaptopropanoic acid (1.45 mL, 2 equiv) in CH_2Cl_2 (80 mL) was added $AlCl_3$ (6.603 g, 6 equiv), and the suspension was stirred for 25 h at room temperature in the dark. The product separated slowly as a gum. At 0 °C, the mixture was quenched with 25% aqueous NH_4OAc and EtOAc.[12] The aqueous layer was acidified with AcOH and extracted with EtOAc. Flash chromatography of the residue on silica with EtOAc–hexane–AcOH, 30:70:1, afforded the title thioether: IR (neat) 2500–3600 (COOH), 2950, 2920, 2225, 1730, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (2 d, 3 H), 0.97–1.45 (m, 2 H), 1.70–2.00 (m, 3 H), 2.07–2.33 (m, 2 H), 2.54 (s, 4 H), 3.66 (2 s, 3 H), 3.77 (t, 1 H), 7.45 (dd, 1 H), 7.55–7.65 (m, 3 H); MS, *m/e* (relative intensity) 368 (21), 367 (100, M + NH_4), 350 (14, M + H), 244 (11, M − S-$(CH_2)_2CO_2H$); exact mass calcd for $C_{18}H_{24}NO_4S$ 350.1426, found 350.1427.

Acknowledgment. We thank Dr. M. A. Bernstein for running the low-temperature NMR experiments and for the structure determination of the products of entry 15 (Table II).