Pergamon

Tetrahedron Letters, Vol. 37, No. 16, pp. 2695-2698, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00339-5

An Efficient Rearrangement of Secondary Alkyl *S*-Methyl Xanthates by Trimethylaluminum (TMA)

Derek H. R. Barton* and Seung-Yong Choi

Department of Chemistry, Texas A&M University, College Station, TX 77843-3255, USA.

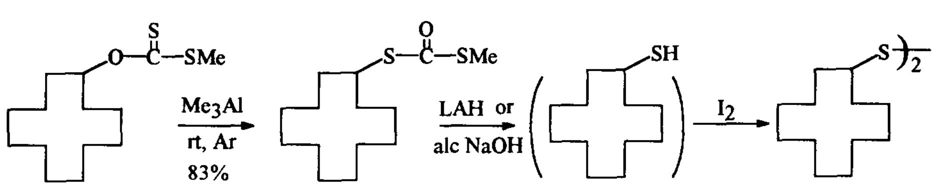
Abstract: The rearrangement of secondary *S*-methyl xanthates to *S*-methyl dithiocarbonates at room temperature using trimethylaluminum has been studied. This reaction affords an efficient and simple method for converting secondary alcohols to thiols. Copyright © 1996 Elsevier Science Ltd

The high temperature rearrangements of xanthates to dithiocarbonates is well-documented for xanthates without a β-hydrogen atom.[1] An analogous high temperature reaction is used in the Newman-Kwart rearrangement, which converts phenols into thiophenols.[2] The Chugaev elimination involves the pyrolysis of alcohol xanthates at fairly high temperatures to afford olefins.[3] It has a unimolecular mechanism and proceeds with *cis*-elimination.[4]

Extensive work by Taguchi[5] has shown that when a cation stabilizing group is present, as in 2-dialkylaminoalkyl *S*-methyl xanthates and allylic *S*-alkyl xanthates, rearrangement to dithiocarbonates occurs at more modest temperatures. An ion pair mechanism is probably involved. On the other hand, rearrangement of ordinary primary[6] or secondary xanthates[7] requires heatings at above 200 °C. A few years ago, the catalytic rearrangement[8] of xanthates to dithiocarbonates was shown to occur under milder conditions using Lewis acid or pyridine *N*-oxide catalysis but the yields are low for secondary xanthates. Recently, an enantioselective synthesis of thiols[9] has been accomplished by treating xanthates with an optically active pyridine *N*-oxide at 100 °C for a prolonged period.

In earlier work[10] we had shown that carbohydrate dimethylketals were smoothly converted into glycol mono-*t*-butyl derivatives with trimethylaluminum. In this letter we report that secondary *S*-methyl xanthates rearrange at room temperature to the corresponding dithiocarbonates upon treatment with trimethylaluminum (TMA) or triethylaluminum. In a typical reaction, to the cyclododecyl *S*-methyl xanthate **1** (200 mg, 0.73 mmol) in 1 mL of hexanes (**Scheme 1**) TMA (1.5 eq.; 2M in hexanes) was added in one portion at 0 °C and stirred at room temperature for 15 hrs under Ar. After quenching by slow addition of water and extraction into ether, the dithiocarbonate **2** was obtained (83%) by column chromatography on silica gel. There was no trace of cyclododecene.[11] The use of triethylaluminum in toluene under the same conditions resulted in a lower yield (70%). The structure of **2** was proven by conversion to the thiol **3** and oxidation to the disulfide **4** in nearly quantitative yield.[11]

Scheme 1

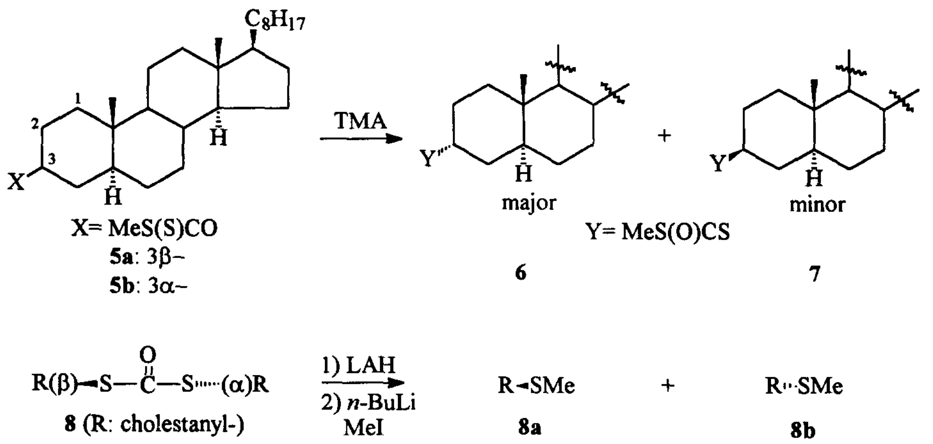


1 2 3 4

A primary xanthate, hexadecyl *S*-methyl xanthate, did not rearrange under the same conditions nor did 2,4,6-trimethylphenoxy *S*-methyl xanthate. The observation that the NMR signals, corresponding to the methine hydrogen and carbon atoms, were significantly shifted after xanthate **1** (^{1}H: δ= 6.5 ppm; ^{13}C: δ= 79.2 ppm, C_6D_6) was treated with 1.2 eq. TMA indicated that xanthate **1** initially coordinated to TMA (^{1}H: δ= 6.1 ppm; ^{13}C: δ= 82.7 ppm, C_6D_6) in a fast reaction. However, the rearrangement is relatively slow (see above).

In order to study the stereoselectivity of the rearrangement, 3β- (**5a**) and 3α-cholestanyl *S*-methyl xanthate (**5b**) were examined (**Scheme 2**). First, the reaction of **5a** with TMA gave a mixture of two products consisting of isomers **6** and **7** in a 4:1 ratio (65-70% isolated yield).

Scheme 2

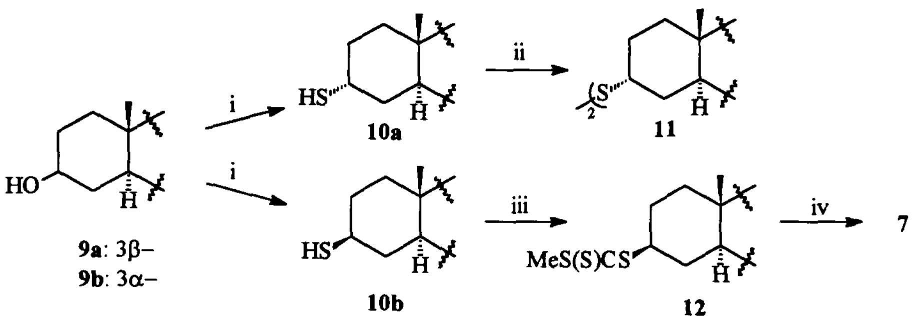


In addition to the rearranged products, the dimeric product[12] **8** was also detected. To elucidate the structure of **8** (200 mg, 0.24 mmol) it was first reduced with LAH and methylated (*n*-BuLi/MeI) to give a 1:1 mixture of the thio ethers **8a** (31 mg, 0.074 mmol, 31%) and **8b** (34 mg, 0.081 mmol, 34%) which were purified by column chromatography (hexanes/EtOAc= 98/2). These were identical with the authentic compounds prepared by methylation (**Scheme 3**) of **10a** and **10b**, respectively. In every reaction with TMA, all of the initial **5a** was consumed without elimination according to TLC and NMR data. The major isomer **6** (w/2= 11 Hz, width of band at half height[13]) was isolated and reduced with LAH to yield cholestan-3α-thiol which was oxidized to give the dicholestan-(3α)-yl disulfide. Authentification[14] (**Scheme 3**) of cholestan-3α-thiol and dicholestan-(3α)-yl disulfide was accomplished by treatment of 3β-cholestanyl tosylate (w/2= 24 Hz) of **9a** with KSCN in acetone to produce 3α-cholestanyl thiocyanide (60%, w/2= 10 Hz) which was reduced by LAH to yield **10a** (81%, w/2= 12 Hz) and oxidized to **11** (84%, w/2= 9 Hz).

Rearranged xanthate **7** (w/2= 26 Hz), as a minor isomer, was also separated and compared with an authentic sample (**Scheme 3**) prepared by reaction of the 3α-cholestanyl tosylate (w/2= 8 Hz) of **9b** with KSCN in acetone to give 3β-cholestanyl thiocyanide (55%, w/2= 25 Hz). This was reduced by LAH to yield thiol **10b** (60%, w/2= 24 Hz). Treatment of thiol **10b** (500 mg, 1.24 mmol) with *n*-BuLi/CS_2 and MeI gave thiocarbonyl compound **12** (430 mg, 0.87 mmol, 70.2%), which was treated at room temperature in THF with 1 eq. of benzeneseleninic anhydride[15] to produce the authentic **7** (55%, w/2= 25 Hz).[16]

We further examined the reaction of **5b** with TMA. Xanthate **5b** was easily prepared from the corresponding **9b** (w/2= 8 Hz) which was obtained by the selective reduction of 3-cholestanone with L-selectride.[17] However, treatment of **5b** with TMA under the same reaction conditions above produced exactly the same results as the xanthate **5a** (**Scheme 2**). The major isomer **6** (w/2 = 10 Hz) was isolated and fully characterized by NMR spectra and mixed m.p. which proved it identical to the major compound from the reaction of **5a** and TMA.

Scheme 3



i. 1) TsCl, Py 2) KSCN 3) LAH ii. I_2 iii. *n*-BuLi, CS_2, MeI iv. $(PhSeO)_2O$ in THF

The original concept that initiated this study was that TMA would complex so strongly with the thiocarbonyl of a secondary xanthate that fragmentation to anion and carbocation might take place. Since the TMA would be more strongly bonded to the potential carbonyl oxygen than to the sulfur the ionic complex might then neutralize itself by forming irreversibly the rearranged dithiocarbonate. The experiment with the cyclododecane xanthate **1** shows that this new reaction does indeed take place in good yield under room temperature conditions. We had expected that the two cholestane xanthate **5a** and **5b** would afford the same mixture of products by this mechanism. Indeed this is the case, but the axial 3α-product is the major constitutent of the mixture in both cases. It would seem very improbable that the 3α-xanthate complexed to TMA would be more stable than its 3β-isomer. Therefore the identical product mixture must come from a more favourable kinetic approach of the anionic complex to the α-side of the molecule opposite to the 10β-methyl group. We presume that the coordination of TMA renders the complex as bulky as adding a *t*-butyl group to the thiocarbonyl of the xanthate.

Acknowledgements: We thank the N.I.H., the Welch Foundation and the Schering-Plough Corporation for supporting this work.

References and Notes

1. (a) Freudenberg, K.; Wolf, A. *Chem. Ber.* **1927**, *60*, 232. (b) Schönberg, A.; Vargha, L. *Chem. Ber.* **1930**, *63*, 178.
2. (a) Kwart, H.; Evans, E. R. *J. Org. Chem.* **1966**, *31*, 410. (b) Newman, M. S.; Hetzel, F. W. *Org Synth.* **1971**, *31*, 139. (c) Newman, M. S.; Karnes, H. A. *J. Org. Chem.* **1966**, *31*, 3980.
3. Tarbell, D. S.; Harnish, D. P. *Chem. Revs.* **1951**, *49*, 56.
4 Barton, D. H. R. *J. Chem. Soc.* **1949**, 2174.
5. (a) Taguchi, T.; Nakao, M. *Tetrahedron*, **1962**, *18*, 245. Taguchi, T.; Kawazoe, Y.; Nakao, M. *Tetrahedron Lett.* **1963**, *3*, 131. (b) Taguchi, T.; Harano, K. *Chem. Pharm. Bull.*(Tokyo) **1972**, *11*, 2357 and **1972**, *20*, 2348. (c) Harano, K; Taguchi, T. *Tetrahedron Lett.* **1974**, 4479.
6. Jenneskens, L. W.; Hoefs, C. A. M.; Wiersum, U. E. *J. Org. Chem.* **1989**, *54*. 5811.
7. McAlpine, I. M. *J. Chem. Soc.* **1931**, 1114.; **1932**, 906. Overberger, C. G.; Borchert, A. E. *J. Am. Chem. Soc.* **1960**, *82*, 4896.

8. (a) Kawata, T.; Harano, K.; Taguchi, T. *Chem. Pharm. Bull.* **1973**, *21(3)*, 604. Komaki, K.; Kawata, T.; Harano, K.; Taguchi, T. *Chem. Pharm. Bull.* **1978**, *21(12)*, 3807. (b) Harano, K.; Shinohara, I.; Murase, M.; Hisano, T. *Heterocycles* **1987**, *26*, 2583. Harano, K.; Kiyonaga, H.; Sugimoto, S-I.; Matsuoka, T.; Hisano, T. *Heterocycles* **1988**, *27*, 2327. Harano, K.; Shinohara, I.; Sugimoto, S-I.; Matsuoka, T.; Hisano, T. *Chem. Pharm. Bull.* **1989**, *37(3)*, 567.

9. Diana, M. B.; Marchetti, M.; Melloni, G. *Tetrahedron: Asymmetry* **1995**, *6*, 1175.

10. Barton, D. H. R.; Zhu, J. *Tetrahedron*, **1992**, *48*, 8837. There is precedent for this reaction which we had unintentionally overlooked: Takano, S.; Ohkawa, T.; Ogasawara, K. *Tetrahedron Lett.* **1988**, *29*, 1823. See also Fujiwara, J.; Fukutani, Y.; Hasegawa, M.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1984**, *106*, 5004. Fukutani, Y.; Maruoka, K.; Yamamoto, H. *Tetrahedron, Lett.* **1984**, *25*, 5911. Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *J. Organomet. Chem.* **1985**, *285*, 83. Maruoka, K.; Nakai, S.; Sakurai, M.; Yamamoto, H. *Synthesis*, **1986**, 130. Maruoka, K.; Yamamoto, H. *Tetrahedron*, **1988**, *44*, 5001.

11. The reaction mixture contained cyclododecanol and cyclododecanone as minor products. Compound **2** was eluted with hexanes/EtOAc (9:1): m.p. 35-36 °C, IR: 2933, 1734, 1639, 1441, 1344, 853 cm^{-1}. ^{1}H NMR: δ 3.74-3.88 (1H, m), 2.41 (3H, s), 1.89-1.20 (22H, b) ^{13}C NMR: δ 190.1, 42.6, 30.6, 23.6, 23.6, 23.5, 23.4, 22.4, 12.9. Anal. Calcd. for $C_{14}H_{26}S_2O$: C, 61.31; H, 9.48; S, 23.38. Found: C, 61.36; H, 9.55; S, 23.31. Compound **4**: m.p. 77.5-78 °C, IR: 2919, 2834, 1455, 1433 cm^{-1}. ^{1}H NMR: δ 2.53-2.58 (2H, m), 1.40-1.02 (44H, b). ^{13}C NMR: δ 47.8, 30.2, 23.8, 23.7, 23.6, 23.0, 22.5. Anal. Calcd. for $C_{24}H_{46}S_2$:C, 72.36; H, 11.56; S, 16.08. Found: C, 72.38; H, 11.46; S, 15.93.

12. Compound **8**: m.p. 267-268 °C. IR: 2927, 2867, 1631, 1442, 843 cm^{-1}. ^{1}H NMR: δ 4.05-4.15 (1H$_{eq}$, b, w/2=8 Hz), 3.45-3.52 (1H$_{ax}$, m, w/2=25 Hz), 1.85-0.80 (80H, b), 0.78 (6H, s), 0.64 (6H, s) ^{13}C NMR: δ 189.2, 56.4(4), 56.4(1), 56.2, 54.2, 54.1, 47.1, 44.5, 44.0, 42.5, 42.3, 39.9, 39.5, 38.8, 36.1, 36.0, 35.7, 35.5, 35.4, 34.4, 34.1, 31.9, 31.8, 28.9, 28.5, 28.4, 28.2, 28.00, 27.6, 24.1, 23.8, 22.8, 22.5, 20.9, 20.7, 18.6, 12.2, 12.0, 11.8. Anal. Calcd. for $C_{55}H_{94}S_2O$; C, 79.14; H, 11.27; S, 7.64. Found: C, 78.91; H,11.31; S, 7.61.

13. Barton, D. H. R.; Houminer, Y. *J. Chem. Soc. Perkin Trans 1.* **1972**, 919 and references there cited.

14. a) Characterized by m.p., [α], ^{1}H NMR spectroscopy (w/2). b) Bourdon, R. *Bull. Soc. Chim. France*, **1962**, 844. Bobbio, P. A.; Bobbio, F. O. *Ber*, **1962**, *95*, 2747.

15. Barton, D. H. R.; Cussans, N. J.; Ley, S. V. *J. Chem. Soc. Chem. Comm.* **1978**, 393; *J. Chem. Soc. Perkin Trans 1.* **1980**, 1650.

16. Authentic **7**: m.p. 101-102 °C. IR: 2920, 2854, 2840, 1633, 1438, 1016, 849 cm^{-1}. ^{1}H NMR: δ 3.59-3.50 (1H, m, w/2= 25.2 Hz), 2.39 (3H, s), 1.99-0.82 (b, 40H) 0.79 (3H, s), 0.64 (3H, s). ^{13}C NMR: δ 189.7, 56.4, 56.2, 54.2, 47.0, 44.6, 42.5, 39.9, 39.5, 38.8, 36.1, 35.7, 35.4, 31.9, 28.85, 28.55, 28.23, 28.01, 24.1, 23.8, 22.8, 22.5, 20.9,18.6, 12.9, 12.1, 12.0. Anal. Calcd. for $C_{29}H_{50}OS_2$: C, 72.74; H, 10.52; S, 13.39. Found: C, 72.92; H, 10.40; S, 13.11.

17. Contreras, R.; Mendoza, L. *Steroids* **1979**, *34(2)*, 121.

(*Received in USA* 11 *January* 1996; *accepted* 21 *February* 1996)