A USEFUL METHOD FOR CONVERTING 2° ALCOHOLS TO THEIR CHLORIDES WITH RETENTION OF CONFIGURATION

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Summary

Xanthate esters of 2° alcohols are converted to their chlorides with retention of configuration in good yield by use of sulfuryl chloride.

During efforts directed toward the total synthesis of the marine natural product, the cis-fused pyranopyran dactomelyne,¹ the need arose to develop a means for converting a hindered axial alcohol to its chloride (e.g., 1 to 2) with retention of configuration. Since all of the standard methods (e.g., SOCl₂, ROCOCl, etc. including double inversion processes involving alcohol inversion, then tosylate formation and attempted displacement with LiCl) failed to provide the desired product, less conventional processes were pursued.



3E-Dactomelyne

Using menthol as the model substrate, a compound which also provides a somewhat hindered alcohol group as evidenced by its failure to react with DEAD, Ph_3P and LiCl,² we first transformed it to its xanthate ester. It was our intention to attempt to convert this xanthate ester to the chloride by a radical-based reaction process akin to some of the procedures elegantly developed by Barton *et al.*³ When this xanthate was exposed to hexabutyldistannane⁴ and AIBN in CCl₄ at 110 °C for 10 h, only starting material was recovered. The result was the same if NCS was substituted for the distannane.

However, when this same chloride was exposed to sulfuryl chloride in chloroform as solvent, menthyl chloride was obtained in 82% yield (see Table 1 for precise reaction conditions). Only formation of the chloride of retained stereochemistry was evident from ¹H NMR. Additionally, isomenthol was converted by the same two step process to isomenthyl chloride. Again, none of the inverted chloride was apparent in the reaction mixture.

O-Cholesteryl S-methyldithiocarbonate could be converted to its β -chloride in 62% yield when reacted with sulfuryl chloride. This xanthate derived chloride was identical to that obtained by reacting cholesterol with thionyl chloride in dioxane at 100 °C. If the xanthate/SO₂Cl₂ reaction was conducted in the presence of an oxygen sweep, the chloride was still obtained but in slightly higher yield. Since products resulting from the oxygen acting as a radical scavenger were not detected, we may conclude that the reaction process probably does not involve passage through a radical intermediate.

The chloride forming reaction was also tested on 2-adamantanol, a system for which backside nucleophilic displacement is made difficult due to the presence of the "locked" axial hydrogens. Again, the reaction proceeded well and delivered the chloride in 89% isolated yield.

As shown in the accompanying table, the xanthate ester of cyclododecanol was converted to the chloride in 77% yield. 1,2:5,6-Di-O-isopropylidene-3-O-[(methylthio)thiocarbonyl]- α -D-glucofuranose⁵ was similarly converted to its chloride in 57% yield. A small amount of the xanthate ester rearrangement product, the dithiol carbonate, was also produced in this case.⁶

Lastly, the hindered axial alcohol present within the dactomelyne related pyran 1 could be transformed cleanly to its chloride in 91% yield by way of the xanthate ester.

A search of the chemical literature revealed that Barany had previously found that the xanthate ester of (R)-2-octanol could be converted to a mixture of (S)-2chlorooctane and (R)-2-chlorooctane (ratio = 66:34) by reaction with methoxycarbonylsulfenyl chloride.⁷ The transition state for this reaction was suggested to have some S_N2 character. Additionally, Barany has shown that reaction of O,S-dimethyl dithiocarbonate with sulfuryl chloride most likely provides an alkoxydichloromethyl-disulfanyl intermediate via intramolecular rearrangement.⁸ No effort was made, however, to look at the stereochemistry of chloride formation in this case since the sulfur compounds were the products of primary interest.

In light of Barany's mechanistic studies, one can suggest that the intermediate disulfanyl intermediate must break down under our reaction conditions via an ion pair mechanism to provide the product corresponding to that arising from a front-side $S_{\rm Ni}$ attack mode. The reaction is thus analogous to the thermal decomposition of alkyl chloroformates⁹.



In conclusion, we believe the present findings offer a useful means for achieving the conversion of an alcohol to its retained chloride. The methodology is especially useful in sterically encumbered situations where thionyl chloride fails to effect the desired conversion.¹⁰

References

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- 10. Satisfactory spectral and analytical data were obtained for all new compounds reported herein.

Entry	Alcohol	Xanthate ester (NaH; CS ₂ ; MeI), % yield	Chloride, % yield; reaction conditions.			
1	, он	92%	82%; SO ₂ Cl ₂ (1 equiv), CHCl ₃ , 0 °C (3h), then rt (7h)			
			72%; PhSeCl, CHCl ₃ 115 °C (12h)			
2	C OH	91%	76%; SO ₂ Cl ₂ (1 equiv) CHCl ₃ , 0 °C (1h), rt (7h)			
3 но		92%	62%; SO ₂ Cl ₂ (2 equiv) CCl ₄ , 0 °C (3h), rt (7h)			
4	OH OH	87%	89%; SO ₂ Cl ₂ (1 equiv) CHCl ₃ , 0 °C (2h), rt (6h)			
5	\bigcirc	87%	77%; SO ₂ Cl ₂ (1 equiv) CHCl ₃ , 0 °C (2h), rt (6h)			
6		92%	57%; SO ₂ Cl ₂ (1.1 equiv) CH ₃ CN, 0 °C (1h), rt (7h)			
⁷ \int_{0}^{0}		Br 88%	91%; SO2Cl2 (1 equiv) CHCl3, 0 ℃ (2h), rt (8h)			

Table I.	Conversion of 2°	Alcohols to	Their	Chlorides	With	Retention	of	
Configuration.								

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