Tetrahedron Letters,Vol.29,No.43,pp 5467-5470,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

A FACILE METHOD FOR THE SYNTHESIS OF β-CHLOROALKYL SULFIDES USING DIMETHYL SULFOXIDE ACTIVATED BY PHENYL DICHLOROPHOSPHATE OR PHOSPHORUS OXYCHLORIDE

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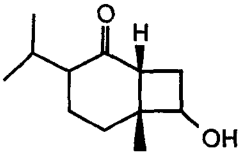
Abstract: A simple procedure has been developed for the transformation of alkenes to β-chloroalkyl sulfides using dimethyl sulfoxide activated with phenyl dichlorophosphate or phosphorus oxychloride.

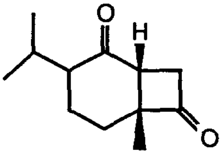
β-Chloroalkyl sulfides are useful synthetic intermediates and certain compounds of this family have been shown to possess antifungal and antibacterial properties.[1] Conventionally, β-chloroalkyl sulfides are prepared by the addition of sulfenyl chlorides to carbon-carbon double bonds.[1] This process proved to be highly convenient. However, the overall efficiency often suffers from the formation of regioisomeric products. We wish to describe a new and equally facile method which gives rise to β-chloroalkyl sulfides with a high degree of regioselectivity.

During the course of our synthetic studies on dendrobine, the oxidation of the keto alcohol 1 with oxalyl chloride, dimethyl sulfoxide and triethylamine was attempted. Interestingly, instead of the expected diketone **2**, the chlorodiketone **3** was obtained as the major product.[2] This result suggested that the combination of dimethyl sulfoxide and oxalyl chloride also served as a chlorinating agent presumably via the intermediacy of complex **4**.[2,3] On the basis of this observation, it is conceivable that treatment of an olefin with oxalyl chloride and dimethyl sulfoxide in the presence of a base could lead to the formation of the corresponding α-chloroketone via the pathway outlined in Scheme 1. In practice, neither 1-octadecene nor cyclohexene gave the expected product under various reaction conditions. In further studies, the combination of dimethyl sulfoxide and phenyl dichlorophosphate, which has also been shown to be an efficient dimethyl sulfoxide activator,[4] was used. Under these conditions, a single compound was produced from 1-octadecene. Unexpectedly, this compound was characterized as the β-chloroalkyl sulfide **5**. On the basis of this finding, a new method for the formation of β-chloroalkyl sulfides has been developed.

In a typical experiment, to a solution of dimethyl sulfoxide (0.7 mL, 10 mmol) in methylene chloride (10 mL) at -20°C under an argon atmosphere,



1



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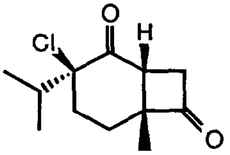
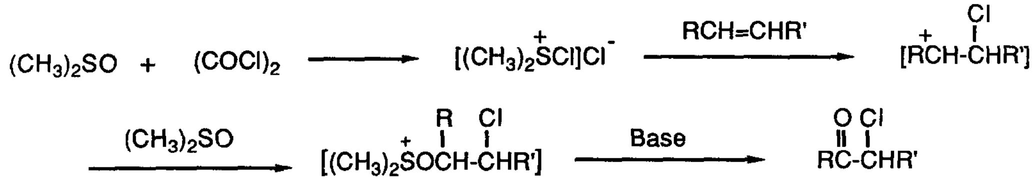


3

$[(CH_3)_2\overset{+}{S}Cl]Cl^-$

4

Scheme 1



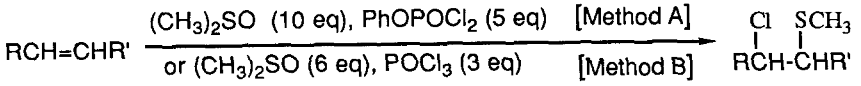
$$(CH_3)_2SO + (COCl)_2 \longrightarrow [(CH_3)_2\overset{+}{S}Cl]Cl^- \xrightarrow{RCH{=}CHR'} [R\overset{+}{C}H\text{-}\overset{Cl}{C}HR']$$

$$\xrightarrow{(CH_3)_2SO} [(CH_3)_2\overset{+}{S}O\overset{R}{C}H\text{-}\overset{Cl}{C}HR'] \xrightarrow{Base} R\overset{O}{\overset{\|}{C}}\text{-}\overset{Cl}{C}HR'$$

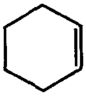
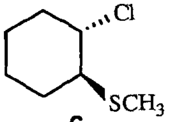
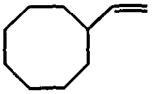
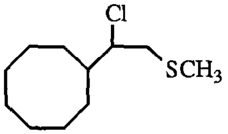
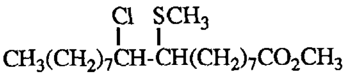
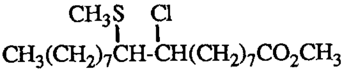
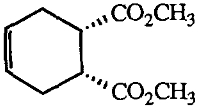
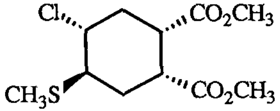
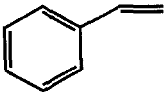
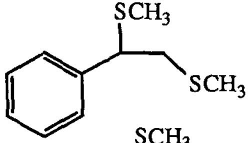
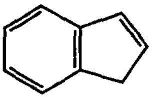
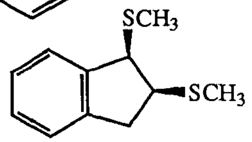
was added phenyl dichlorophosphate (0.75 mL, 5 mmol). After 5 min, 1-octadecene (0.35 mL, 1 mmol) was introduced. The mixture was stirred at -20°C for 5 min and then allowed to warm up slowly to room temperature. After 1 h, water was added, the organic layer separated and the aqueous layer extracted with methylene chloride. The combined organic solutions were washed with saturated sodium chloride solution, dried with magnesium sulfate and filtered. Concentration followed by flash chromatography of the residue on silica gel, eluting with ethyl acetate-petroleum ether (1:4), gave the β-chloroalkyl sulfide 5 (264 mg, 79% yield).

Table 1 summarizes the results obtained for a number of olefins studied. It is noted that, with unsymmetrically substituted double bonds (Entries 1, 3 and 4), the addition proceeded in a completely regioselective manner with the methylthio group being added to the carbon bearing the greater number of hydrogen atoms. This is in contrast to the application of sulfenyl chloride addition in both the orientation and the degree of selectivity.[1] The stereoselectivity on the other hand was found to be the same as that observed for sulfenyl chlorides with exclusive trans-addition.[1] Thus, the reaction of cyclohexene (Entry 2) gave adduct **6** as the sole product. The method was also found to be applicable to compounds containing other functionalities such as the ester group (Entries 5 and 6) and aromatic double bonds (Entries 7 and 8). Two abnormal cases were observed. In each case, the starting material possesses a double bond in conjugation with a benzene ring (Entries 7 and 8). Each substrate led to the formation of a disulfide as the only detectable product in high yield, presumably as a result of the replacement of the benzylic chloride in the expected product by a methylthio group.[5]

Table 1: Conversion of olefins to β-chloroalkyl sulfides



$$\mathrm{RCH{=}CHR'} \xrightarrow[\text{or } (CH_3)_2SO\ (6\ eq),\ POCl_3\ (3\ eq)\quad [\text{Method B}]]{(CH_3)_2SO\ (10\ eq),\ PhOPOCl_2\ (5\ eq)\quad [\text{Method A}]} \mathrm{R\overset{Cl}{C}H\text{-}\overset{SCH_3}{C}HR'}$$

Entry	Substrate	Time (min)[a]	Product	% Yield[b] (Method)	
1	$CH_3(CH_2)_{15}CH{=}CH_2$	70	$CH_3(CH_2)_{15}CH(Cl)CH_2SCH_3$ **5**	79(A)	76(B)
2		60	 **6**	80(A)	52(B)
3	$CH_3(CH_2)_{11}CH{=}CH_2$	70	$CH_3(CH_2)_{11}CH(Cl)CH_2SCH_3$	81(A)	78(B)
4		45		83(A)	81(B)
5	$CH_3(CH_2)_7CH{=}CH(CH_2)_7CO_2CH_3$	75	 $CH_3(CH_2)_7\overset{Cl}{C}H\text{-}\overset{SCH_3}{C}H(CH_2)_7CO_2CH_3$ + (~ 1:1)  $CH_3(CH_2)_7\overset{CH_3S}{C}H\text{-}\overset{Cl}{C}H(CH_2)_7CO_2CH_3$	81(A)	79(B)
6		70		80(A)	82(B)
7		60		83(A)	81(B)
8		60		82(A)	81(B)

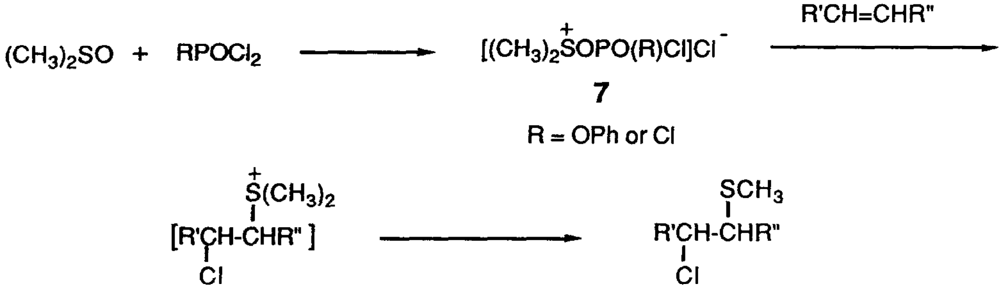
[a] All reactions were carried out at -20 → 20°C using methylene chloride as a solvent.

[b] All yields given are for isolated products.

The use of phosphorus oxychloride and dimethyl sulfoxide was also explored and found to be equally effective. Similar results were obtained with the exception of cyclohexene (Entry 2). The yield of product **6** was substantially lower when phosphorus oxychloride was employed. Two other phosphorus-containing reagents were also examined. Both diethyl chlorophosphate and diphenyl chlorophosphate proved ineffective.

As outlined in Scheme 2, the formation of β-chloroalkyl sulfides can be rationalized by invoking the initial formation of complex **7**, arising from dimethyl sulfoxide and the phosphorus reagents, which serves as the electrophile.

Scheme 2



Acknowledgement: We are grateful to the Natural Sciences and Engineering Research Council of Canada and the University of Alberta for financial support. J.M.N. wishes to thank the National Council for Scientific Research, Zambia for granting the study leave.

References and Notes

1. For leading references, see: (a) Kharasch, N.; Ariyan, Z.S.; Havlik, A.J. Quart. Rept. Sulfur Chem. **1966**, 1, 93. (b) Kühle, E. Synthesis, **1971**, 563. (c) Rasteikiene, L.; Greiciute, D.; Lin'kova, M.G.; Knunyants, I.L. Russian Chem. Rev. **1977**, 46, 548.
2. Smith, A.B., III; Leenay, T.L.; Liu, H.J.; Nelson, L.A.K.; Ball, R.G. Tetrahedron Lett. **1988**, 29, 49.
3. Omura, K.; Swern, D. Tetrahedron, **1978**, 34, 1651.
4. Liu, H.J.; Nyangulu, J.M. Tetrahedron Lett. in press.
5. Dimethyl sulfide could serve as a source of the required methylthio moiety. The former could be derived from the disproportionation of complex **4** which in turn could be produced from the initial complex **7**.

(Received in USA 22 June 1988)