Tetrahedron Letters No. 42, pp 4339 - 4342, 1972. Pergamon Press. Printed in Great Britain.

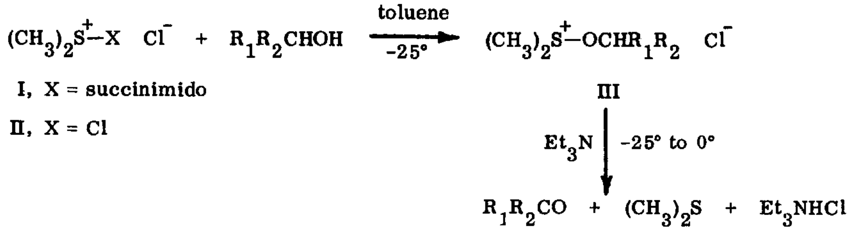
A METHOD FOR SELECTIVE CONVERSION OF ALLYLIC AND BENZYLIC ALCOHOLS TO HALIDES UNDER NEUTRAL CONDITIONS

E. J. Corey, C. U. Kim, and Makoto Takeda
Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138, USA

(Received in USA 25 August 1972; received in UK for publication 19 September 1972)

Reagents which are sufficiently selective to distinguish between functional groups of the same class are exceedingly valuable in syntheses involving multifunctional molecules, since they permit operations which are either impossible or dependent upon the use of protecting groups. For example, active manganese dioxide (1) has found many applications because of its selective oxidizing action on allylic or benzylic hydroxyl groups in the presence of other types of hydroxyl groups and other oxidizable functional groups as well. We describe here a reagent for the replacement of hydroxyl by halogen under neutral conditions which shares with manganese dioxide the characteristic of being selective for allylic or benzylic alcohols and also extremely mild.

We have recently described a method for the oxidation of primary and secondary alcohols to aldehydes and ketones, respectively, which involves the use of the complex I or II formed from *N*-chlorosuccinimide (2) or Cl_2 (3, 4) and methyl sulfide. Reaction of I or II with the alcohol in toluene at -25° for *ca.* 2 hr.



$$\begin{tikzcd} (CH_3)_2\overset{+}{S}{-}X\ \ Cl^- \ + \ R_1R_2CHOH \arrow[r, "\text{toluene}", "-25^\circ"'] & (CH_3)_2\overset{+}{S}{-}OCHR_1R_2\ \ Cl^- \arrow[d, "Et_3N"', "-25^\circ \text{ to } 0^\circ"] \\ & R_1R_2CO \ + \ (CH_3)_2S \ + \ Et_3NHCl \end{tikzcd}$$

I, X = succinimido
II, X = Cl
III

affords the sulfoxonium derivative III (4) which upon treatment with triethylamine for *ca.* 5 min. undergoes carbonyl-forming elimination to form the aldehyde or ketone and methyl sulfide (5). In this way, for instance, 4-*t*-butylcyclohexanol was converted into 4-*t*-butylcyclohexanone in 97% yield (5). We have also observed that in the case of alcohols which correspond to stabilized cations, e.g., benzhydrol, the oxidation process becomes only a minor pathway, since the sulfoxonium intermediate is relatively unstable and tends to form the corresponding chloride. If in such cases the formation and decomposition of the sulfoxonium intermediate are allowed to proceed in methylene chloride without addition of tertiary amine, chlorides are formed cleanly. Thus, formation of the complex I from equivalent amounts of methyl sulfide

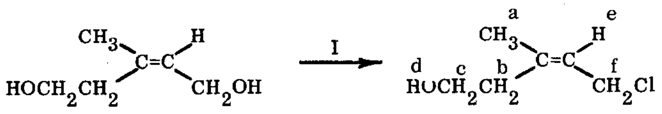
$$\underset{\text{III}}{(CH_3)_2\overset{+}{S}{-}OCHR_1R_2\ \ Cl^-} \longrightarrow R_1R_2CHCl + (CH_3)_2SO$$

and N-chlorosuccinimide in methylene chloride, cooling to -25°, and addition of an equivalent of benzhydrol produces after 4 hr. at -25° benzhydryl chloride in >95% yield. Under the same conditions 2-cyclohexen-1-ol converted to 3-chlorocyclohexene in >95% yield and benzyl alcohol is transformed cleanly into benzyl chloride.

Use of the 1 : 1 complex between methyl sulfide and N-bromosuccinimide instead of I as the reagent in a similar way converts benzyl alcohol, benzhydrol, and 2-cyclohexen-1-ol to the corresponding bromides in 80-90% yield.

Under the same conditions saturated primary and secondary aliphatic and cycloaliphatic alcohols are recovered essentially unchanged, suggesting a high selectivity between different types of alcohols. This selectivity was directly and dramatically demonstrated. Reaction of one equivalent each of cyclohexanol, 2-cyclohexen-1-ol and the chloro reagent I in methylene chloride with stirring at -10° for 1.5 hr. and +5° for 1 hr. produced 3-chlorocyclohexene (95% yield, uncontaminated by cyclohexyl chloride) (6) and cyclohexanol (99% recovery, uncontaminated by 2-cyclohexen-1-ol) (6).

In an equally impressive experiment Z-3-methyl-2-penten-1,5-diol (IV) (7) upon reaction with complex I with stirring in methylene chloride briefly at -20° and then at 0° for 1 hr. was transformed cleanly into the allylic monochloride V which was isolated in 87% yield. To our knowledge selective conversions such as IV → V have not previously been achieved under mild, neutral conditions. The propensity of IV and V to undergo cyclization to a dihydropyran, a possibly critical complication, poses no difficulties for the method outlined here. The simplicity of the experimental operation is indicated by the following procedure.



IV V

Z-5-Chloro-3-methyl-2-penten-1-ol (V): To a solution containing 294 mg. (2.2 mmol.) of N-chlorosuccinimide in 10 ml. of anhydrous methylene chloride (mag. stirring, nitrogen atm.) was added dropwise at 0° 0.176 ml. (2.4 mmol.) of methyl sulfide. The reaction mixture was cooled to -20°, and 232 mg. (2.0 mmol.) of Z-3-methyl-2-pentene-1, 5-diol (IV) in 1 ml. of methylene chloride was added gradually over a few min. The resulting solution was warmed to 0°, stirred for 1 hr. and poured into 10 ml. of ice-cold brine. After shaking and separating the mixture, the aqueous phase was extracted with two 4-ml. portions of ether. The combined organic phase was washed with two 4-ml. portions of cold brine and dried ($MgSO_4$). Filtration and evaporation of solvents gave 234 mg. (87%) of monochloride V as a colorless oil: t.l.c., $\underline{R}_f$ 0.59 (9:1 $CHCl_3$--CH_3OH); i.r. (neat) 2.98 (OH), 3.36, 6.90, 9.58 μ; n.m.r. ($CDCl_3$) (p.p.m.) 1.82 (s., 3 H, H^a), 2.40 (t., 2 H, J_{bc} = 6.3 Hz, H^b), 3.54 (s., 1 H, H^d), 3.70 (t., 2 H, J_{bc} = 6.3 Hz, H^c), 4.14 (d., 2 H, J_{ef} = 8.0 Hz, H^f), 5.58 (t., 1 H, J_{ef} = 8.0 Hz, H^e); mass spectrum of trimethylsilyl ether (8), M^+ at 206.0890 (calcd. 206.0894), M^+-Cl at 171 *m/e*.

The use of the reagent derived from *N*-bromosuccinimide may be illustrated by a procedure for the conversion of geraniol to geranyl bromide.

Geranyl Bromide: To a solution containing 540 mg. (3.0 mmol.) of *N*-bromosuccinimide in 10 ml. of anhydrous methylene chloride (mag. stirring, nitrogen atm.) was added dropwise at 0° over a period of 3 min. 0.264 ml. (3.6 mmol.) of methyl sulfide. The mixture was cooled to -20°, and 309 mg. (2.0 mmol.) of geraniol in 1 ml. of methylene chloride was added dropwise over a few min. Then the reaction mixture was warmed to 0° and stirred for 3.0 hr, diluted with pentane, and poured into 15 ml. of ice water. The organic phase was washed with cold brine, filtered through 500 mg. of silica gel, and concentrated to give 354 mg. (82%) of spectrally pure geranyl bromide.

Although the reaction of the chloro reagent I with alcohols such as cyclohexylmethanol, 2-phenylethanol and cyclohexanol is too slow to be of much value in the preparation of the corresponding chlorides (for example, only 43% reaction of I with cyclohexylmethanol at +5° after 100 hr.), it is possible that the use of reagents derived from other sulfides or other conditions may extend the scope of the halogenation principle which is disclosed here. In addition, it should be noted that the reagent from methyl sulfide and *N*-bromosuccinimide is somewhat more effective in halogenation of non-allylic or non-benzylic alcohols than is I. For example, cyclohexylmethanol and 2-phenylethanol are converted to the corresponding bromides with the former reagent in *ca.* 70% yield after 36 hr. at 20° (9).

References

1. For a review, see S. P. Korshunov and L. I. Vereshchagin, *Russ. Chem. Rev.*, **35**, 942 (1966).
2. E. Vilsmaier and W. Sprügel, *Tetrahedron Lett.*, 625 (1972).
3. E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Chemical Publishing Co., New York, N. Y., Vol. II, p. 48.
4. H. Meerwein, K.-F. Zenner, and R. Gipp, *Ann. Chem.*, **688**, 67 (1965).

5. E. J. Corey and C. U. Kim, J. Amer. Chem. Soc., in press.
6. As determined by vapor phase chromatographic analysis.
7. The diol IV was prepared by reduction using AlH_3--ether of diethyl Z-3-methyl-2-pentene-dioate which was in turn obtained by fractional distillation of the commercially available mixture of E and Z isomers; see E. J. Corey and E. Hamanaka, J. Amer. Chem. Soc., **89**, 2758 (1967), and E. Hamanaka, Ph.D. dissertation, Harvard University, 1967.
8. Prepared in 91% yield by the method of A. R. Wellburn and F. W. Hemming, J. Chromatog., **23**, 51 (1966).
9. This work was supported in part by grants from the National Science Foundation and the National Institutes of Health. We are grateful to Dr. Ronald Ruden for helpful discussion.