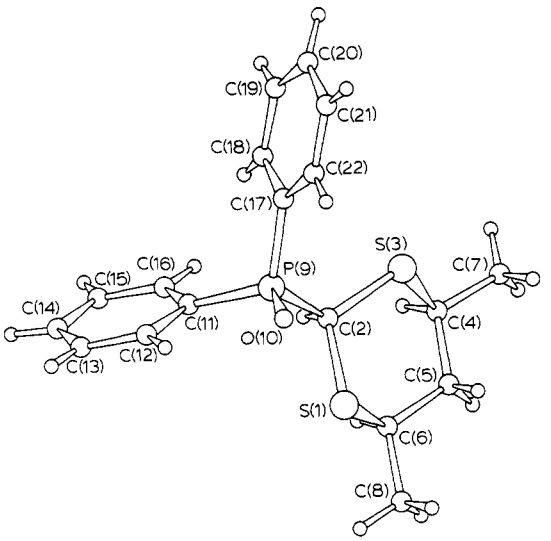

Figure 1. Structure and solid-state conformation of 2; small circles denote hydrogen atoms.

$R = 0.048$[13] over 2128 reflections. A view of the solid-state conformation is in Figure 1. The 1,3-dithiane ring has a chair conformation[14] with an equatorially oriented substituent at C(2), and the diphenylphosphinoyl oxygen atom is gauche to both sulfur atoms but is asymmetrically disposed[15] with respect to them in order to accomodate nonbonded interactions between the bulky substituent and the ring atoms. The heterocyclic ring in 2 is slightly more puckered around C(2) than in 3[10] and significantly more puckered than in 1-axial where relief must be gained from severe 1,3-diaxial nonbonded interactions between the phosphinoyl substituent and the ring hydrogen atoms at C(4) and C(6).

Selected bond lengths and angles for 2 together with corresponding values for 1-axial and 3 are in Table I. Comparison of these values reveals that although the mean S(1)–C(6) distance in 2 is slightly longer than that in 1-axial, it is very close to that in 3, and accordingly, the elongation may be ascribed to the introduction of the methyl substituents into the 1,3-dithiane ring.[10] The C–P distance in 2 is quite similar to, but possible significantly longer than, that in 1-axial. This latter observation, as well as the lack of any significant difference in the mean S(1)–C(2) lengths, is contrary to expectations if an $n_S \rightarrow \sigma^*_{C-P}$ interaction makes an important contribution to the preferred axial conformation in 1. Alternative rationalizations of the effect(s) responsible for the conformational behavior of 1 will be discussed in a forthcoming paper.[16]

Experimental Section

***r*-2-(Diphenylphosphinoyl)-*c*-4,*c*-6-dimethyl-1,3-dithiane (2).** *cis*-4,6-Dimethyl-1,3-dithiane (3)[17] (297 mg, 2 mmol) was placed in a dry round-bottomed flask provided with a magnetic stirring bar and capped with a rubber septum. The flask was flushed with nitrogen prior to the addition of 7 mL of dry THF via a cannula, after which the solution was cooled to −22 °C and *n*-butyllithium (1.53 mL of a 1.37 M hexane solution, 2.1 mmol, 5% excess) was syringed into it dropwise. The resulting solution was stirred for 90 min at −20 °C following which it was added to a THF solution (ca. 10 mL) of chlorodiphenylphosphine (530 mg, 2.4 mmol, 20% excess) and tetramethylethylenediamine (232 mg, 2 mmol) also at −20 °C. The reaction mixture was stirred at this temperature for 90 min and subsequently at room temperature for a further 3 h before being quenched with saturated aqueous ammonium chloride. Extraction with $CHCl_3$ followed by the usual workup procedure afforded 146 mg (21% yield) of 2 as a white solid: mp 233–235 °C; ^{1}H NMR (90 MHz, $CDCl_3$; Me_4Si) δ 1.23 (d, $^3J_{CH_3-C-H} = 6.6$ Hz, 6 H), 1.3 (d of t, $J_{gem} = 14.1$ Hz, $J_{anti} = 12$ Hz, 1 H), 2.06 (d of t, $J_{gem} = 14.1$ Hz, $J_{gauche} = 2.5$ Hz, 1 H), 2.9 (m, 2 H), 4.98 (d, $^2J_{P-C-H} = 15$ Hz, 1 H), 7.3–8.15 (m, 10 H); IR 3090 (w), 2882 (s), 1439 (s), 1194 (vs) cm^{-1}; MS, *m/e* 348 (M^+), 315 ($M^+ - 33$), 201 ($M^+ - 147$), 147 ($M^+ - 201$), 77 ($M^+ - 271$).

Crystal Data: $C_{18}H_{21}OPS_2$ (2) M_r 348.47; monoclinic; $a = 38.886$ (16) Å, $b = 5.773$ (2) Å, $c = 16.651$ (7) Å, $\beta = 104.60$ (1)°, $U = 3617.3$ Å^3, $Z = 8$, $d_{calcd} = 1.280$ g cm^{-3}; absorption coefficient for Cu Kα radiation ($\lambda = 1.5418$ Å), $\mu = 33.8$ cm^{-1}. Space group $Cc(C_s^4)$ or $C2/c(C_{2h}^6)$ from systematic absences: *hkl* when $h + k \neq 2n$, *h0l* when $l \neq 2n$; shown to be the latter by structure solution and refinement.

Intensity data ($hk\pm l$), recorded on an Enraf-Nonius CAD-3 automated diffractometer from a crystal of dimensions ca. 0.16 × 0.18 × 0.80 mm as described previously[10] (Ni-filtered Cu Kα radiation; θ–2θ scans, $\theta_{max} = 67°$), yielded 3239 independent values from which those 2128 with $I > 2.0\sigma(I)$ were retained for the structure analysis.

Structure Analysis and Refinement. The crystal structure of 2 was solved by direct methods.[11] Full-matrix least-squares adjustment of atomic positional and thermal parameters converged to $R = 0.048$.[13] For structure-factor calculations, scattering factors for carbon, oxygen, phosphorus, and sulfur were from ref 18, and for hydrogen from ref 19; the values for phosphorus and sulfur were corrected for anomalous dispersion effects.[20] In the least-squares iterations, the weighting scheme used: $w^{1/2} = 1$ for $|F_o| \leq 60.0$, and $w^{1/2} = 60.0/|F_o|$ for $|F_o| > 60.0$, showed no systematic dependence of $\langle w\Delta^2 \rangle$ when analyzed in ranges of $|F_o|$ and sin θ. Final atomic positional and thermal parameters are in Tables II–IV in supplementary material.[12]

Registry No. 1, 83476-36-2; 2, 83463-92-7; 3, 22452-23-9.

Supplementary Material Available: Fractional atomic coordinates (Tables II and IV), anisotropic thermal parameters (Table III), bond lengths and angles (Table V), torsion angles (Table VI), displacements of atoms from selected least-squares planes (Table VII), and a list of observed and calculated structure amplitudes (Table VIII) (22 pages). Ordering information is given on any current masthead page.

(11) Main, P.; Lessinger, L.; Woolfson, M. M.; Germain, G.; Declerq, J.-P. "MULTAN76, A System of Computer Programmes for the Automatic Solution of Crystal Structures"; Universities of York and Louvain, 1976.
(12) Supplementary material; see paragraph at end of paper.
(13) $R = \sum||F_o| - |F_c||/\sum|F_o|$.
(14) Endocyclic torsion angles, ω_{ij} (°), around the bonds between atoms *i* and *j* in 2 follow: $\omega_{1,2} = -64.9°$, $\omega_{2,3} = 64.1°$, $\omega_{3,4} = -59.2°$, $\omega_{4,5} = 65.2°$, $\omega_{5,6} = -65.4°$, $\omega_{6,1} = 59.5°$; corresponding values are −61.8°, 61.8°, −56.8°, 63.8°, −64.2°, 57.3° in 3, and −55.4°, 54.3°, −55.8°, 66.4°, −67.3°, 58.6° in 1-axial.
(15) S–C–P–O torsion angles are 32.9° and −91.5° in 2.
(16) Juaristi, E.; Valle, L.; Valenzuela, B. A., unpublished results.
(17) Prepared according to Eliel, E. L.; Hartmann, A. A.; Abatjoglou, A. G. *J. Am. Chem. Soc.* **1974**, *96*, 1807–1816.
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(19) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175–3187.
(20) "International Tables for X-Ray Crystallography", Kynoch Press: Birmingham, England, 1968; Vol. III, p 214.

Reaction of Alcohols with Zinc Halide, Diethyl Azodicarboxylate, and Triphenylphosphine. An Effective Method for the Preparation of Halides

Pak-Tsun Ho* and Nancy Davies

Guelph-Waterloo Center for Graduate Work in Chemistry, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1

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Alkyl halides are important intermediates in organic synthesis. The conversion of alcohols into their corresponding halides is frequently a useful and necessary synthetic operation. During recent research in the syn-

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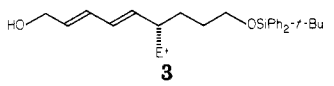
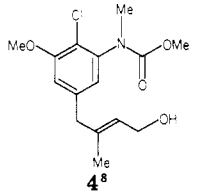
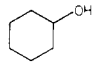
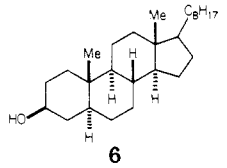
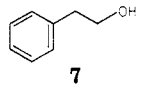
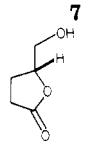
Table I. Conversion of Alcohols into Halides

entry	substrate	product[a] (halide)	isolated yield, %	reactn time
1	 **3**	**9** (chloride)	90	20 min
2	 **4**[8]	**10** (chloride) **11** (bromide)	66 72	20 min 20 min
3	 **5**	**12** (chloride)	90	2 h
4	 **6**	**13** 3α-cholestanyl, chloride	92	2 h
5	 **7**	**14** (chloride)	80	$^1/_2$ h
6	 **8**[9]	**15** (chloride) **16** (bromide) **17** (iodide)	85 76 72	$^1/_2$ h $^1/_2$ h $^1/_2$ h

[a] Satisfactory spectral data and analyses were obtained for all new compounds.

thesis of antibiotics, our synthetic strategy required the preparation of a sensitive dienyl chloride from the corresponding alcohol.

Conversion of alcohols into halides can be accomplished in several ways. Reaction of an alcohol with phosphorus tribromide to give the bromide is one of the classical methods.[1] A two-step procedure involved the transformation of an alcohol to the tosylate followed by an S_N2 halide ion displacement has been a standard method for the preparation of primary iodide. Some newer methods have also appeared such as the use of triphenylphosphine–carbon tetrahalide complex,[2] the reagent of triphenylphosphine and *N*-halo imide,[3] and the combination of trimethylsilyl chloride and sodium iodide.[4] The conversion of 3β-cholestanol into 3α-iodocholestane using O. Mitsunobu's reagent, diethyl azodicarboxylate, and triphenylphosphine in the presence of methyl iodide as a source of nucleophile has recently been reported by E. Zbiral and H. Loibner.[5] However, no application of this procedure to various alcohols has been given. Unfortunately, we found that all of these available methods gave either poor yields or undesired products on our compounds.

In searching for an efficient method for the preparation of the rather sensitive halide, we found a mild and effective procedure for converting alcohols to the corresponding halides. When an alcohol was treated with diethyl azodicarboxylate and triphenylphosphine in tetrahydrofuran in the presence of anhydrous zinc chloride, the pure chloride was isolated in good yield.

It is generally assumed that the reaction of alcohol with diethyl azodicarboxylate and triphenylphosphine gives the ionic species **1**.[6] The use of zinc halide for this reaction was hypothesized on the idea that a considerable covalent bond character between zinc metal and oxygen atom will lead to the formation of the reactive alkoxyphosphonium halide **2** (Scheme I). Subsequently, an S_N2-type displacement of the resulting alkoxyphosphonium species by halide anion completes the reaction. The exact mechanism for this reaction is not clear. However, it is true that the reaction gave either no detectable amount of halides or poor yields, if the reaction was carried out under the same conditions using other inorganic halides with poorer covalent character of metal–oxygen bond such as sodium iodide, lithium bromide, and magnesium chloride. Therefore, the use of zinc halide in this one-step process is essential. Crystalline 3α-cholestanyl chloride (**13**) was obtained in 92% yield, when 3β-cholestanol (**6**) was treated with triphenylphosphine, diethyl azodicarboxylate, and zinc chloride in tetrahydrofuran. The reaction which proceeds with clean inversion of configuration agrees with the S_N2 reaction mechanism. Our results agree with the recent tosylation of alcohols with inversion using zinc tosylate and diethyl azodicarboxylate–triphenylphosphine complex.[7]

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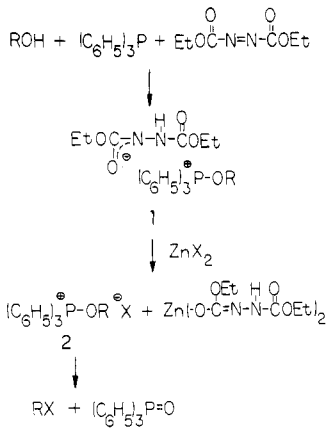
(5) Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, *59*, 2100.
(6) Mitsunobu, O. Synthesis, **1981**, 1.
(7) Galynker, I.; Still, W. C. *Tetrahedron Lett.* **1982**, *23*, 4461.

Scheme I



Primary, secondary, and allylic alcohols under the same conditions have been converted in good yields into the corresponding halides. The reaction is generally complete in minutes at room temperature. The generality of this effective procedure for the preparation of halides is apparent from the results compiled in Table I. We emphasize that the reaction conditions employed are sufficiently mild for acid- and base-sensitive molecules. Thus, sensitive unsaturated alcohols such as **3** and **4** (entries 1 and 2) are stable under these conditions and were converted in good yields into the allylic halides **9** and **10**, respectively. The preparation of β-phenylethyl chloride (**14**) from its alcohol (entry 5) with no detectable elimination illustrates further the mildness of the reaction conditions. The method works equally well with zinc bromide and iodide. Bromides or iodides were obtained in comparable yields, when zinc bromide or zinc iodide was used instead of zinc chloride under similar reaction conditions.

In summary, the present investigation has demonstrated that the use of diethyl azodicarboxylate, triphenylphosphine, and zinc halide constitutes a useful and convenient method for the halogenation of a wide variety of alcohols under very mild conditions.

Experimental Section

Preparation of 3α-Cholestanyl Chloride (13). (3α-Cholestanol (**6**, 390 mg, 1 mmol) and triphenylphosphine (790 mg, 43 mmol) were dissolved in anhydrous tetrahydrofuran (10 mL) under argon. Anhydrous zinc chloride (135 mg, 1 mmol) in 10 mL of tetrahydrofuran and diethyl azodicarboxylate (522 mg, 3 mmol) in 2 mL of tetrahydrofuran were added at room temperature consecutively. The mixture was stirred under argon at room temperature for 2 h. The reaction mixture was poured onto a short silica gel column and purified by chromatography with 1% ethyl acetate in hexane to give crystalline 3α-cholestanyl chloride (**13**) as the sole product (376 mg, 92%): mp 104 °C (lit. mp 105 °C); $[\alpha]_D$ +29° (*c* 4.89, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.65 (s, 3 H, CH_3), 0.78 (s, 3 H, CH_3), 0.86 (d, 6 H, *J* = 6 Hz, $CH(CH_3)_2$), 0.89 (d, 3 H, *J* = 6 Hz, CH_3), 0.75–2.00 (m, 31 H) 4.50 (m, 1 H, CHCl). Anal. Calcd for $C_{27}H_{47}Cl$: C, 79.66; H, 11.63. Found: C, 79.62; H, 11.64.

Generation of Halides from Alcohols. The conditions used for the generation of halides from alcohols were identical with those illustrated in the preparation of 3α-cholestanyl chloride (**13**). Yields and reaction times are compiled in Table I. Satisfactory spectral data were obtained for all new compounds. The synthesis of the dienyl alcohol **3** will be reported in a separated publication. Proton NMR data (δ) taken in $CDCl_3$ and analytical data include the following. **9**: 0.82 (t, 3 H, *J* = 6.5 Hz, CH_3) 1.05 (s, 9 H, *t*-Bu), 3.65 (t, 2 H, *J* = 5.9 Hz, $SiOCH_2$), 4.17 (d, 2 H, *J* = 8 Hz, CH_2Cl), 5.1–6.25 (m, 4 H, *J* = 15 Hz, *J* = 10 Hz, *J* = 8 Hz, vinyl protons), 7.35–7.65 (m, 10 Ar). Calcd for $C_{27}H_{37}ClOSi$ *m/e* 440, found *m/e* 440. **10**: 1.69 (s, 3 H, CH_3), 3.19 (s, 3 H, NCH_3), 3.32 (s, 2 H, benzylic), 3.65 (s, 3 H, $COOCH_3$), 3.90 (s, 3 H, OCH_3), 4.12 (d, 2 H, *J* = 7.8 Hz, CH_2Cl), 5.57 (br t, 1 H, *J* = 7.8 Hz, vinyl), 6.71 (s, 2 H, Ar). Calcd for $C_{15}H_{19}Cl_2NO_3$ *m/e* 331.0744, found *m/e* 331.0736. **11**: (s, 3 H, CH_3), 3.20 (s, 3 H, NCH_3), 3.30 (s, 2 H, benzylic), 3.65 (s, 3 H, $COOCH_3$), 3.89 (s, 3 H, OCH_3), 4.03 (d, 2 H, *J* = 8 Hz, CH_2Br), 5.61 (t, 1 H, *J* = 8 Hz, vinyl), 6.72 (s, 2 H, Ar). Calcd for $C_{15}H_{19}BrClNO_3$: C, 47.83; H, 5.08. Found: C, 47.75; H, 5.16. **14**: 3.01 (t, 2 H, *J* = 7.5 Hz, CH_2Ph), 3.68 (t, 2 H, *J* = 7.5 Hz, CH_2Cl), 7.18 (s, 5 H, Ar). **15**: 2.10–2.70 (m, 4 H, CH_2CH_2), 4.18 (m, 2 H, CH_2Cl), 4.82 (m, 1 H, CHOOC). Calcd for $C_5H_7ClO_2$: C, 45.31; H, 3.80. Found: C, 45.42; H, 3.72. **16**: 2.10–2.75 (m, 4 H, CH_2CH_2), 4.05 (m, 2 H, CH_2Br), 4.86 (m, 1 H, CHOOC). Calcd for $C_5H_7BrO_2$: C, 33.93; H, 2.85. Found: C, 33.98; H, 2.61. **17**: 2.20–2.75 (m, 4 H, CH_2CH_2), 3.95 (m, 2 H, CH_2I), 4.90 (m, 1 H, CHOOC). Calcd for $C_5H_7IO_2$: C, 26.81; H, 2.25. Found: C, 26.68; H, 2.48.

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Registry No. **3**, 90605-46-2; **4**, 90605-47-3; **5**, 108-93-0; **6**, 80-97-7; **7**, 60-12-8; **8**, 10374-51-3; **9**, 90605-48-4; **10**, 90605-49-5; **11**, 90605-50-8; **12**, 542-18-7; **13**, 1474-58-4; **14**, 622-24-2; **15**, 39928-72-8; **16**, 32730-32-8; **17**, 1729-32-4; PPh_3, 603-35-0; $EtO_2CN{=}NCO_2Et$, 1972-28-7; $ZnCl_2$, 7646-85-7; $ZnBr_2$, 7699-45-8.

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Evidence of Side-Arm Involvement in Lariat Ether Complexes: A Lanthanide Shift Reagent Study

Angel Kaifer,† Luis Echegoyen,*‡ and George W. Gokel§,‡

Departments of Chemistry, University of Puerto Rico, Rio Piedras, Puerto Rico 00931, University of Miami, Coral Gables, Florida 33124, and University of Maryland, College Park, Maryland 20742

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Lariat ethers[1] are a class of macrocyclic polyether ligands whose structures consist of a side-arm group covalently bonded to a crown macroring. When the side arm contains one or more donor sites, binding cooperativity with the macroring is feasible, resulting in complexes of intermediate stability and microdynamic properties between those of simple crowns and those of the rigid bicyclic cryptands. This point has been addressed in previous work[2] using ^{13}C NMR T_1 measurements to monitor the individual mobilities of the carbon atoms in the free ligands as compared to those of corresponding alkali and alkaline-earth cation complexes. Previous results have clearly established the cooperative participation of the side arm in the complexation of the ring-bound cation in solution, reaching a maximum in cases where the location of the side-arm donor sites is optimized, the cation charge-to-size ratio is large, and the degree of rigidity of the "pivot" point (covalent attachment point of the side arm to the macroring) is minimized.[2] Participation of the side arm in the binding mechanism has also been unequivocally demonstrated in the solid phase by means of an X-ray study of lariat ether complexes.[3]

In order to expand our studies to trivalent cations and to obtain further confirmation of the side-arm participation

† University of Puerto Rico.
‡ University of Miami.
§ University of Maryland.

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