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A FACILE REPLACEMENT OF HYDROXYL BY HALOGEN WITH INVERSION[1]

Ajay K. Bose and Bansi Lal

Department of Chemistry and Chemical Engineering
Stevens Institute of Technology
Hoboken, N.J. 07030

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A convenient method for phosphorylation involves the reaction of an alcohol 2 with a phosphite[2] (1, R=CH_2Ph or CH_2-CH=CH_2) and an N-haloimide or N-haloamide. The intermediate is believed to be a quaternary phosphonium salt[3] 3 which cleaves to give the desired trialkyl phosphate 4 with the concomitant formation of an alkyl halide ($PhCH_2X$ or CH_2 = $CHCH_2X$) and an imide or an amide (Chart 1, path A).

If the cleavage of the intermediate 3 occurred along path B, the halide instead of the phosphate will be formed from the alcohol 2. A search through the literature showed that ethyl[4] and furfuryl alcohols[5] have been converted to their bromides by reaction with triphenylphosphine and N-bromosuccinimide in an analogous reaction.

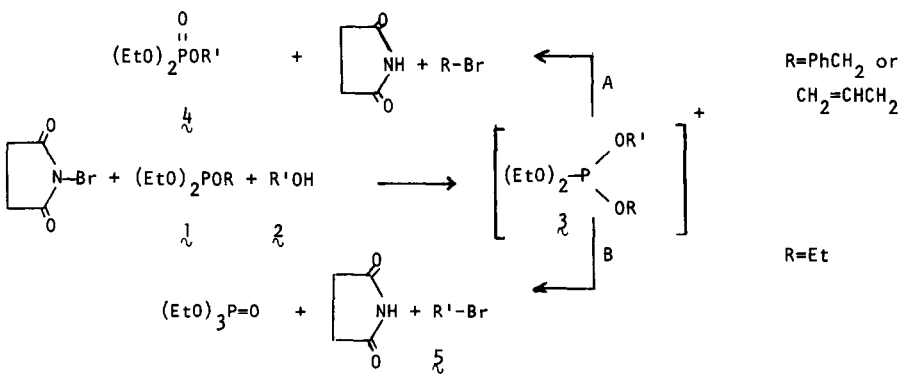

Chart 1

Path A should be inoperative if triphenyl phosphite be used in place of 1; the reaction then should follow path B and lead exclusively to the halide 5. We have now investigated the synthetic utility of the reaction of phosphites and phosphines in conjunction with N-haloimides or N-haloamides for the preparation of halides. We have studied several sterols as the alcohol component and found that the replacement of the hydroxy group with a halogen proceeds

in high yield under mild conditions (1-2 hr at room temperature, see Table). There was complete inversion of stereochemistry during the substitution indicating that a S_N2 process is involved and the reaction has high stereospecificity. The stereochemistry of the steroid halides was conveniently determined from their proton NMR spectra. A typical experiment is described below

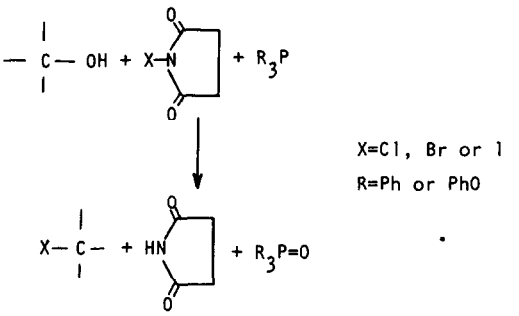

Chart 2

3-α-Cholestanyl bromide. To a magnetically stirred solution of N-bromosuccinimide (1.78g, 0.01 mole) in tetrahydrofuran (60 ml), a solution of triphenylphosphine (2.62g, 0.01 mole) in THF was added dropwise; an exothermic reaction occurred with separation of a solid. To this suspension a solution of dihydrocholesterol (3.88g, 0.01 mole) in THF (25 ml) was added and stirring continued until most of the solid went into solution (ca. 1 hr). The reaction mixture was stripped of solvent under reduced pressure and the residue was treated with water and ether. The organic layer was washed with water, dried over anhyd. Na_2SO_4, and evaporated. The crude product was submitted to chromatography on a Florisil column using hexane as the eluent; the title compound (recryst. from MeOH) was obtained in 85% yield, m.p. 111-112° [6].

In the above reaction triphenylphosphite can replace triphenylphosphine without lowering the yield of the bromo steroid; trialkyl phosphites, however, were poor substitutes for these phosphorus compounds because of competing phosphorylation reaction. N-Bromoacetamide was as effective as N-bromosuccinimide as the brominating agent. N-chlorosuccinimide and N,N-dichlorourethane were successfully used for obtaining chlorosteroids. The reaction of iodine, triphenyl phosphine and 3β-cholestanol has been reported to give 3α-iodocholestane[7]

in 33% yield. In contrast, N-iodosuccinimide, triphenylphosphine and 3β-cholestanol gave 85% yield of the same iodo compound.

Unlike the esterification process described in our previous publication[1] which is sensitive to steric hindrance, the haloqenation reaction described here can be applied successfully to axial alcohols and hindered alcohols (see Table). Substitution of the 3β-hydroxy group with halogen even in Δ^5-3β-sterols proceeds mainly with inversion.

Replacement of a hydroxyl group in a stereospecific manner is an important transformation for steroids, carbohydrates and some other classes of compounds. The reaction described here because of its high stereospecificity, mild reaction conditions, high yield and fast reaction velocity promises to be a useful synthetic method - especially for polyfunctional molecules.

Table. Halides[†] from alcohols

Alcohol	Halide	Yield(%)	Reagent[***]	Lit.
3β-Cholestanol	3α-Cholestanyl bromide	95	[A], [B], [D]	[6]
3α-Cholestanol	3β-Cholestanyl bromide	ca.80	[A]	[6]
3β-Cholestanol	3α-Cholestanyl iodide	85	[E]	[7]
5α-Androstan-3-ol-17-one	3β-Chloro-5α-androstan-17-one	76	[C]	[8]
5α-Androstan-3β-ol-17-one	3α-Chloro-5α-androstan-17-one	92	[C]	[8]
4-Estren-17β-ol-3-one	17α-Bromo-4-estren-3-one	75	[A]	
Cholesterol	Cholesteryl bromide (3α:3β = 75:25)	65	[A]	
5-Androsten 3β-ol-17-one	3-Bromo-5-androsten-17-one (3α:3β = 80:20)	75	[A]	
Benzyl alcohol	Benzyl Chloride	95[**]	[C]	
Cycloheptanol	Cycloheptyl bromide	78[**]	[A]	

[***] A = N-Bromosuccinimide/triphenylphosphine; B = N-Bromosuccinimide/triphenylphosphite
C = N-chlorosuccinimide or N,N-dichlorourathane/triphenyl phosphite;
D = N-Bromoacetamide/triphenylphosphine, E = N-iodosuccinimide/triphenylphosphine
[**] Identified by comparison with authentic samples. [†] These compounds gave satisfactory spectroscopic data.

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