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A NEW GENERAL SYNTHESIS OF HALOHYDRINS

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Abstract: *A new synthetic method has been devised for the rapid conversion of epoxides to chloro-, bromo- and iodo-hydrins in quantitative yield, under mild conditions and in the absence of protic acids.*

In connection with other work on the conversion of epoxides to alkenes[1], we report in this communication some preliminary results concerning a very simple, high yield, general synthesis of chloro-, bromo- and iodo-hydrins which can be effected in a one-pot treatment of epoxides with triphenylphosphine and the proper halogen in anhydrous dichloromethane at room temperature.

Triphenylphosphine in fact is well known[2] to react readily with halogens to give partially ionic[3,4] adducts, as is depicted below:

$$Ph_3P: \quad X-X \quad \rightleftharpoons \quad Ph_3P^+-X \quad X^- \quad \rightleftharpoons \quad Ph_3PX_2 \qquad \text{(Eq.1)}$$

The electrophilic nature of the phosphorus atom in such adducts prompted us to exploit them in order to achieve the mild opening of epoxide rings leading to halohydrins. We assumed this to be caused likely by phosphorylation of the oxygen atom and the subsequent nucleophilic attack by the halide ion which is available *in situ* (see Eq.1) at the carbon atoms of the three-membered ring.

The first experiments, performed by using a 1:1.1:1.1 epoxide:triphenylphosphine:halogen ratio, were quite satisfactory and the results have been sumarized in the Table. Halohydrin formation is almost immediate and nearly quantitative in all the cases we have examined. Utilizing a conformationally rigid epoxide (e.g., either 1,2-epoxy-4-*t*-butylcyclohexanes or 2α,3α-epoxy-5α-cholestane) as the substrate, the oxirane bridge cleavage appears to be quite stereoselective leading only to the product resulting from the usual *anti* opening of the ring.

*2β-Iodo(*or *2β-Bromo)-3α-hydroxy-5α-cholestane - General procedure* - To a magnetically-stirred solution of iodine (0.35 g;1.36 mmol) in anhydrous dichlorometha-

ne (40 ml), triphenylphosphine (0.36 g; 1.36 mmol) was added in one portion. The brown solution turned immediately to a pale yellow colour and then 2α,3α-epoxy-5α-cholestane (0.48 g; 1.24 mmol) was added also in one portion. TLC monitoring showed that the epoxide was consumed totally within 5'. Then the reaction mixture was poured into ice *N* aq $NaHCO_3$ (130 ml) and worked-up in the usual way. The crude material was dissolved in *n*-hexane and, after filtration through silica gel (1:10) to eliminate Ph_3PO, afforded a crystalline product which was recrystallized from acetone to give the pure title iodohydrin, yield 0.59 g (93%), m.p. 131-133°C (lit.[15] 132-133°C).

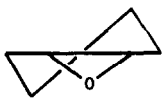
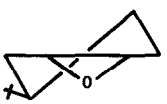
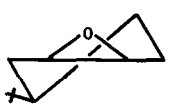
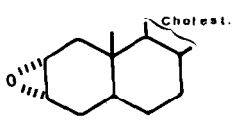
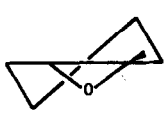
Use of bromine (0.22 g; 1.36 mmol), under the conditions reported above, afforded 2β-bromo-3α-hydroxy-5α-cholestane, yield 0.55 g (95%), m.p. 123-125°C (from acetone) (lit.[16] 115-118°C).

2β-Chloro-3α-hydroxy-5α-cholestane - A solution of triphenylphosphine (0.36 g; 1.36 mmol) in anhydrous dichloromethane (40 ml) cooled in an ice bath was saturated with chlorine and then left to reach r.t. At this stage 2α,3α-epoxy-5α-cholestane (0.48 g; 1.24 mmol) was added in one portion to the pale greenish-yellow solution. The epoxide was instantaneously consumed (TLC) and the reaction mixture, after work-up as described above, afforded the title chlorohydrin, yield 0.48 g (92%), m.p. 121-124°C (from acetone) (lit.[16] 118-120°C).

In order to obtain information about the orientation, i.e. to relate orientation to the effect of substituent groups in the oxirane ring, we examined the behaviour, under our experimental conditions, of 1-methylcyclohexene oxide which possesses both secondary and tertiary oxirane ring-forming carbon atoms. The results we obtained, which are reported also in the Table, show that the nucleophile attacks preferentially the less-substituted carbon atom, although the orientation appears to be affected also by the bulkiness of the halide ion. As a matter of fact, the larger the halide ion the higher the percentage of its attack onto the less-substituted carbon atom.

On the basis of the above data, the course of the overall reaction can be interpreted as follows: the triphenylphosphine-halogen adduct, formerly obtained in the reaction mixture, first undergoes a nucleophilic attack at the positive phosphorus atom by the oxirane oxygen[5]. The species therefrom then undergoes, in its turn, a nucleophilic attack by the halide ion which has been formed *in situ* at the carbon atom(s) of the phosphorylated oxirane ring. This leads to the ring opening and the formation of an halohydrin *O*-triphenylphosphonium halide. The addition of water to the reaction mixture finally accomplishes a rapid hydroli-

Table- Conversion of epoxides to halohydrins by Ph_3P/Hal_2

Epoxide	Hal	% Yield[a,b]	Halohydrin(s)
	I	95	*trans*-2-Iodocyclohexanol[9]
	Br	97	*trans*-2-Bromocyclohexanol[10]
	Cl	94	*trans*-2-Chlorocyclohexanol[11]
	I	93	*trans*-2-Iodo-*trans*-5-*t*Bu-cyclohexanol[c]
	Br	95	*trans*-2-Bromo-*trans*-5-*t*Bu-cyclohexanol[12]
	Cl	93	*trans*-2-Chloro-*trans*-5-*t*Bu-cyclohexanol[12]
	I	96	*trans*-2-Iodo-*cis*-4-*t*Bu-cyclohexanol[c]
	Br	95	*trans*-2-Bromo-*cis*-4-*t*Bu-cyclohexanol[13]
	Cl	96	*trans*-2-Chloro-*cis*-4-*t*Bu-cyclohexanol[14]
	I	93	2β-Iodo-3α-hydroxy-5α-cholestane[15]
	Br	95	2β-Bromo-3α-hydroxy-5α-cholestane[16]
	Cl	94	2β-Chloro-3α-hydroxy-5α-cholestane[16]
	I	82	*trans*-2-Iodo-1-methylcyclohexanol[17]
		13	*trans*-2-Iodo-2-methylcyclohexanol[17]
	Br	68	*trans*-2-Bromo-1-methylcyclohexanol[18]
		22	*trans*-2-Bromo-2-methylcyclohexanol[19]
	Cl	50	*trans*-2-Chloro-1-methylcyclohexanol[11]
		42	*trans*-2-Chloro-2-methylcyclohexanol[11]

[a] *Yield of isolated product with purity ⩾ 95%.* [b] *All the reactions were almost immediate and complete within 5'.* [c] *Structure assignment based on ^1H N.M.R. analysis.*

sis[6] of the latter product thereby leading to the expected halohydrin, accompanied by triphenylphosphine oxide and hydrogen halide.

In this view the ring-cleavage step in our reaction may be regarded as paralleling with a general epoxide opening under acidic conditions. Our preliminary data concerning substituent effects[7], as well as the influence of the steric hindrance of the halide ion[8], suggest that the attack by the nucleophile at the more substituted position of the ring takes place by a borderline S_N2 mechanism[7].

On the other hand, the general prevalence of the nucleophile attack at the less substituted position may be accounted for by the nature of the solvent which favours the less polar transition state[7].

However, work is still in progress in our laboratory to study the behaviour of variously substituted epoxides, under our experimental conditions, in order to understand the mechanistic course of the whole reaction.

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