

Papers

Facile, high regio- and chemoselective conversion of epoxides to β -chlorohydrins using chlorodiphenylphosphine under solvent-free conditions

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A new method is described for the mild and high regioselective conversion of epoxides to β -chlorohydrins in high yields even in the presence of alcohols, carboxylic acids, oximes, amides, thiols and tetrahydropyranyl ethers using chlorodiphenylphosphine (ClPPh₂) under solvent-free and neutral conditions at room temperature and in short reaction times. In addition, some other functional groups such as carbon-carbon double bonds, ester groups and also phenyl ring that are present in the epoxide molecules remain intact in this method.

Keywords: Epoxides, β -chlorohydrins, chemoselectivity, chlorodiphenylphosphine, solvent-free

Synthetic chemistry continues to develop various techniques for obtaining better products with less environmental impact. One of the more promising approaches is solvent-free reactions¹. The elimination of volatile organic solvents in organic syntheses is a most important goal in 'green' chemistry. Furthermore, these reactions have some other advantages such as low costs, simplicity in process and handling, formation of cleaner products, enhanced selectivity, improved reaction rates and prevent waste solvent generation, hazards, and toxicity. These factors are especially important in the chemical industry. The development of solvent-free organic synthetic methods has thus become an important and popular research area.

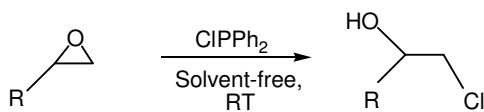
On the other hand, epoxides are important intermediates in organic synthesis² and due to their particular polarity and strained three member ring system, a large variety of nucleophiles can be employed for ring opening of these compounds^{3,4}. In this connection, due to the considerable importance of β -halohydrins in organic synthesis⁵ and in order to avoid the use of strongly acidic hydrogen halides for their synthesis from epoxides⁶ especially containing acid-sensitive functional groups, different reagents have been used in recent years for this transformation. Some of these reagents which have been used are ammonium halides in presence of metal salts⁷, phosphoferrocene as a catalyst with TMSCl⁸, silica gel in the presence of lithium halides⁹, a mixture of elemental halogen and 2-phenyl-2-(pyridyl) imida-

zolidine (PPI)¹⁰, phenyl hydrazine¹¹ or crown ethers¹², bis-chlorodibutyltin oxide¹³, Ce(IV) as ceric ammonium nitrate in the presence of quaternary ammonium halides¹⁴, triphenylphosphine (PPh₃)/N-halo imides¹⁵, metal halides in ionic liquids¹⁶, niobium pentachloride¹⁷, dimethoxyboron chloride¹⁸ and monobromoborane-dimethylsulfide¹⁹.

However, some of these methods have disadvantages such as producing undesired side products, use of reagents that are not easily available or long reaction times. In addition, in many cases the method does not provide chemoselectivity or at least, chemoselectivity of the method is ambiguous.

Results and discussion

Recently, a report has appeared on the application of PPh₃/DDQ/tetraalkylammonium halides in refluxing acetonitrile in the synthesis of β -halohydrins from epoxides²⁰. In continuation of the work on the new applications of trivalent phosphorus in organic synthesis²⁰⁻²⁴ and due to the importance of β -halohydrins in organic synthesis⁵ and their formation from epoxides especially in a chemoselective way and also advantages of solvent-free reactions, is now reported a new, more facile and milder method avoiding the use of molecular halogen with respect to its harsh handling for the efficient conversion of epoxides to β -chlorohydrins using chlorodiphenylphosphine (ClPPh₂) under solvent-free and neutral conditions at RT with excellent chemo- and regioselectivity (**Scheme I**).



Scheme I — Solvent-free conversion of epoxides to β -chlorohydrins using ClPPh_2 at RT

First, glycidyl phenyl ether was selected as an example and its conversion to the corresponding β -chlorohydrine was studied (**Scheme II**). As shown in **Scheme II**, 1-chloro-3-phenoxy-2-propanol was produced by the treatment of glycidyl phenyl ether with ClPPh_2 (1:1.3) in CH_2Cl_2 at RT in 40% yield after 8.75 hr. Surprisingly, it was found that this reaction could be efficiently carried out using ClPPh_2 (1 eq.) *via* grinding of reactants in a glass test tube under solvent-free conditions at RT within only 20 min, so that 1-chloro-3-phenoxy-2-propanol was obtained after column chromatography of crude product in 95% yield.

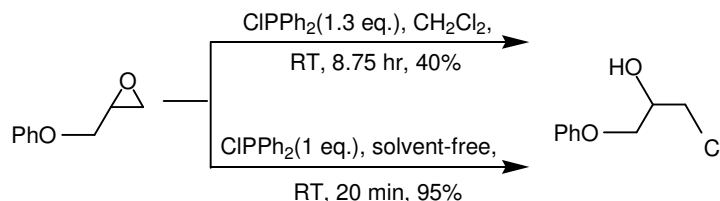
Thereafter, this efficient solvent-free condition was applied for the conversion of other structurally different epoxides to their corresponding β -chlorohydrins. The results are shown in **Table I**. As shown in **Table I**, epoxides were efficiently converted to the corresponding β -chlorohydrins under solvent-free conditions within relatively short reaction times at RT and in high yields. Also, the ring opening of epoxides occurred with high regioselectivity and the chloride anion attacked at the less-hindered side of the epoxide ring due to steric factors except for the epoxy styrene which attacked at the more-hindered side of the three membered ring moiety due to electronic factors (**Table I**, entry 3). Also, functional groups such as carbon-carbon double bonds, the ethereal bonds, ester groups and also phenyl ring that are present in the epoxide molecules remained intact under these reaction conditions.

In addition, for obtaining deeper insight into the applicability, selectivity and limitations of this new method, the possibility of the conversion of glycidyl phenyl ether to 1-chloro-3-phenoxy-2-propanol was studied in the presence of some other functional

groups in different binary mixtures. For this purpose, ClPPh_2 (1 eq.) was added to each binary mixture (1:1) in a glass test tube and the mixture was then ground under solvent-free conditions at RT for 20 min. The conversion yields obtained for these selective reactions of different binary mixtures are shown in **Scheme III**. Surprisingly, in addition to the various selectivities mentioned above, also, as shown in **Scheme III**, epoxides can be efficiently converted to their corresponding β -chlorohydrins in the presence of alcohols, carboxylic acids, oximes, amides, thiols and tetrahydropyranyl ethers with excellent selectivity using the present method.

In this connection, the selectivity of the present new method was compared with the mixture of $\text{Ph}_3\text{P/DDQ}$ /tetrahexyl ammonium chloride (Hex_4NCl) of the previous work²⁰ in the conversion of epoxides to β -chlorohydrins in the binary mixture of epoxide/alcohol. It was found that in treatment of the mixture of $\text{Ph}_3\text{P/DDQ}$ with the binary mixture containing glycidyl phenyl ether and 3-phenylpropanol in refluxing acetonitrile as solvent with gradually addition of Hex_4NCl (method A of ref. 20), not only was 1-chloro-3-phenoxy-2-propanol produced as expected but also, 1-chloro-3-phenylpropane was formed in 40% conversion yield. In addition, the completely opposite selectivity has been observed in the use of $\text{Ph}_3\text{P/DDQ}$ /quaternary ammonium halides for the binary mixture of epoxide and alcohol in CH_2Cl_2 instead of CH_3CN as solvent at RT (Ref. 21). In this case, alcohols are immediately converted to the corresponding alkyl halides but epoxides remain completely unchanged.

It is suggested that in the case where the mixture of $\text{Ph}_3\text{P/DDQ}$ is used, due to formation of positive phosphorus in the reaction mechanism^{20,21}, the present alcoholic OH bond is activated so that the epoxides are not selectively converted to β -halohydrins in the presence of alcohols by this reagent but the present method, due to the lack of formation of positive phosphorus, provides excellent chemoselectivity in this conversion (**Scheme III**, entry 1).

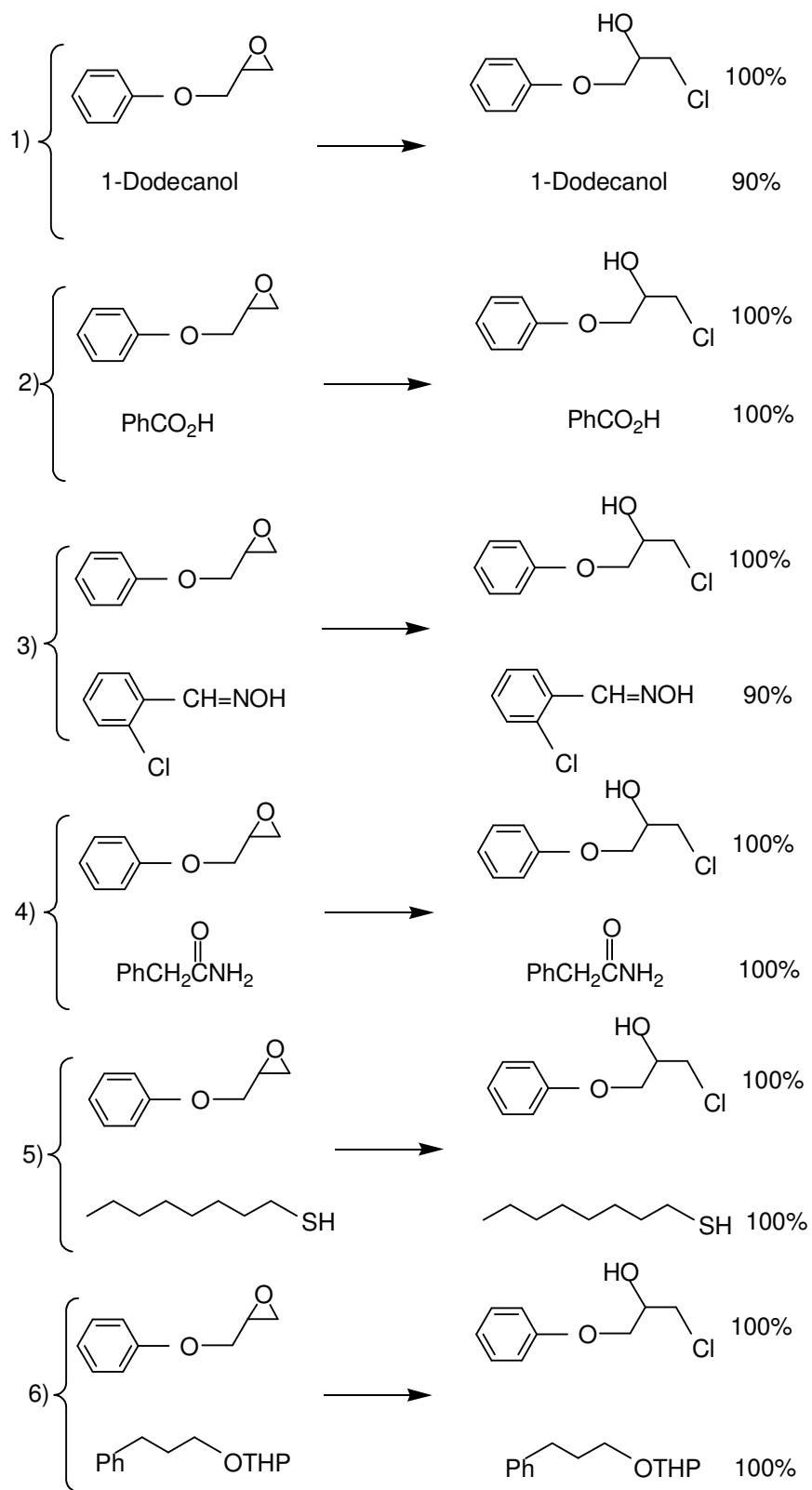


Scheme II — Conversion of glycidyl phenyl ether to 1-chloro-3-phenoxy-2-propanol under two different conditions

Table I — Solvent-free conversion of epoxides to β -chlorohydrins using ClPPh₂ at RT ^a

Entry	Epoxides	β -Chlorohydrins	Time (min)	Yield (%) ^b
1			20	95
2			30	93
3			15	85(5) ^{c, d}
4			30	90
5			40	90
6			30	85
7			35	88 ^e
8			45	97
9			20	94

^aMolar ratio 1/1 of epoxide/ClPPh₂ was used in these reactions. ^bIsolated yield. ^cYield is based on GC and NMR analysis. ^dNumber in parenthesis is related to 2-chloro-1-phenylethanol. ^eYield is based on GC analysis.



Scheme III — Chemoselectivities in the reaction of glycidyl phenyl ether with ClPPh₂ under solvent-free conditions

Experimental Section

Solvents, reagents and chemicals were obtained from Merck (Germany) and Fluka (Switzerland) Chemical Companies. Products are known compounds^{9,14,20} and were characterized by comparison of their physical or spectral data with those prepared according to known literature procedures. FT-IR spectra were recorded on a Perkin Elmer RXI spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Bruker Avance DPX-250 or Bruker Avance DRX-500 spectrometers. Mass spectra were determined on a Shimadzu GCMS-QP 1000 EX at 70 eV. GC spectra were recorded on a Shimadzu GC-14A. Thin layer chromatography was carried out on silica-gel 254 analytical sheets obtained from Fluka.

General procedure for the conversion of epoxides to β -chlorohydrins

Epoxide (1 mmole) was thoroughly mixed with ClPPh₂ (0.18 mL, 1 mmole) in a glass test tube. The resultant mixture was finely ground at RT for appropriate time after which TLC showed complete disappearance of epoxide (**Table I**). Pure β -chlorohydrin was obtained in 85-97% yields after column chromatography of crude mixture over silica gel using petroleum ether-ethyl acetate as eluent.

1-Chloro-3-phenoxy-2-propanol

¹H NMR (CDCl₃, 250 MHz): δ 2.64-2.66(d, 1H, J = 5 Hz), 3.68-3.81(m, 2H), 3.98-4.08(m, 2H), 4.12-4.22(m, 1H), 6.89-7.01(m, 3H), 7.24-7.32(m, 2H); ¹³C NMR (CDCl₃, 62.9 MHz): δ 46.37, 68.79, 70.29, 114.94, 121.86, 130.01, 158.08; FT-IR (neat): 3422(br, s), 3063(w), 3041(w), 2927(s), 2875(m), 1599(s), 1496(s), 1243(s), 1044(s), 813(w), 753(s), 691(s) cm⁻¹; MS: m/z (%) 188(M + 2, 34.9), 186(M, 100), 169(M-OH).

1-Chloro-2-tetradecanol

¹H NMR (CDCl₃, 500 MHz): δ 0.914-0.942(t, 3H, J = 7 Hz), 1.29-1.31(m, 20H), 1.543-1.575(br, t, 2H, J = 8 Hz), 2.54 (br, s, 1H), 3.489-3.525 (dd, 1H, J = 11, 7 Hz), 3.645-3.673(dd, 1H, J = 11, 3 Hz), 3.80-3.83 (m, 1H); ¹³C NMR (CDCl₃, 125.77 MHz): δ 14.51, 23.09, 25.93, 29.53, 29.76, 29.84, 29.92, 29.96, 29.98, 30.05, 32.33, 34.64, 50.91, 71.89; FT-IR (neat): 3401 (br), 2924(s), 2854(s), 1466(m), 1048(w), 739(w), 722(w) cm⁻¹.

1-Chloro-3-(4-chlorophenoxy)-2-propanol

¹H NMR (CDCl₃, 500 MHz): δ 3.03(s, 1H), 3.73-

3.81(m, 2H), 4.05-4.10(m, 2H), 4.22-4.26(m, 1H), 6.86-6.88(d, 2H, J = 10 Hz), 7.26-7.28(d, 2H, J = 10 Hz); ¹³C NMR (CDCl₃, 125.77 MHz): δ 46.31, 69.34, 70.18, 116.31, 126.75, 129.88, 157.30; FT-IR (neat): 3410(br), 3099(w), 3073(w), 2929(s), 2878(m), 1596(s), 1493(s), 1458(s), 1285(s), 1243(s), 1093(s), 1040(s), 824(s), 751(m), 670(s) cm⁻¹.

Conclusion

In conclusion, the present investigation has demonstrated that the use of ClPPh₂ under solvent-free conditions offers a simple and efficient method avoiding the use of molecular halogen with respect to its harsh handling and also halogenated hydrocarbon solvents such as dichloromethane for the mild conversion of a wide variety of epoxides to their corresponding β -chlorohydrins. This method can be efficiently used for preparation of β -chlorohydrins even in the presence of many reactive functional groups with excellent chemoselectivity. Commercial availability, ease of handling and lower cost of the reagent, reduced pollution, easy work up, excellent regioselectivity, high yields and operation at room temperature in neutral media are considered as other advantages of this method. Further studies towards the other applications of this reagent in organic synthesis are under progress.

Acknowledgments

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