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Anhydrous $ZnCl_2$: A Highly Efficient Reagent for Facile and Regioselective Conversion of Epoxides to β-Chlorohydrins

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Facile conversion of structurally different epoxides to the corresponding β-chlorohydrins was carried out successfully with anhydrous $ZnCl_2$ in CH_3CN. The reactions were carried out within 10-50 min to give β-chlorohydrins with perfect regioselectivity and high yields (80-97%).

1. Introduction

β-Chlorohydrins are one of the most versatile intermediates in organic synthesis to achieve a variety of functional groups,[1] halogenated marine products,[2] chiral auxiliaries,[3] biologically active compounds[4] including lipid mediators,[5-9] and unnatural amino acids.[10] Furthermore, protected chlorohydrins have found wide applications in total synthesis of natural products and steroid chemistry.[11,12] Halohydrins are also essential substrates for preparation of a specific class of enzymes and halohydrin dehalogenases. They are effective in both asymmetric synthesis[13] (chiral resolution of racemic synthons[14]) and bioremediation of the environment (removal of pollutants from soil, groundwater or waste water).[15]

The most common and straightforward method for synthesis of chlorohydrins involves ring opening of epoxides by chloride ion nucleophile. The literature review shows that HCl[12], LiCl supported on

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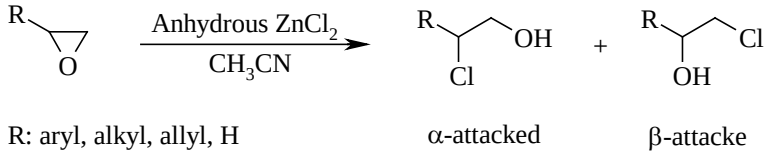
silicagel,[16] TCT/morpholine,[17] TMSCl/ZnO,[18] $NbCl_5$,[19] TMSCl/[bmim][PF_6],[20] $SiCl_4$/chiral bipyridine *N*,*N'*-dioxides,[21] HCl/(salen)Co,[22] TMSCl/(*R*)-(+)-BINOL-Ti,[23] $ClPPh_2$,[24] $AlCl_3$,[25] $NH_4Cl/LiClO_4$,[26] $BiCl_3$,[27] $BHBr_2$-SMe_2,[28] HX or LiX/β-cyclodextrine,[29] chloride ion/halohydrin dehalogenase,[30] Cl_2/phenyl hydrazine,[31] $ZrCl_4$,[32] $InBr_3$,[33] TMSCl/phosphazirconocene,[34] TMSCl/phosphaferrocene,[35] $LiClO_4$,[36] polyvinylpyrolidone/thionylchloride,[37] and $La(NO_3)_3 \cdot 6H_2O$[38] are some of the reagents which have been used for the preparation of β-chlorohydrins from epoxides. Although most of the mentioned methods are efficient, however, some of them suffer from disadvantages such as long reaction times, high cost, poor regioselectivity, difficult work-up procedure, formation of side-products and low yields. Thus, the introduction and development of an efficient method in this context is still demanded.

Herein, in line of the outlined strategies and our ongoing attention to the nucleophilic ring opening of epoxides,[39-45] we wish to report the facile and regioselective synthesis of β-chlorohydrins from epoxides using anhydrous $ZnCl_2$ as an efficient promoter and source of active chloride nucleophile (**Scheme 1**).



Scheme 1. Ring opening of epoxides with anhdrous $ZnCl_2$

2. Results and Discussion

Nowadays, one of the most urgent challenges for organic chemists is providing economical methods using more efficient and easily available reagents or catalysts. A literature review shows that though the preparation of chlorohydrins form epoxides has been achieved by various metal halides (LiCl, $NbCl_5$, $SiCl_4$, $AlCl_3$, $BiCl_3$ and $ZrCl_4$), however, the capability of anhydrous $ZnCl_2$ for regioselective conversion of epoxides into β-chlorohydrins has not been investigated yet. In addition, $ZnCl_2$ as an easily available and inexpensive metal halide has been found wide useful applications in organic synthesis.[46] Thus the mentioned strategies encouraged us to investigate the capability of anhydrous $ZnCl_2$ for the titled transformation.

We preliminary optimized reaction conditions by performing the ring opening of styrene oxide with anhydrous $ZnCl_2$ in CH_3CN, EtOAc and *n*-hexane or under solvent-free conditions (**Table 1**). Investigation of the results revealed that the kind of solvent, temperature of the reaction and the amount of $ZnCl_2$ dramatically influence the rate of transformation. Entry 1 shows that using the molar equivalents of 1:1 for epoxide/$ZnCl_2$ in CH_3CN and room temperature condition was the optimums to afford 2-chloro-2-phenylethanol (α-attacked) in perfect regioselectivity and efficiency. In addition, the temperature effect on the kind of resulted product is noteworthy: when the reaction was carried out under reflux conditions, 2-chloro-2-phenylacetaldehyde was obtained as a sole product in high yield (entry 4).

We also found that the transformation of styrene oxide to chlorohydrin or chloroaldehyde was carried out only in the presence of anhydrous $ZnCl_2$. In the case of hydrated one ($ZnCl_2 \cdot 2H_2O$), the reaction did not any take place even under reflux conditions (entry 8).

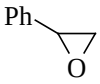
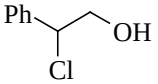
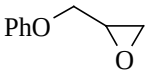
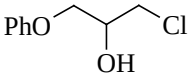
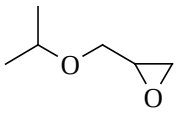
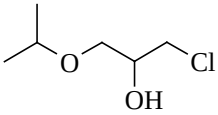
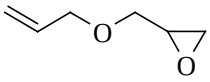
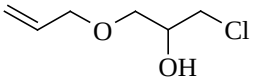
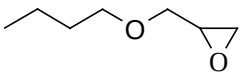
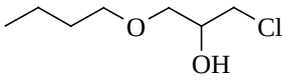
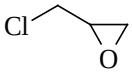
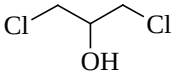
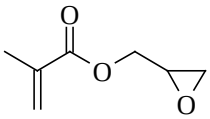
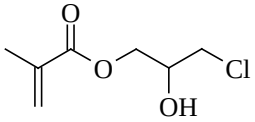
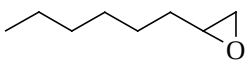
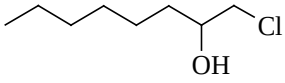
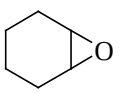
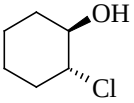
Table 1. Optimization experiments for the reaction of styrene oxide with anhydrous $ZnCl_2$[a]

Entry	Molar ratio	Condition	Time (min)	β-Chloro hydrin (%)	α-Chloro aldehyde(%)	Epoxide (%)[b]
1	Epoxide/$ZnCl_2$ (1:1)	CH_3CN/r.t.	35	100	0	0
2	Epoxide/$ZnCl_2$ (1:0.5)	CH_3CN/r.t.	60	100	0	0
3	Epoxide/$ZnCl_2$ (1:2)	CH_3CN/r.t.	25	100	0	0
4	Epoxide/$ZnCl_2$ (1:1)	CH_3CN/reflux	10	0	100	0
5	Epoxide/$ZnCl_2$ (1:1)	EtOAc/r.t.	40	100	0	0
6	Epoxide/$ZnCl_2$ (1:1)	*n*-Hexane/r.t.	40	40	0	60
7	Epoxide/$ZnCl_2$ (1:1)	Solvent-free r.t. grinding	5	70	30	0
8	Epoxide/$ZnCl_2 \cdot 2H_2O$ (1:1)	CH_3CN/reflux	60	0	0	100

[a]All reactions were carried out with 1 mmol of styrene oxide. [b]Yields of recovered styrene oxide.

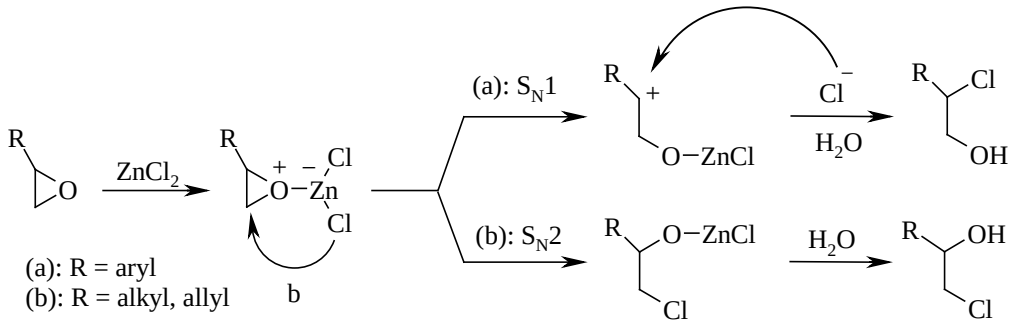
The suitability and scope of this synthetic method was further examined by the reaction of various epoxides bearing electron donating and withdrawing groups with anhydrous $ZnCl_2$ at the optimized reaction conditions. All epoxides were easily and efficiently converted to the corresponding β-chlorohydrins in excellent yields and regioselectivity. The reactions were completed within 10-50 min without formation of any side-products (**Table 2**). As seen, the nucleophilic ring opening of epoxides with anhydrous $ZnCl_2$ took place easily at room temperature except phenyl and methacrylate glycidyl ethers and 1,2-epoxyoctane that their reactions were completed under reflux conditions (**Table 2**, entries 2, 7 and 8).

Table 2. Conversion of epoxides to β-chlorohydrins with anhydrous $ZnCl_2$ in CH_3CN[a]

Entry	Epoxide	β-Chlorohydrin	Time (min)	Yield (%)[b]	Reference
1			35	95	47
2[c]			15	97	47
3			30	92	22
4			50	94	24
5			25	95	22
6			25	80	47
7[c]			10	97	24
8[c]			15	94	47
9			30	88	47

[a]All reactions were carried out with the molar ratio of epoxide:$ZnCl_2$ (1:1) in CH_3CN (2 mL) at room temperature.
[b]Yields refer to isolated pure products. [c]The reactions were carried out under reflux conditions.

Although the exact mechanism of this synthetic protocol is not clear, however, we think that the following mechanistic pathways maybe play a role in the formation of products (**Scheme 2**).



Scheme 2. A proposed mechanism for nucleophilic ring opening of epoxides with anhydrous $ZnCl_2$

Obviously, the regioselectivity of the ring opening of epoxides is dependent on the mechanism of the reaction and particularly on steric and electronic factors. As shown in Table 2, for epoxides carrying alkyl groups, it is the steric factor which predominates and the nucleophilic attack of chloride anion is strongly favored on the primary carbon atom of epoxides (S_N2 type mechanism). In contrary, for epoxides carrying aryl groups, the electronic factor predominates and the nucleophilic attack of chloride anion is strongly favored on the more stabilized "carbocation" with participation of the phenyl group (S_N1 type mechanism).

3. Conclusions

In summary, we have shown that anhydrous $ZnCl_2$ is a highly efficient reagent for conversion of various epoxides to the corresponding β-chlorohydrins in high yields and regioselectivity. The reactions were carried out within 10-50 min in CH_3CN at room temperature or under reflux conditions. This transformation offers several advantages in terms of mild reaction conditions, perfect regioselectivity, short reaction times, clean reaction profile, and use of inexpensive $ZnCl_2$ that make this protocol a practical useful addition to the present methodologies.

Acknowledgments

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Experimental

All reagents and substrates were purchased from commercial sources with the best quality and they were used without further purification. FT-IR, ^1H and ^{13}C NMR spectra were recorded on Thermo Nicolet Nexus 670 FT-IR and 300 MHz Bruker Avance spectrometers, respectively. The products were characterized by their spectra data and comparison with the reported data in literature. All yields refer to isolated pure products. TLC was applied for the purity determination of substrates, products and reaction monitoring over silica gel 60 F254 aluminum sheet.

Preparation of Anhydrous $ZnCl_2$

In a Pyrex test tube equipped with a clamp, $ZnCl_2 \cdot 2H_2O$ (0.20 g) was placed and then heated on an alcohol lamp for 5 min. During the process, water of crystalline lattice of hydrated zinc chloride was evaporated to afford anhydrous $ZnCl_2$ (0.15 g).

Conversion of Epoxides to β-Chlorohydrins by Freshly Prepared Anhydrous $ZnCl_2$: A General Procedure

In a round-bottomed flask (10 mL) equipped with a magnetic stirrer and condenser, a solution of epoxide (1 mmol) in CH_3CN (2 mL) was prepared. Anhydrous $ZnCl_2$ (0.136 g, 1 mmol) was then added and depending to the kind of epoxide, the mixture was stirred magnetically at room temperature or under reflux conditions for the specified time in Table 2. Progress of the reaction was monitored by TLC (CCl_4:Et_2O / 5:2), and the epoxides carrying aliphatic groups were visualized by use of iodine vapor. CH_3CN was evaporated and ethyl acetate (5 mL) was then added followed by stirring for 5 min. The mixture was filtered and the organic layer was evaporated to give the crude chlorohydrin. Further purification by a short column chromatography over silica gel (CCl_4/Et_2O) affords the product in 80–97% yield. The structure of the products was confirmed by FT-IR, ^{1}HNMR, ^{13}CNMR spectra, and comparison with authentic samples prepared by other reported methods.

Spectral data for β-chlorohydrins (Table 2, Entries 1-9) are as the followings:

2-Chloro-2-phenylethanol (Entry 1): Pale yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40-7.27 (m, 5H), 4.99 (t, *J* = 6 Hz, 1H), 3.93 (d, *J* = 7.5 Hz, 2H), 2.58 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.20, 128.90, 128.89, 127.44, 67.91, 64.89; FT-IR (ν_{max}/cm^{-1}, neat) 3428, 3062, 3032, 2922, 2856, 1493, 1453, 1068, 757, 701.

1-Chloro-3-phenoxy-2-propanol (Entry 2): Pale yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33-7.28 (m, 2H), 7.02-6.91 (m, 3H), 4.22 (m, 1H), 4.10 (m, 1H), 3.82-3.70 (m, 2H), 2.71 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.17, 129.61, 121.45, 114.54, 69.88, 68.39, 45.96; FT-IR (ν_{max}/cm^{-1}, neat) 3415, 3064, 3039, 2926, 2879, 1648, 1595, 1495, 1461, 1295, 1242, 1173, 1109, 1080, 1044, 755, 692, 510.

1-Chloro-3-isopropoxy-2-propanol (Entry 3): Pale yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.97-3.91 (m, 1H), 3.64-3.59 (m, 3H), 3.55 (d, *J* = 6.3 Hz, 2H), 2.35 (bs, 1H), 1.18 (d, *J* = 6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 72.38, 70.38, 68.49, 45.93, 22.01, 21.97; FT-IR (ν_{max}/cm^{-1}, neat) 3448, 2925, 2857, 1463, 1377, 1251, 1129, 933, 847, 751.

1-(Allyloxy)-3-chloro-2-propanol (Entry 4): Pale yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.98-5.84 (m, 1H), 5.32-5.19 (m, 2H), 4.08 (d, *J* = 5.1 Hz, 2H), 3.76-3.38 (m, 5H), 2.60 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 134.17, 117.53, 72.37, 70.64, 70.26, 46.00; FT-IR (ν_{max}/cm^{-1}, neat) 3429, 2920, 2855, 1426, 1352, 1262, 1108, 997, 931, 749.

1-Butoxy-3-chloro-2-propanol (Entry 5): Pale yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.98-3.95 (m, 1H), 3.67-3.46 (m, 6H), 2.60 (bs, 1H), 1.58-1.54 (m, 2H), 1.40-1.25 (m, 2H), 0.92 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ, 71.42, 71.18, 70.26, 45.99, 31.59, 19.22, 13.84; FT-IR (ν_{max}/cm^{-1}, neat) 3435, 2958, 2930, 2869, 1462, 1378, 1256, 1120, 843, 750.

1,3-Dichloro-2-propanol (Entry 6): Colourless to pale yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.08 (m, 1H), 3.71 (d, *J* = 5.1 Hz, 4H), 2.22 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 70.83, 45.73; FT-IR (ν_{max}/cm^{-1}, neat) 3450, 2928, 2854, 1463, 1377, 1242,731.

3-Chloro-2-hydroxypropyl methacrylate (Entry 7): Pale yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.16 (s, 1H), 5.64 (m, 1H), 4.31 (d, *J* = 5.1 Hz, 1H), 4.17-4.10 (m, 1H), 3.90 (d, *J* = 4.8 Hz, 1H), 3.78-3.60 (m, 2H), 2.12 (bs, 1H), 1.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.42, 135.70, 126.48, 69.71, 65.47, 46.05, 18.27; FT-IR (ν_{max}/cm^{-1}, neat) 3457, 2923, 2854, 1717, 1635, 1452, 1299, 1168, 1021, 947, 816, 754, 653.

1-Chloro-2-octanol (Entry 8): Colourless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.81-3.78 (m, 1H), 3.68-3.62 (m, 2H), 2.20 (bs, 1H), 1.74 (m, 1H), 1.53 (m, 1H), 1.43-1.26 (m, 8H), 0.88 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 71.47, 50.55, 34.27, 31.59, 29.33, 25.46, 22.66, 14.07; FT-IR (ν_{max}/cm^{-1}, neat) 3434, 2928, 1463,1637, 1078, 730.

2-Chlorocyclohexanol (Entry 9): Colourless to pale yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.69-3.48 (m, 1H), 3.54-3.48 (m, 1H), 2.88 (bs, 1H), 2.25-2.10 (m, 2H), 1.75-1.59 (m, 2H), 1.42-1.26 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 75.34, 67.50, 35.13, 33.09, 25.64, 23.95; FT-IR (ν_{max}/cm^{-1}, neat) 3445, 2922, 2853, 1540, 1461, 1396, 1244, 1088.

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