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Convenient Synthesis of Chlorohydrins from Epoxides Using Zinc Oxide: Application to 5,6-Epoxysitosterol

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ABSTRACT: *Efficient synthesis of protected and unprotected chlorohydrins has been achieved by ring opening of epoxides with acetyl/benzoyl chloride and TMSCl using a catalytic amount of ZnO as a reusable catalyst. The applicability of ZnO is further extended by performing the cleavage of the natural product 5,6-epoxysitosterol with acetyl chloride.* © 2009 Wiley Periodicals, Inc. Heteroatom Chem 20:157–163, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20529

INTRODUCTION

Chlorohydrins are useful intermediates for the synthesis of a range of biologically active natural and synthetic products, along with chiral auxiliaries for asymmetric synthesis [1]. Furthermore, protected halohydrins are most important intermediates in the total synthesis of natural products and in steroid chemistry [2,3]. Recently reported methodologies for the synthesis of chlorohydrins include cleavage of epoxide with hydrogen halides [3], lithium halides supported on silica gel [4], or with hydrohalogenic acids in the presence of a Lewis acid such as indium(III) bromide, phosphazirconocene, phosphaferrocene, $LiClO_4$, PVP/thionyl-chloride complex, $La(NO_3)_3{\cdot}6H_2O$ [5–10], and so on. Most of the mentioned procedures have disadvantages such as the use of large amounts of toxic reagents, long reaction time, and low yields. It is clearly evident that the need for the development of a new and flexible protocol is required. The surface of many metal oxides exhibits both Lewis acid and base characters, especially TiO_2, Al_2O_3, ZnO, Fe_2O_3, etc., and they are excellent adsorbents for a wide variety of organic compounds and they also increase the reactivity of the reactants [11]. ZnO is certainly one of the most interesting metal oxides, because it has surface properties, which suggests very rich organic chemistry [12–19]. In continuation of our studies on the preparation of ZnO and its applications in organic synthesis [20–22], we became interested in exploring further organic reactions catalyzed by ZnO. Herein, we wish to report the synthesis of protected and unprotected chlorohydrins by ring opening of epoxides with acetyl/benzoyl chloride and TMSCl, respectively, using a catalytic amount of commercially available ZnO as an efficient, reusable, and inexpensive heterogeneous catalyst.

RESULTS AND DISCUSSION

To find optimal conditions, the ring opening of glycidyl phenyl ether (Table 2, entry 2) was investigated as a model substrate with acetyl chloride under

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TABLE 1 Optimization of the Amount of ZnO for the Catalyzed Model Reaction

Entry	*Catalyst (mol%)*	*Solvent*	*Time (min)*	*Yields (%)*
1	No catalyst	CH_2Cl_2	300	30
2	ZnO (5%)	CH_2Cl_2	120	83
3	ZnO (10%)	CH_2Cl_2	30	90
4	ZnO (20%)	CH_2Cl_2	30	93
5	ZnO (10%)	Solvent-free	30	60
6	ZnO (10%)	CH_2Cl_2	30	73[a]

[a]Yield after recycling the catalyst three times.

different conditions at room temperature. In the absence of catalyst, the product was obtained in low yield even after a long time (Table 1, entry 1). However, good results were obtained in the presence of ZnO (Table 1, entries 2–4). Upon optimization of the amount of catalyst, we found that 10 mol% of ZnO could effectively catalyze the reaction to afford the desired product. Using more than 10 mol% ZnO did not have any effect on the yield and time of the reaction (Table 1, entry 4). Reaction in CH_2Cl_2 was clean, and the product was obtained without the formation of any by-products. A low yield of the desired product was observed in the absence of solvent (Table 1, entry 5). To check the efficiency of the recycled catalyst, glycidyl phenyl ether was subjected to the ring opening reaction using acetyl chloride and after three runs, the yield of corresponding protected chlorohydrin remained relatively high (Table 1, entry 6).

We then examined the substrate scope under the optimized reaction conditions. It was found that ZnO catalyzes the ring opening of both aromatic and aliphatic epoxides at high rates. As shown in Table 2, the corresponding protected chlorohydrins were obtained in excellent yields (87%–97%). The regioselectivity for the unsymmetrical epoxides is governed by both steric and electronic effects. High selectivity for nucleophilic attack at the less hindered carbon was observed. Styrene oxide showed a strong preference for the opposite regioselectivity to that observed in the aliphatic epoxides, suggesting electronic control in the ring opening [6]. In this case the reaction likely proceeds partly through the attack of nucleophile on the more stabilized "carbocation" with participation of the phenyl group.

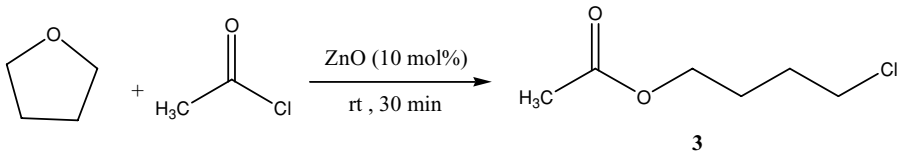
Mechanistically, it is conceivable that the reaction involves the initial formation of an acyl cation as in Friedel–Crafts reactions and then forms an acyl oxonium species with the epoxide. The acyl oxonium is attacked by the chloride leading to desired product.

Furthermore, ZnO was also an effective catalyst for the reaction of epoxides with TMSCl to provide the corresponding chlorohydrins in high yields (Table 3).

The applicability of ZnO was further extended by performing the cleavage of tetrahydrofuran with acetyl chloride. The reaction worked well, and the yield of product was satisfactory (Scheme 1).

The superiority of the present protocol can be seen by comparing our results with those reported in the literature, as shown in Table 4. The ring opening of styrene oxide with TMSCl was compared in terms of mol% of the catalyst, solvent, reaction time, yield, and regioselectivity. Some catalysts such as $LiCl/SiO_2$ (3 equiv/250 mg) and PVP/thionyl-chloride complex (190%) require high loading of catalyst, whereas only low amounts of ZnO are sufficient for our methodology. Most of the catalysts show low regioselectivity, but ZnO preceded ring opening with a high regioselectivity.

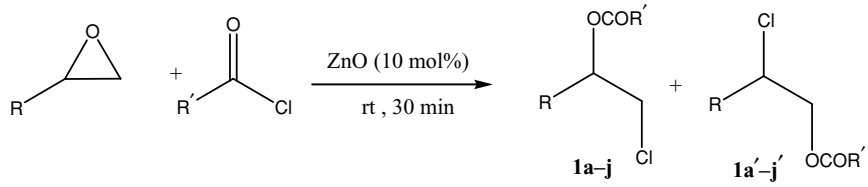
Many chlorine-containing natural products display potent antibiotic or cytotoxic properties. Therefore, it is worth to develop methods for the introduction of chlorine into organic natural compounds [23–25]. Encouraged by the results obtained with various epoxides, we turned our attention to β-sitosterol, a natural product that has been isolated from *Salvia sahendica* in our laboratory [26]. To the best of our knowledge, this is the first demonstration of

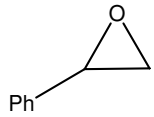
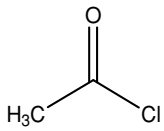
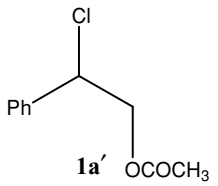
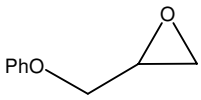
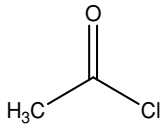
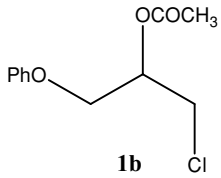
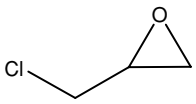
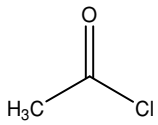
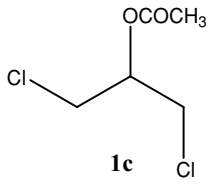
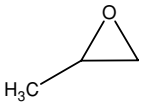
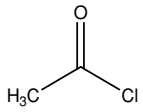
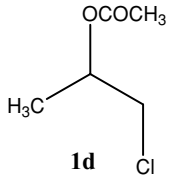
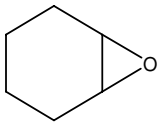
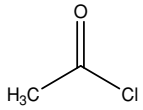
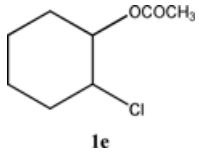
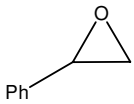
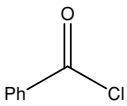
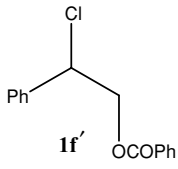
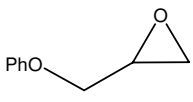
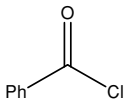
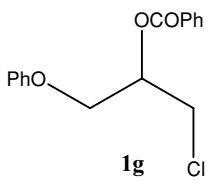


3

SCHEME 1 Cleavage of tetrahydrofuran with acetyl chloride.

TABLE 2 Synthesis of Protected Chlorohydrins Using ZnO as Catalyst



Entry	*Epoxide*	*Acyl Chloride*	*Product*	*Yield (%) Ratio[a]* **(1a–j:1a'–j')**
1				97 (00:100)
2				90 (67: 33)
3				92 (100:00)
4				89 (100:00)
5				87 (cis/trans: 0/100)
6				90 (00:100)
7				87 (83:27)

Continued

TABLE 2 Continued

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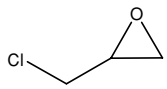
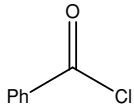
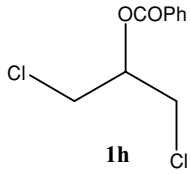
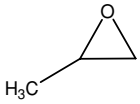
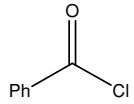
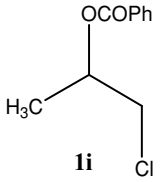
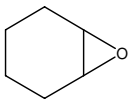
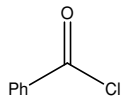
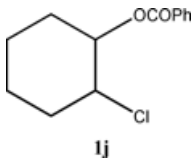
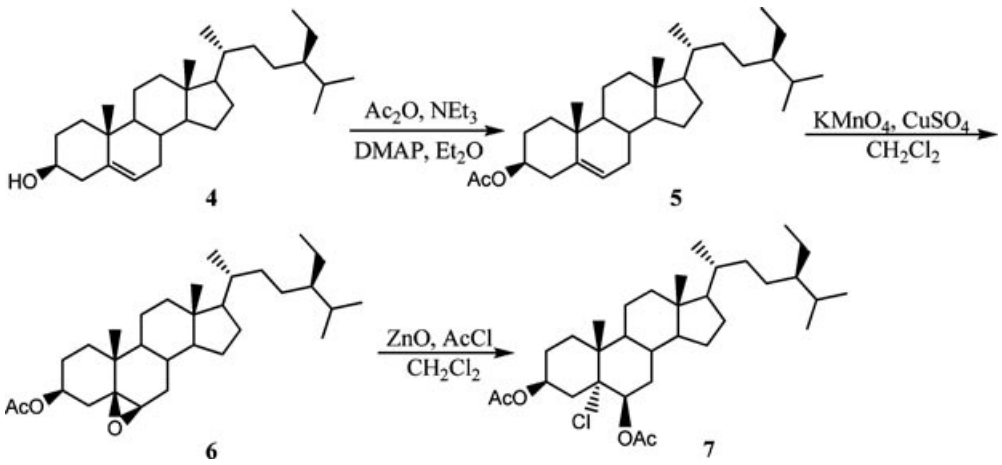
8			 **1h**	90 (100:00)
9			 **1i**	92 (100:00)
10			 **1j**	88 (cis/trans: 0/100)

[a]Ratio obtained from ^{1}H NMR measurement of the crude reaction mixture.

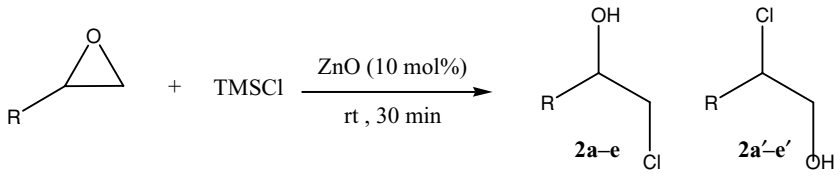
the ZnO-based ring opening of 5,6-epoxysitosterol, which was synthesized according to reported procedures for other steroids with epoxide moieties. The hydroxyl function of β-sitosterol was protected using acetic anhydride in the presence of catalytic amount of DMPA in Et_2O [27], followed by epoxidation with $KMnO_4/CuSO_4$ in CH_2Cl_2 to afford 5,6-epoxysitosterol (**6**) [28,29]. The ring opening of 5,6-epoxysitosterol with acetyl chloride in the presence of ZnO gave the corresponding chlorohydrin (**7**) in high yield (86%) (Scheme 2). The stereochemistry of compound **7** was determined in analogy with similar compounds [30,31].

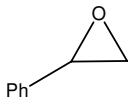
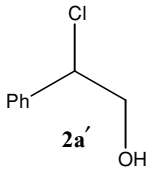
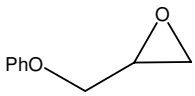
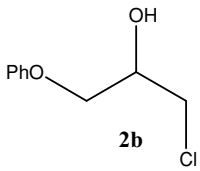
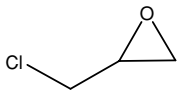
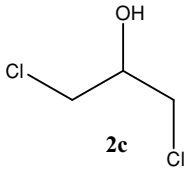
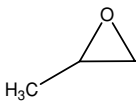
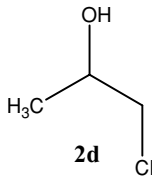
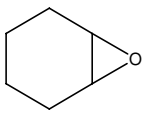
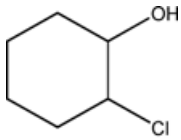
In summary, we have developed an efficient procedure for the synthesis of protected and unprotected chlorohydrin derivatives using ZnO as a reusable, nontoxic, noncorrosive, inexpensive, and commercially available heterogeneous catalyst. The method also offers some advantages such as clean reaction, low loading of catalyst, high yields of



SCHEME 2 Synthesis of chlorohydrin β-sitosterol.

TABLE 3 Synthesis of Chlorohydrins Using ZnO as Catalyst



Entry	*Epoxide*	*Product*	*Yield (%)*
1		 **2a′**	95
2		 **2b**	86[a]
3		 **2c**	89
4		 **2d**	85
5		 **2e**	90 (cis/trans: 0/100)

[a]Ratio of isomers = 71:29.

products, short reaction time, and applicability of various substrates.

EXPERIMENTAL

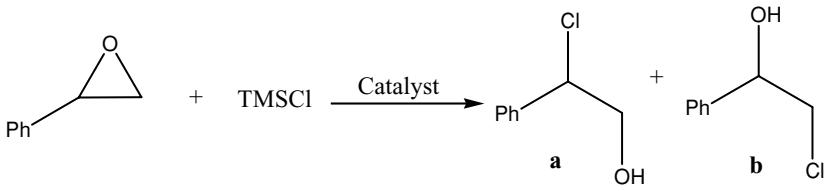
General

All chemicals were purchased from Fluka and Aldrich and were used without any further purification. NMR spectra were recorded at 500 MHz for proton and at 125 MHz for carbon nuclei in $CDCl_3$. The products were purified by column chromatography carried out on silica gel by using ethyl acetate/petroleum.

General Procedure for the Synthesis of Protected Chlorohydrins

To a stirred suspension of ZnO (10 mol%) in acetyl or benzoyl chloride (2 mmol) in CH_2Cl_2 (0.5 mL), an epoxide (2 mmol) was added. The reaction mixture was stirred at room temperature for 30 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was filtered and zinc oxide was recovered. (The recovered ZnO was dried at 100°C for 4 h before reusing.) The solvent was removed by a rotary evaporator to give the desired product. Further purification was carried out by short column chromatography on silica gel.

TABLE 4 Comparison of the Ring Opening of Styrene Oxide with Previously Reported Methods



Entry	*Catalyst (mol%)*	*Solvent*	*Time (h)*	*Yield* (**a**: **b**)
1	$LiCl/SiO_2$ (3 equiv/250 mg)	Solvent-free	5 days	80 (3.7: 1) [4]
2	PVP/thionyl-chloride complex (190%)	CH_2Cl_2	10 min	95 a [9]
3	Phosphaferrocene (5%)	CH_2Cl_2	6 min	88 (2.7: 1) [7]
4	$LiClO_4$ (10%)	MeOH	5	82 (7.3: 1) [8]
5	ZnO (10%)	CH_2Cl_2	30	95a

General Procedure for the Synthesis of Unprotected Chlorohydrins

To a stirred suspension of ZnO (10 mol%) and TMSCl (2 mmol) in CH_2Cl_2 (2 mL), an epoxide (2 mmol) was added. The reaction mixture was stirred at room temperature for 30 min. The progress of the reaction was monitored by TLC. After completion of the reaction, 1 mL of water was added to the mixture and the mixture was stirred for an additional 30 min. The organic layer was separated and dried with Na_2SO_4. The solvent was removed to give the desired product. Further purification was carried out by short column chromatography on silica gel. The structure of the products was confirmed by ^{1}H NMR, ^{13}C NMR spectra, and comparison with authentic samples prepared by other reported methods.

Representative Spectroscopic Data. 2-Chloro-2-phenylethyl acetate (**1a**′). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.32 (d, $J = 7.01$ Hz, 2H), 7.27–7.21 (m, 3H), 5.05 (q, $J = 6.21$ Hz, 1H), 4.42 (m, 2H), 2.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.47, 138.10, 129.32, 129.16, 127.81, 68.27, 59.92, 21.05.

2-Chloro-2-phenylethyl benzoate (**1f**). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.08 (d, $J = 8.44$ Hz, 2H), 7.53 (t, $J = 7.4$ Hz, 1H), 7.50 (d, $J = 6.96$, 2H), 7.43–733 (m, 5H), 5.27 (q, $J = 6.12$ Hz, 1H), 4.76–4.69 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 166.13, 138.28, 133.66, 130.27, 130.24, 129.44, 129.30, 128.92, 127.97, 68.76, 60.32.

2-Chloro-2-phenylethanol (**2a**′). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.44–7.34 (m, 5H), 4.97 (t, $J = 5.62$ Hz, 1H), 3.96–3.88 (m, 2H), 2.89 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 138.50, 129.14, 129.10, 127.93, 86.24, 65.03.

1,3-Dichloro-2-propanol (**2c**). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.07 (m, 1H), 3.68 (d, $J = 5.20$ Hz, 4H), 2.67 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 71.29, 46.18.

2-Chlorocyclohexanol (**2e**). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.71–3.46 (m, 2H), 2.88 (br s, 1H), 2.19–1.23 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 75.71, 67.70, 35.55, 33.57, 25.99, 24.34; 4-*Chlorobutyl acetate* (**3**).^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.08 (t, $J = 6.02$ Hz, 2H), 3.54 (t, $J = 6.02$ Hz, 2H), 2.02 (s, 3H), 1.84–1.60 (m, 4H).

6: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.68 (s, 3H, 18-CH_3), 0.85, 0.87 (2d, $J = 7.2$ Hz, each 3H, 26-CH_3 and 27-CH_3), 0.94 (d, $J = 6.2$ Hz, 21-CH_3), 1.04 (s, 3H, 19-CH_3), 2.07 (s, 3H, CH_3COO), 3.11 (m, 1H, 6α-H), 4.79–4.83 (tt, $J_1 = 10.4$ Hz and $J_2 = 5.1$ Hz, 1H, 3α-H).

7: Mp: 127–129°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.72 (s, 3H, 18-CH_3), 0.86, 0.87 (2d, $J = 6.8$ Hz, each 3H, 26-CH_3 and 27-CH_3), 0.96 (d, $J = 6.5$ Hz, 21-CH_3), 1.30 (s, 3H, 19-CH_3), 2.13 (s, 3H, CH_3COO), 2.14 (s, 3H, CH_3COO), 5.15 (m, 1H, 6α-H), 5.37–5.41 (tt, $J_1 = 10.6$ Hz and $J_2 = 5.5$ Hz, 1H, 3α-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 170.71, 170.09, 81.70, 75.95, 70.93, 56.37, 56.05, 46.27, 46.10, 43.11, 40.45, 40.09, 37.74, 36.57, 34.31, 33.44, 31.50, 31.23, 29.56, 28.62, 26.74, 26.43, 24.45, 23.48, 21.78, 21.75, 21.57, 20.23, 19.45, 19.13, 17.95, 12.63, 12.40; Anal Calcd for $C_{33}H_{55}ClO_4$: C, 71.90; H, 10.06. Found: C, 71.78, H, 10.13.

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