Regio- and Stereoselective Ring Opening of Epoxides and Aziridines Using Zirconyl Chloride: An Efficient Approach for the Synthesis of β-Chlorohydrins and β-Chloroamines

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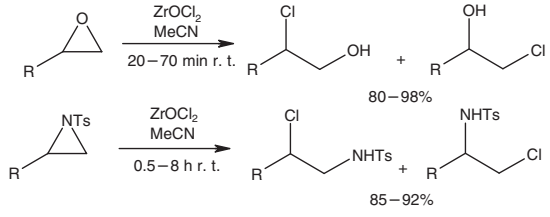
Zirconyl chloride mediated regio- and stereoselective ring opening of epoxides and aziridines at room temperature affords the corresponding β-chlorohydrins and β-chloroamines, respectively in high yields.

Ring opening of epoxides and aziridines with nucleophiles to prepare 1,2-difunctional molecules is an important transformation in organic synthesis.[2] With halide nucleophiles, they can be converted into vicinal halohydrins and haloamines which are useful precursors for the synthesis of halogenated natural products and other bioactive compounds.[3] The ring opening of epoxides to form halohydrins can be accomplished with halogens, hydrogen halides, and metal halides.[4] Additionally, some other chlorides, such as TMSCl,[5a,5b] $SOCl_2$,[5c] $SiCl_4$,[5d] Bu_4NCl, and NH_4Cl[5e] have been used for conversion of epoxides into β-chlorohydrins. Aziridine rings can also be cleaved with metal halides.[3b,4d,6] However, many of the earlier methods are associated with different disadvantages such as high temperature, unavailability of the reagents, unsatisfactory yields, and low regioselectivity. Hence, it is desirable to develop a convenient and efficient general method for the preparation of vicinal halohydrins and haloamines from epoxides and aziridines, respectively.

In recent years, Zr^{IV} salts have gained much attention as reagents and catalysts due to their interesting reactivity, easy availability, and low toxicity.[7] $ZrCl_4$ has already been utilized in various chemical transformations.[8] However, like other metal oxysalt-based organic reactions, zirconyl chloride ($ZrOCl_2$)-mediated synthetic transformations are limited.[9] The utilities of the reagent in organic syntheses are yet to be explored. In continuation of our work[8e,8f] on the applications of zirconium compounds for the development of useful synthetic methodologies, we have recently observed that $ZrOCl_2$ can efficiently be employed for ring opening of both epoxides and aziridines (Scheme 1).

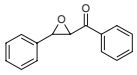
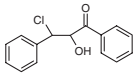
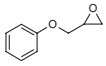
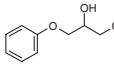
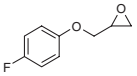
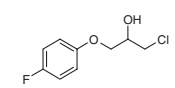
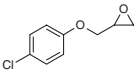
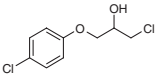
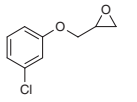
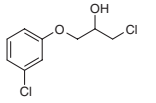
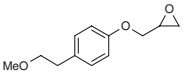
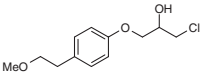
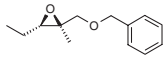
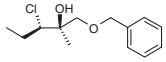
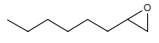
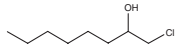
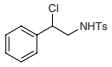
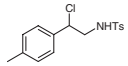
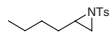
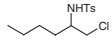
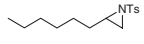
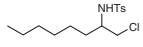
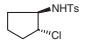
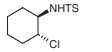
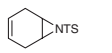
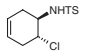
Several epoxides and *N*-tosyl aziridines were treated[10] with $ZrOCl_2$ at room temperature to prepare the corresponding β-chlorohydrins and β-chloroamines, respectively in high yields (Table 1). The epoxides were converted within short period but aziridines took somewhat longer times.

The ring opening of epoxides and aziridines with $ZrOCl_2$



Scheme 1.

Table 1. Ring opening of epoxides and aziridines with $ZrOCl_2$[a]

Entry	Epoxide/Aziridine **1**	Product **2**	Time /min	Isolated yield/%[b]
a			20	98
b			30	82
c			40	98
d			40	95
e			40	96
f			45	94
g			70	80
h			50	81
i			30	95
j			40	89
k			20	98
l			25	98
m			30	92
n			45	90
o			7.5[c]	83(7)
p			8[c]	80(6)
q			7[c]	88
r			7[c]	86
s			8[c]	85

[a]The structures of the products were established from their spectral (^{1}H NMR and MS) and analytical data. [b]Yield reported in parentheses is for other regioisomer. [c]The reaction time in h.

was found to occur with high regio- and stereoselectivity. 2-Arylepoxides and *N*-tosyl-2-arylaziridines formed the products by nucleophilic attack of the chloride ion at the benzylic position while 2-alkylepoxides and *N*-tosyl-2-alkylaziridines afforded the products by the attack at the terminal position. Only one regioisomer was obtained by ring opening of chalcone oxide (Table 1, Entry b) under the present experimental conditions. Previously, the same reaction using other catalysts provided both the regioisomers of the corresponding β-chlorohydrins.[4d,5a] Thus, the present method employing $ZrOCl_2$ is more advantageous to the earlier related methods. However, in the case of *N*-tosyl-2-alkylaziridines minor amounts of other regioisomers were also obtained. The ring opening of bicyclic epoxides and *N*-tosyl aziridines yielded the corresponding β-chlorohydrins and β-chloroamines, respectively with trans-configuration. The structures and stereochemistry of the products were characterized from their analytical and spectral (^{1}H NMR and MS) data.[10]

In conclusion, $ZrOCl_2$ has efficiently been utilized for the first time for regio- and stereoselective ring opening of epoxides and aziridines at room temperature to produce the corresponding 2-chlorohydrins and 2-chloroamines, respectively in high yields.

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References and Notes

1 Part 97 in the series "Studies on novel synthetic methodologies." IICT Communication No. 061117.

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10 **General experimental procedure**: To a solution of an epoxide or *N*-tosylaziridine (1 mmol) in MeCN (5 mL) $ZrOCl_2$ (1.2 mmol) was added and the mixture was stirred at room temperature. After completion of the reaction (TLC) the mixture was diluted with EtOAc (10 mL) followed by washing with brine (20 mL) and water (2 × 10 mL). The organic portion was dried and concentrated. The crude material was purified by column chromatography (silica gel, hexane–EtOAc) to furnish pure β-chlorohydrin or *N*-tosyl-β-chloroamine. The spectral (IR, ^{1}H NMR and MS) and analytical data of some representative products are given below.

Product **2a**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.40–7.28 (5H, m), 4.89 (1H, t, $J = 7.0$ Hz), 3.88–3.76 (2H, m), 2.83 (1H, brs); FABMS: m/z 159, 157 $[M + H]^{+\bullet}$; Anal. Calcd for C_8H_9ClO: C, 61.34; H, 5.75%. Found: C, 61.46; H, 5.64%.

Product **2g**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.09 (2H, d, $J = 8.0$ Hz), 6.80 (2H, d, $J = 8.0$ Hz), 4.12 (1H, m), 4.05–3.98 (2H, m), 3.79–3.62 (2H, m), 3.51 (2H, t, $J = 7.0$ Hz), 3.31 (3H, s), 2.75 (2H, t, $J = 7.0$ Hz), 2.72 (1H, brs); FABMS: m/z 247, 245 $[M + H]^{+\bullet}$; Anal. Calcd for $C_{12}H_{17}ClO_3$: C, 58.90; H, 6.95%. Found: C, 58.82; H, 6.91%.

Product **2h**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.33–7.21 (5H, m), 4.54 (2H, s), 3.81 (1H, dd, $J = 11.0$, 2.0 Hz), 3.70 (1H, d, $J = 9.0$ Hz), 3.29 (1H, d, $J = 9.0$ Hz), 2.50 (1H, brs), 2.12 (1H, m), 1.51 (1H, m), 1.16 (3H, s), 1.08 (3H, d, $J = 7.0$ Hz); FABMS: m/z 245, 243 $[M + H]^{+\bullet}$; Anal. Calcd for $C_{13}H_{19}ClO_2$: C, 64.33; H, 7.83; Cl, 14.64%. Found: C, 64.38; H, 7.79; Cl, 14.69%.

Product **2l**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.68 (1H, ddd, $J =$ 9.8, 9.1, 3.8 Hz), 3.46 (1H, ddd, $J = 9.5$, 9.1, 3.8 Hz), 2.51 (1H, brs), 2.30–2.06 (2H, m), 1.85–1.52 (4H, m), 1.41–1.22 (2H, m); FABMS: m/z 137, 135 $[M + H]^{+\bullet}$; Anal. Calcd for $C_6H_{11}ClO$: C, 53.53; H, 8.18%. Found: C, 53.46; H, 8.24%.

Product **2m**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.73 (2H, d, $J =$ 8.0 Hz), 7.39–7.25 (7H, m), 4.92 (1H, t, $J = 7.0$ Hz), 4.87 (1H, t, $J = 7.0$ Hz), 3.48–3.34 (2H, m), 2.45 (3H, s); FABMS: m/z 312, 310 $[M + H]^{+\bullet}$; Anal. Calcd for $C_{15}H_{16}ClNO_2S$: C, 58.16; H, 5.17; N, 4.52%. Found: C, 58.28; H, 5.24; N, 4.45%.

Product **2o**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.75 (2H, d, $J =$ 8.0 Hz), 7.24 (2H, d, $J = 8.0$ Hz), 5.32 (1H, d, $J = 6.0$ Hz), 3.48–3.33 (2H, m), 3.20 (1H, m), 2.39 (3H, s), 1.52–1.30 (2H, m), 1.22–1.01 (4H, m), 0.82 (3H, t, $J = 7.0$ Hz); FABMS: m/z 292, 290 $[M + H]^{+\bullet}$; Anal. Calcd for $C_{13}H_{20}ClNO_2S$: C, 53.89; H, 6.91; N, 4.84%. Found: C, 53.94; H, 6.95; N, 4.81%.

Product **2r**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.82 (2H, d, $J = 8.0$ Hz), 7.31 (2H, d, $J = 8.0$ Hz), 5.85 (1H, d, $J = 6.0$ Hz), 4.05 (1H, ddd, $J = 9.5$, 9.0, 3.7 Hz), 3.54 (1H, m), 2.42 (3H, s), 2.22–2.01 (2H, m), 1.85–1.69 (2H, m), 1.63–1.32 (4H, m); FABMS: m/z 290, 288 $[M + H]^{+\bullet}$; Anal. Calcd for $C_{13}H_{18}ClNO_2S$: C, 54.26; H, 6.26; N, 4.87%. Found: C, 54.38; H, 6.32; N, 4.81%.

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