Regio- and Stereoselective Reaction of α-Epoxyketones with $AlCl_3$: An Efficient Approach for the Synthesis of Functionalized β-Chlorohydrines

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A simple and efficient synthesis of functionalized β-chlorohydrins is described from the regio- and stereoselective reaction of α-epoxyketones with $AlCl_3$ in acetonitrile at room temperature.

Keywords: α-Epoxyketones; Chalcone oxides; β-Chlorohydrins; Stereoselective reaction; Ring opening reaction.

INTRODUCTION

Epoxides are versatile intermediates in a broad variety of syntheses and special attentions have been focused on their reactions. Their meaningful utilization depends on the availability of stereo- and regioselective Lewis acid catalyzed ring opening reactions with nucleophiles such as the regioselective formation of amino- and azido alcohols and β-halohydrins.[1] The vicinal halohyrins are useful synthetic intermediates and have found wide applications in organic transformations[2] and in the synthesis of marine natural products.[3] The β-chlorohydrins preparation by direct reaction of an epoxide with a metal chloride has been reported.[4] However, only in few of these reports the concerted improvement is observed in all of the characteristic features of the reaction. For example, $CeCl_3$ in acetonitrile failed to give any product at room temperature.[4d] Furthermore, the unsymmetrical 1,2-disubstituted epoxides such as α-epoxyketones have been rarely tested and both of the regio- and stereoselectivity of the reactions have not been satisfactorily observed concertedly.[4a,4c,4d,4i,4j] Therefore, as there is a continued interest in the selective ring opening of epoxides to give β-halohydrins, it is important to use suitable reagents or effective methodology to synthesize these compounds or to modify the reactions.

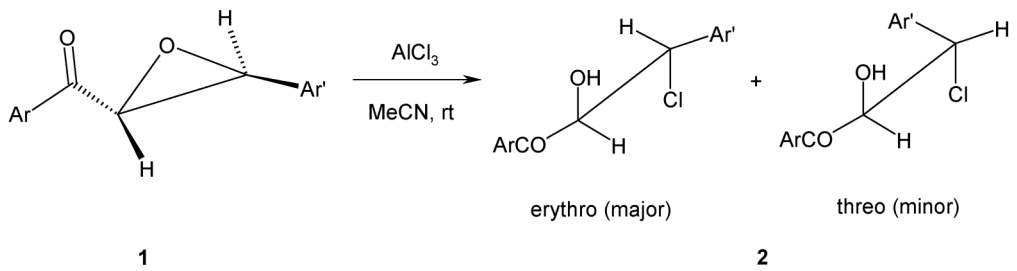
RESULTS AND DISCUSSION

Here, we report the regio- and stereoselective formation of functionalized β-chlorohydrins **2** from the reaction of chalcone oxides **1** with $AlCl_3$ in MeCN at room temperature (Scheme I). The procedure is simple and the reaction conditions are mild. Good product yields obtain with good to high stereoselectivity (with the exception of **2g**) in short reaction times. Results are summarized in Table 1.

The stereochemistry of the major products was identified as *erythro*. The *erythro*-configuration of these β-chlorohydrines is more stable than the *threo*.[5] Also, based on our previous investigation on the acetolysis of α-epoxyketones **1**,[6] in the *erythro*-configuration, the C_α-H and C_β-H (especially C_α-H) appear in lower field in ^{1}H NMR, in comparison with those in *threo*-orientation, because of the anisotropic effect of C_α-aroyl and C_β-aryl groups; furthermore, the coupling-constants of $H_\alpha H_\beta$ in the *erythro*-configurations are larger than of those in the *threo* (Fig. 1).

Although we made no attempts to characterize the produced organoaluminum intermediates in the reactions, the proposed mechanism is shown in Scheme II. It is rea-

Scheme I



1 **2**

Table 1. Reaction of the α-epoxyketones **1a-1h** with $AlCl_3$ in MeCN at room temperature

	Ar	Ar′	Time/min	Conversion/%[a]	Yield **2**/%[b]	Ratio/%[c]	
						erythro	*threo*
a	Ph	Ph	30	100	75	86	14
b	4-MePh	Ph	20	90	79	100	-
c	4-MePh	4-MePh	15	95	83	63	37
d	4-ClPh	Ph	20	100	83	100	-
e	4-MeOPh	Ph	15	100	80	100	-
f	Ph	2-MeOPh	10	100	75	92	8
g	Ph	4-MeOPh	10	100	84	49	51
h	Ph	3-NO_2Ph	45	70	60	100	-

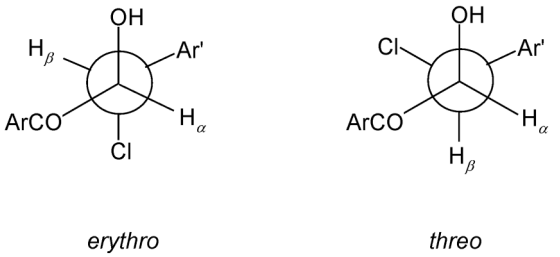
[a] Based on consumed α-epoxyketones.
[b] Isolated yield based on consumed α-epoxyketones.
[c] Estimated from ^{1}H NMR.

sonable to assume that **2** results from an initial acid-base reaction of $AlCl_3$ with α-epoxyketones **1** and subsequent ring opening of the intermediate **3** through the transition state **4** or the intermediate **6**. Nucleophilic attack of the chloride anion to the C_β of **4** with inversion of configuration following with hydrolysis of the intermediate **5** under the reaction conditions employed leads to the *erythro*-configuration **2**. However, Nucleophilic attack of the chloride anion to the C_β of **6** may leads to the equal ratio of *erythro* and *threo*-configuration. This is observed in the case of **2g** in which the very strong electron-donating group in *para*-position stabilizes the benzyl carbocation and eliminates the stereoselectivity. Since the observed stereoisomers of the products have more *erythro*-configuration (with the exception of **2g**), the transition state **4** is more probable for progression of the reaction.

Acetonitrile seems to be the solvent of choice since **1** did not react with $AlCl_3$ in $CHCl_3$, CH_2Cl_2, toluene, *DMF* or in solvent free conditions.

CONCLUSION

In conclusion, $AlC1_3$ in acetonitrile can be a convenient reagent for regio- and stereoselective synthesizing of the functionalized β-chlorohydrins **2** from α-epoxyketones **1**. In comparison to the previous reports, significant improvements are observed in the reaction times and the regio- and stereoselectivy of the reaction.



erythro *threo*

Fig. 1

EXPERIMENTAL

Melting points were measured with an Electrothermal 9100 apparatus. IR spectra were measured with a Shimadzu IR-460 spectrometer. NMR spectra were recorded with a Bruker DRX-250 AVANCE instrument (250.1 MHz for ^{1}H and 62.9 MHz for ^{13}C). Chemical shifts are given in ppm (δ) relative to internal *TMS*, and coupling constants *J* are reported in Hz. Mass spectra were recorded with a Finnigan-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. The synthesis of the α-epoxyketones was achieved by using the published methods.[7]

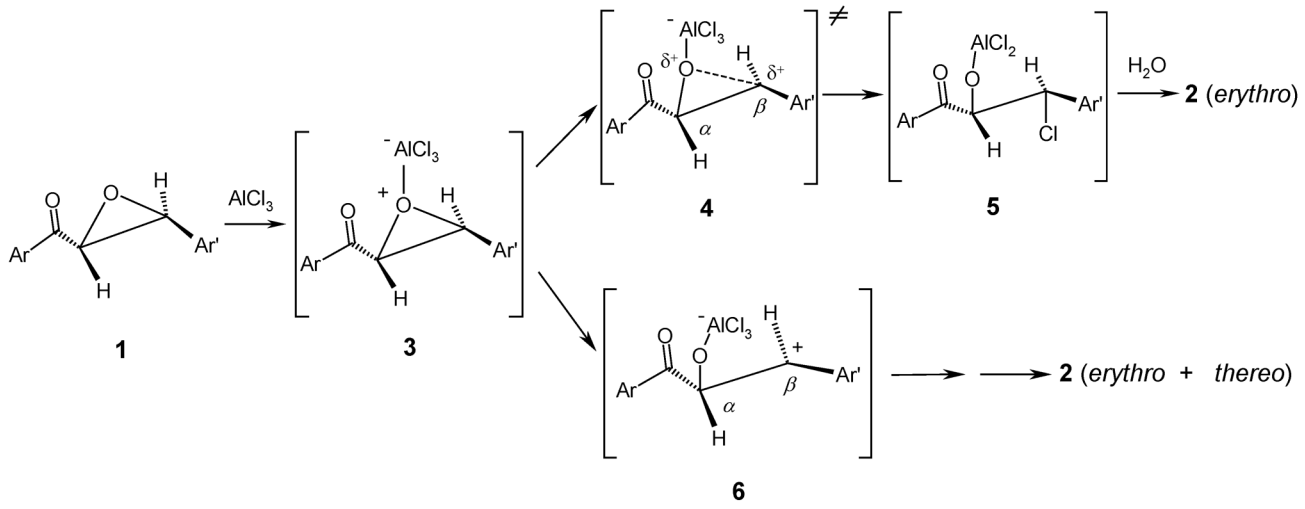
General reaction procedure

In a 10 mL round bottom flask, 1 mmol of α-epoxyketones **1a-1h** was dissolved in 2 mL of MeCN. To this solution, 0.133 g (1 mmol) of anhydrous $AlCl_3$ was added and the mixture was stirred for the times as indicated in Table 1. Then, the solvent was removed under reduced pressure and the residue was washed with cold water. The products were separated and purified by thin-layer chromatography on 20 × 20 plates of silicagel 60 GF_{254} with *n*-hexane/EtOAc as eluent.

3-Chloro-2-hydroxy-1,3-diphenylpropanone (2a)

Mp 88-90 °C (Ref. [4j] 90 °C).

Scheme II



3-Chloro-2-hydroxy-1-(4-methylphenyl)-3-phenylpropanone (2b)

Mp 78-80 °C. IR (KBr): $\bar{\nu}$ = 3445 (OH), 1672 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 7.77 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar-H), 7.31 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar-H), 7.28-7.15 (m, 5H, Ar-H), 5.53 (dd, $^3J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 3.5 Hz, 1H, C_α-H), 5.28 (d, $^3J_{HH}$ = 3.5 Hz, 1H, C_β-H), 3.72 (d, $^3J_{HH}$ = 7.5 Hz, 1H, OH), 2.46 (s, 3H, CH_3) ppm; ^{13}C NMR (69.2 MHz, $CDCl_3$): δ = 197.0, 145.7, 135.5, 131.6, 129.8, 128.8, 128.2, 128.1, 128.0, 76.8, 63.4, 21.9 ppm; MS (EI): *m*/*z* (%) = 275 ($M^{+\cdot}$, 5), 239 (9), 224 (10), 223 (8), 208 (19), 105 (100), 77 (62); Anal. Calcd. for $C_{16}H_{15}ClO_2$ (274.75): C, 69.95; H, 5.50. Found: C, 69.91; H, 5.52%.

3-Chloro-2-hydroxy-1,3-bis(4-methylphenyl)propanone (mixture of *erythro*- and *threo*-2c)

Mp 99-101 °C. IR (KBr): $\bar{\nu}$ = 3360 (OH), 1680, 1661 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 7.83 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar-H), 7.79 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar-H), 7.45 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar-H), 7.36 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar-H), 7.32 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar-H), 7.19 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar-H), 7.05 (m, 4H, Ar-H), 5.51 (d, $^3J_{HH}$ = 3.5 Hz, 1H, C_α-H *erythro*), 5.36 (d, $^3J_{HH}$ = 1.7 Hz, 1H, C_α-H *threo*), 5.25 (d, $^3J_{HH}$ = 3.5 Hz, 1H, C_β-H *erythro*), 5.23 (d, $^3J_{HH}$ = 1.7 Hz, 1H, C_β-H *threo*), 4.15 (bs, 1H, OH), 3.70 (bs, 1H, OH), 2.47 (s, 6H, $2CH_3$), 2.36 (s, 3H, CH_3), 2.31 (s, 3H, CH_3) ppm; ^{13}C NMR (69.2 MHz, $CDCl_3$): δ = 197.2, 197.0, 145.7, 145.5, 138.8, 135.4, 132.5, 131.6, 130.9, 129.8 (2C), 129.3, 129.2, 128.9 (2C), 128.7, 127.9, 127.8, 76.9, 76.5, 63.9, 63.2, 21.8 (2C), 21.2 (2C) ppm; MS (EI): *m*/*z* (%) = 291 [($M^{+\cdot}$ + 2), 4], 289 ($M^{+\cdot}$, 10), 270 (2), 252 (1), 149 (12), 139 (55), 119 (100), 105 (25), 91 (34); Anal. Calcd. for $C_{17}H_{17}ClO_2$ (288.77): C, 70.71; H, 5.93. Found: C, 70.68; H, 5.90%.

3-Chloro-1-(4-chlorophenyl)-2-hydroxy-3-phenylpropanone (2d)

Mp 88-90 °C. IR (KBr): $\bar{\nu}$ = 3450 (OH), 1681 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 7.79 (d, $^3J_{HH}$ = 7.8 Hz, 2H, Ar-H), 7.46 (d, $^3J_{HH}$ = 7.8 Hz, 2H, Ar-H), 7.32-7.18 (m, 5H, Ar-H), 5.47 (d, $^3J_{HH}$ = 4.0 Hz, 1H, C_α-H), 5.24 (d, $^3J_{HH}$ = 4.0 Hz, 1H, C_β-H), 3.62 (bs, 1H, OH) ppm; ^{13}C NMR (69.2 MHz, $CDCl_3$): δ = 196.6, 141.0, 135.5, 132.7, 130.1, 129.4, 129.0, 128.3, 128.0, 76.7, 63.2 ppm; MS (EI): *m*/*z* (%) = 299 [($M^{+\cdot}$ + 4), 3], 297 [($M^{+\cdot}$ + 2), 10], 295 ($M^{+\cdot}$, 15), 276 (2), 260 (1), 258 (3), 139 (100), 125 (96), 120 (76), 91 (50); Anal. Calcd. for $C_{15}H_{12}Cl_2O_2$ (295.16): C, 61.04; H, 4.10. Found: C, 60.98; H, 4.08%.

3-Chloro-2-hydroxy-1-(4-methoxyphenyl)-3-phenylpropanone (2e)

Mp 108-110 °C. IR (KBr): $\bar{\nu}$ = 3435 (OH), 1667 (CO) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ = 7.86 (d, $^3J_{HH}$ = 6.7 Hz, 2H, Ar-H), 7.28-7.23 (m, 3H, Ar-H), 7.21-7.18 (m, 2H, Ar-H), 6.99 (d, $^3J_{HH}$ = 6.7 Hz, 2H, Ar-H), 5.50 (d, $^3J_{HH}$ = 3.7 Hz, 1H, C_α-H), 5.27 (d, $^3J_{HH}$ = 3.7 Hz, 1H, C_β-H), 3.89 (s, 3H, OCH_3), 3.86 (bs, 1H, OH) ppm; ^{13}C NMR (69.2 MHz, $CDCl_3$): δ = 195.6, 164.6, 135.6, 131.2, 128.9, 128.2, 128.1, 126.9, 114.3, 76.8, 63.5, 55.6 ppm; MS (EI): *m*/*z* (%) = 291 ($M^{+\cdot}$, 1), 272 (1), 254 (4), 165 (18), 135 (100), 120 (35), 107 (17), 92 (24); Anal. Calcd. for $C_{16}H_{15}ClO_3$ (290.75): C, 66.10; H, 5.20. Found: C, 66.01; H, 5.18%.

3-Chloro-2-hydroxy-3-(2-methoxyphenyl)-1-phenylpropanone (mixture of *erythro*- and *threo*-2f)

IR (Liquid film): $\bar{\nu}$ = 3435 (OH), 1667 (CO) cm^{-1}; ^1H

NMR (250 MHz, $CDCl_3$): δ = 8.12 (d, $^3J_{HH}$ = 7.5 Hz, 2H, Ar-H), 8.04 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar-H), 7.93 (d, $^3J_{HH}$ = 7.7 Hz, 1H, Ar-H), 7.84 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar-H), 7.72 (d, $^3J_{HH}$ = 8.0 Hz, 2H, Ar-H), 7.66 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar-H), 7.59 (d, $^3J_{HH}$ = 7.7 Hz, 2H, Ar-H), 7.56 (d, $^3J_{HH}$ = 7.5 Hz, 1H, Ar-H), 7.49 (d, $^3J_{HH}$ = 7.5 Hz, 1H, Ar-H), 7.34 (dd, $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 8.0 Hz, 2H, Ar-H), 7.08 (d, $^3J_{HH}$ = 7.5 Hz, 1H, Ar-H), 7.04 (d, $^3J_{HH}$ = 7.7 Hz, 1H, Ar-H), 6.92 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar-H), 6.76 (d, $^3J_{HH}$ = 8.0 Hz, 1H, Ar-H), 5.91 (d, $^3J_{HH}$ = 2.7 Hz, 1H, C_α-H *erythro*), 5.85 (s, 1H, C_α-H *threo*), 5.62 (d, $^3J_{HH}$ = 2.7 Hz, 1H, C_β-H *erythro*), 5.46 (s, 1H, C_β-H *threo*), 4.08 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 3.57 (s, 1H, OH), 3.39 (s, 1H, OH) ppm; ^{13}C NMR (69.2 MHz, $CDCl_3$): δ = 197.8, 155.0, 134.0, 133.3, 129.8, 129.5, 128.9, 128.8, 125.9, 121.0, 109.9, 74.7, 59.0, 55.6 ppm; MS (EI): *m*/*z* (%) = 293 [($M^{+\cdot}$ + 2), 5], 291 ($M^{+\cdot}$, 2), 272 (3), 254 (5), 165 (32), 135 (33), 107 (39), 105 (100), 77 (55); Anal. Calcd. for $C_{16}H_{15}ClO_3$ (290.75): C, 66.10; H, 5.20. Found: C, 66.03; H, 5.22%.

3-Chloro-2-hydroxy-3-(4-methoxyphenyl)-1-phenylpropanone (mixture of *erythro*- and *threo*-2g)

IR (Liquid film): $\bar{\nu}$ = 3455 (OH), 1681 (CO) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.91 (d, $^3J_{HH}$ = 7.7 Hz, 2H, Ar-H), 7.93 (d, $^3J_{HH}$ = 7.5 Hz, 2H, Ar-H), 7.83 (d, $^3J_{HH}$ = 8.5 Hz, 2H, Ar-H), 7.60-7.43 (m, 5H, Ar-H), 7.07 (d, $^3J_{HH}$ = 8.7 Hz, 2H, Ar-H), 6.99 (d, $^3J_{HH}$ = 8.5 Hz, 2H, Ar-H), 6.87-6.72 (m, 3H, Ar-H), 5.31 (d, $^3J_{HH}$ = 4.5 Hz, 1H, C_α-H *erythro*), 5.13 (d, $^3J_{HH}$ = 3.0 Hz, 1H, C_α-H *threo*), 4.62 (d, $^3J_{HH}$ = 3.0 Hz, 1H, C_β-H *threo*), 4.49 (d, $^3J_{HH}$ = 4.5 Hz, 1H, C_β-H *erythro*), 4.14 (bs, 1H, OH), 3.86 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.61 (bs, 1H, OH) ppm; ^{13}C NMR (69.2 MHz, $CDCl_3$): δ = 192.6, 192.1, 169.5, 158.5, 133.4, 133.0, 132.0, 130.1, 128.8, 128.6, 128.5 (2CH), 128.3, 128.2, 116.1, 114.3, 113.7, 113.6, 76.6, 76.5, 65.1 (2CH), 55.6, 55.5 ppm; MS (EI): *m*/*z* (%) = 291 ($M^{+\cdot}$, 2), 272 (3), 254 (7), 165 (18), 135 (27), 107 (35), 105 (100), 77 (64); Anal. Calcd. for $C_{16}H_{15}ClO_3$ (290.75): C, 66.10; H, 5.20. Found: C, 66.11; H, 5.17%.

3-Chloro-2-hydroxy-3-(3-nitrophenyl)-1-phenylpropanone (2h)

IR (Liquid film): $\bar{\nu}$ = 3450 (OH), 1681 (CO), 1526, 1347 (NO_2) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.14 (d, $^3J_{HH}$ = 7.7 Hz, 1H, Ar-H), 7.99 (s, 1H, Ar-H), 7.57 (d, $^3J_{HH}$ = 7.7 Hz, 2H, Ar-H), 7.70 (2d, $^3J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 7.2 Hz, 1H, Ar-H), 7.58-7.43 (m, 4H, Ar-H), 5.57 (d, $^3J_{HH}$ = 2.5 Hz, 1H, C_α-H), 5.32 (d, $^3J_{HH}$ = 2.5 Hz, 1H, C_β-H), 3.83 (bs, 1H, OH) ppm; ^{13}C NMR (69.2 MHz, $CDCl_3$): δ = 197.3, 147.8, 137.7, 134.9, 134.2, 133.9, 129.4, 129.2, 128.7, 123.8, 123.2, 76.8, 61.7 ppm; MS (EI): *m*/*z* (%) = 308 [($M^{+\cdot}$ + 2), 67], 306 ($M^{+\cdot}$, 25), 272 (1), 254 (4), 165 (18), 135 (22), 105 (100), 77 (55); Anal. Calcd. for $C_{15}H_{12}ClNO_4$ (305.72): C, 58.93; H, 3.96; N, 4.58. Found: C, 58.89; H, 4.00; N, 4.56%.

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