Nucleophilic Addition Reaction of Aromatic Compounds in the Presence of Lewis Acid

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Abstract: The epoxide **1** obtained by the Darzens condensation reaction of aldehydes with methyl dichloroacetate, reacted with aromatic compounds in the presence of aluminium chloride to afford α -aryl- -chloro- α -hydroxyalkanoate **3**. Scope and limitation of this reaction were studied for various aldehydes and aromatic compounds. The reaction was also studied in the presence of aluminium chloride supported on alumina or silica gel, which is thought to be a mild Lewis acid and harmless for the environment.

Key words: Darzens condensation, Lewis acid, nucleophilic addition, epoxide, aromatic compound

Friedel–Crafts reaction is one of the most typical organic reaction.¹ Concerning the reaction of epoxides with aromatic compounds in the presence of Lewis acid, some reactions using only simple epoxides are reported.² In our laboratory, we have studied Darzens condensation continuously for more than twenty years. By Darzens condensation, aldehydes react with methyl dichloroacetate in the presence of potassium *tert*-butoxide at -78 °Cto give α chloro- α ,-epoxyalkanoates **1**, which can be rearranged to afford isomerization products 2. Using the product obtained by Darzens condensation, we have carried out various reactions. As a link of this study, we examined the reaction of α -chloro- α , β -epoxyalkanoates **1** with aromatic compounds in the presence of Lewis acid (Scheme). Interestingly, this reaction didn't give Friedel-Crafts reaction products, but a nucleophilic addition product of aromatic compounds to 1, α -aryl- β -chloro- α -hydroxyalkanoate 3. Lewis acid-promoted addition reaction of aromatic compounds to α -chloroglycidates **1** to give alcohol **3** has never been reported. Here, we report the results about this reaction. In 1974, Coutrot et al. has obtained compound **3** by the addition of organomagnesium compounds to β chloro- α -ketoesters.³

 α -Chloro-, -epoxyalkanoates **1** were prepared in good yields by Darzens condensation of aldehydes with methyl dichloroacetate in the presence of potassium tert-butoxide at -78 °C. Then, the reaction of α -chloro- α , -epoxyalkanoates 1 with aromatic compounds in the presence of AlCl₃ was carried out. The results are shown in Table 1. α -Aryl- -chloro- α -hydroxyalkanoates **3** were obtained in a yield of 19.1–87.4%. The main product was syn type. The structure of syn-3 was confirmed by single-crystal Xray analysis of syn-3d ($R_1 = i$ -Pr, $R_2 = CH_3$). ORTEP drawing in Figure 1 illustrates the geometrical aspect of the molecule⁶ and explains the chemical structure reasonably. When the substitution group R_1 became long, this reaction was more active, and the product yield became high. The activity of aromatic compounds became high in the following order: benzene< toluene< ethylbenzene< nbutylbenzene. Moreover, we tried other aromatic compounds (Table 2). In the case of naphthalene, the addition products were obtained in a good yield of 47-84% (entries 1-5). But, in the case of anthracene or N,N-dimethylaniline, the addition product was obtained in a low yield of 31–35% (entries 6 and 8). On the other hand, the reaction



Scheme

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Table 1 The Reactions of 2-Chloro-2,3-epoxyalkanoates with Aromatic Compounds in the Presence of Lewis Acid.

ОΗ

H,,,, R ¹	CO ₂ Me R ²	Lewis acid	$CO_2Me + R + CI + CI + R^2$ anti-3 anti-3	CO ₂ Me		
Entry	R ₁	R ₂	Lewis acid	Conditions	Yield	syn/anti
1	(CH ₃) ₂ CH-	Н	AlCl ₃ (3 equiv)	r.t., 1 h; 50 °C, 1 h	3a , 19.1%	79:21
2	CH ₃ (CH ₂) ₂ -	Н	AlCl ₃ (3 equiv)	r.t., 1 h	3b , 53.3%	74:26
3	CH ₃ (CH ₂) ₆ -	Н	AlCl ₃ (3 equiv)	r.t., 1 h	3c , 68.7%	79:21
4	(CH ₃) ₂ CH-	CH ₃ -	AlCl ₃ (3 equiv)	r.t., 50 min	3d , 55.9%	79:21
5	(CH ₃) ₂ CH-	CH ₃ -	AlCl ₃ (5 equiv)	r.t., 50 min	3d , 50.5%	79:21
6	(CH ₃) ₂ CH-	CH ₃ -	AlCl ₃ (10 equiv)	r.t., 40 min	3d , 42.1%	78:22
7	CH ₃ (CH ₂) ₂ -	CH ₃ -	AlCl ₃ (3 equiv)	r.t., 50 min	3e , 57.9%	79:21
8	CH ₃ (CH ₂) ₄ -	CH ₃ CH ₂ -	AlCl ₃ (3 equiv)	r.t., 50 min	3f , 63.6%	81:19
9	CH ₃ (CH ₂) ₈ -	CH ₃ (CH ₂) ₃ -	AlCl ₃ (3 equiv)	r.t., 50 min	3g , 87. %	77:23
10	(CH ₃) ₂ CH	Н	TiCl ₄ (3 equiv)	50 °C, 2 h	3a , 8.8%; 2a , 47.2%	79:21
11	CH ₃ (CH ₂) ₂ -	CH ₃ -	TiCl ₄ (3 equiv)	50 °C, 2 h	3e ,13.0%; 2e , 51.1%	80:20
12	CH ₃ (CH ₂) ₂ -	Н	FeCl ₃ (3 equiv)	r.t., 2 h	3b , 9.0%; 2b , 53.4%	79:21
13	(CH ₃) ₂ CH-	CH ₃ -	FeCl ₃ (3 equiv)	r.t., 2 h	3d ,14.4%; 2d , 52.3%	79:21

QН

of aniline or phenol gave the addition product only in a poor yield of 15-18% (entries 7 and 9). In the case of bromobenzene or nitrobenzene, the reaction gave no product. Besides these, we investigated how the stoichiometry of AlCl₃ influences the reaction. Using 3 equiv, 5 equiv or 10 equiv of AlCl₃ we carried this reaction and found that increasing the relative amounts of AlCl₃ afforded the product in a lower yield, and had no influence on the stereoselectivity (Table 1, entries 4–6). So, using 3 equiv of AlCl₃ was best.



Figure 1 ORTEP drawing of syn-3d⁶

In order to look for better Lewis acid, we examined the reaction in the presence of TiCl₄ or FeCl₃ instead of AlCl₃. But we got unsatisfactory results, and the addition product was obtained only in 9-14% yield. The isomerization prevailed in such case to give $-chloro-\alpha-oxoalkanoates 2$ in a good yield of 70–76% (Table 1, entries 10–13). Furthermore, we also investigated this reaction in the presence of aluminium chloride supported on alumina or silica gel, which is thought to be a mild Lewis acid and harmless for the environment (Table 3). In the case of reactions in the presence of AlCl₃ supported on Al₂O₃, although the yield of addition products 3 became higher than that of only in the presence of AlCl₃, the stereoselectivities changed well somewhat (entries 4-6). And in the case of reactions in the presence of AlCl₃ supported on SiO₂, the yield of addition products 3⁵ depends on the nature of substrate. For example, when $R_1 = iPr$ or *n*Pr, the yield became higher (entries 10 and 11), but with increasing the number of the carbon in R₁, the yield became lower than that of only in the presence of AlCl₃ (entry 12). All the stereoselectivities were not changed so much. And then, we examined effects of the ratio of AlCl₃ and Al₂O₃ or SiO₂. Using AlCl₃ supported on Al_2O_3 or SiO_2 with the ratio of 1:2, 1:5 or 1:10, we carried this reaction and found that using AlCl₃ supported on Al_2O_3 or SiO_2 with the ratio of 1:2 afforded the product in a highest yield, and no influence on the stereoselectivity was observed (entries 1 and 7).

H,,,,,,,,,,CI R ¹ CO ₂ Me 1	$\underbrace{\overset{Aromatic \ compound}{}}_{AICl_3, \ CH_2Cl_2} R^1$	Cl Ar CO2Me + R ¹	H OH CO ₂ Me anti-3		
Entry	R ₁	Aromatic compounds	Conditions	Yield	syn/anti
1	(CH ₃) ₂ CH-	naphtalene	r.t., 1 h	3h , 46.8%	89:11
2	CH ₃ (CH ₂) ₂ -	naphtalene	r.t., 50 min	3i , 52.2%	90:10
3	CH ₃ (CH ₂) ₄ -	naphtalene	r.t., 40 min	3j , 56.4%	75:25
4	CH ₃ (CH ₂) ₆ -	naphtalene	r.t., 30 min	3k , 73.2%	75:25
5	CH ₃ (CH ₂) ₈ -	naphtalene	r.t., 15 min	31 , 83.6%	78:22
6	CH ₃ (CH ₂) ₄ -	anthracene	r.t., 40 min	3m , 31.2%	71:29
7	CH ₃ (CH ₂) ₄ -	anliline	r.t., 1 h	3n , 18.5%	80:20
8	CH ₃ (CH ₂) ₈ -	N,N-dimethylaniline	r.t., 20 min	30 , 35.4%	77:23
9	CH ₃ (CH ₂) ₈ -	phenol	r.t., 2 h	3p , 15.3 %	70:30

Table 2 The Reactions of 2-Chloro-2,3-epoxyalkanoates with Naphtalene, Anthracene and Aniline Conductor in the Presence of AlCl₃

Table 3 The Reactions of 2-Chloro-2,3-epoxyalkanoates with Aromatic Compounds in the Presence of AlCl₃ Supported on Al₂O₃ or SiO₂



Entry	R ₁	R ₂	Conditions	Yield	syn/anti
1	CH ₃ (CH ₂) ₂ -	CH ₃ -	AlCl ₃ -Al ₂ O ₃ =1:2 ; r.t., 50 min	3e , 70.1%	82:18
2	CH ₃ (CH ₂) ₂ -	CH ₃ -	AlCl ₃ -Al ₂ O ₃ =1:5 ; r.t., 50 min	3e , 51.7%	73:27
3	CH ₃ (CH ₂) ₂ -	CH ₃ -	AlCl ₃ -Al ₂ O ₃ =1:10 ; r.t., 50 min	3e , 45.8%	80:20
4	(CH ₃) ₂ CH-	Н	AlCl ₃ -Al ₂ O ₃ =1:2 ; r.t., 1 h	3a , 37.2%	84:16
5	CH ₃ (CH ₂) ₂ -	Н	AlCl ₃ -Al ₂ O ₃ =1:2 ; r.t., 1 h	3b , 59.6%	78:22
6	CH ₃ (CH ₂) ₆ -	Н	AlCl ₃ -Al ₂ O ₃ =1:2 ; r.t., 1 h	3c , 76.7%	80:20
7	CH ₃ (CH ₂) ₂ -	CH ₃ -	AlCl ₃ -SiO ₂ =1:2 ; r.t., 2 h	3e , 63.2%	83:17
8	CH ₃ (CH ₂) ₂ -	CH ₃ -	AlCl ₃ –SiO ₂ =1:5 ; r.t., 2 h	3e , 57.2%	77:23
9	CH ₃ (CH ₂) ₂ -	CH ₃ -	AlCl ₃ –SiO ₂ =1:10 ; r.t., 1 h	3e , 54.0%	81:19
10	(CH ₃) ₂ CH-	Н	AlCl ₃ -SiO ₂ =1:2 ; r.t., 1 h	3a , 33.9%	79:21
11	CH ₃ (CH ₂) ₂ -	Н	AlCl ₃ -SiO ₂ =1:2 ; r.t., 1 h	3b , 62.0%	81:19
12	CH ₃ (CH ₂) ₆ -	Н	AlCl ₃ -SiO ₂ =1:2 ; r.t., 1 h	3c , 55.3%	81:19

In summary, we found that the reaction of α -chloro- α , β -epoxyalkanoates with aromatic compounds in the presence of Lewis acid doesn't give Friedel–Crafts reaction products, but α -aryl- β -chloro- α -hydroxyalkanoates, and

the major products are syn products. Utilization of this reaction for total synthesis of a natural product, donaxaridine⁴ is currently under investigation.

LETTER

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- (5) Typical procedure for (\pm)-2-hydroxy-2-(*p*-ethylphenyl)-3chlorooctanoate(**3f**): To a stirred solution of aluminium chloride (430 mg, 3 mmol) in CH₂Cl₂ (4 mL) was added the solution of methyl 2-chloro-2,3-epoxyoctanoate (206 mg, 1 mmol) and ethylbenzene (319 mg, 3 mmol) in CH₂Cl₂ (2 mL) at room temperature. The mixture was stirred for 50 minutes, then reaction was stopped by pouring the ice (10 mL), and the aqueous layer was extracted with EtOAc. The combined extract was washed with saturated NaHCO₃ solution and brine, then dried over MgSO₄. Removal of the solvent gave 232 mg of a clean oil, which was purified by column chromatography (hexane–ether = 160:1) to give 161 mg (51.5%) of (*S*,*S*)-(\pm)-**3f** and 38 mg (12.1%) of (*S*,*R*)-(\pm)-**3f**.

(S,S)- (\pm) -**3f**: yellow liquid, $R_f = 0.30$ (hexane–ether = 2:1); ¹H NMR (200 MHz, CDCl₃) δ 0.83 (t, J = 6.4 Hz, 3 H), 1.24 (t, J = 7.6 Hz, 3 H), 1.18–1.76 (m, 8 H), 2.66 (q, J = 7.6 Hz, 2 H), 3.82 (s, 3 H), 3.91 (s, 1 H), 4.68 (dd, *J* = 1.8 Hz and 10.8 Hz, 1 H), 7.21 (d, J = 8.4 Hz, 2 H), 7.57 (d, J = 8.4 Hz, 2 H); ¹³C NMR (200 MHz, CDCl₃) δ 13.89, 15.28, 22.38, 26.58, 28.37, 30.51, 30.87, 53.53, 68.30, 81.23, 125.85, 127.98, 134.97, 144.34, 173.58; IR(neat): 3514, 2958, 2932, 2864, 1742, 1512, 1437, 1257, 1147, 756 cm⁻¹; Anal. Calcd for C₁₇H₂₅ClO₃: C, 65.27; H, 8.05; Found: C, 65.51; H, 8.22. (S,R)-(±)-**3f**: yellow liquid, R_f = 0.23 (hexane–ether = 2.1); ¹H NMR(200 MHz, CDCl₃) δ 0.90 (t, J = 6.4 Hz, 3 H), 1.24 (t, J = 7.6 Hz, 3 H), 1.20–2.10 (m, 8 H), 2.66 (q, J = 7.6 Hz, 2 H), 3.73 (s, 1 H), 3.81 (s, 3 H), 4.61 (dd, J = 1.6 Hz and 10.8 Hz, 1 H), 7.21 (d, J = 8.4 Hz, 2 H), 7.53 (d, J = 8.4 Hz, 2 H); ¹³C NMR (200 MHz, CDCl₃) δ13.97, 15.22, 22.42, 26.57, 28.37, 31.05, 33.11, 53.58, 67.65, 81.25, 125.70, 127.83, 136.63, 144.32, 173.10; IR(neat): 3512, 2962, 2934, 2864, 1734, 1514, 1458, 1253, 1143, 835, 665 cm⁻¹; Anal. Calcd for C₁₇H₂₅ClO₃: C, 65.27; H, 8.05; Found: C, 65.51; H. 8.22.

(6) X-ray crystallographic data of *syn*-**3d**: data collection, solution, and refinement.

Chemical formula: $C_{14}H_{19}O_3Cl; F.W. = 270.76$; crystal size: $0.50 \times 0.25 \times 0.43 \text{ mm}^3$; crystal system: triclinic; lattice parameters: a = 10.495(3), b = 11.755(3), c = 6.608(2) Å, a = 100.36(2), $\beta = 107.25(3)$, $\gamma = 69.213(18)^\circ$, V = 725.4(4)Å³; space group: P (#2); Z = 2; $Dcalc = 1.240 \text{ g/cm}^3$; F(000) = 288; $\mu(Mo K\alpha) = 0.26 \text{ mm}^{-1}$; diffractometer: Rigku AFC5R; $T: 25 \,^{\circ}$ C; no. of reflections measured: total 3880, unique 3334; structure solution: direct methods (SIR92); refinement: full-matrix least-squares on F^2 ; function minimized: $\Sigma w (Fo^2 - Fc^2)^2$; least squares weights: $1/\sigma^2(Fo) = 4Fo^2/\sigma^2 (Fo^2)$; no. obsd $[I > 0.5\sigma (I)]$: 2886; no. variables: 240; residuals R_1 , wR_2 : 0.063, 0.099; goodness of fit indicator: 1.94; $_{max} / \rho_{min}$: 0.23 $/ - 0.28 \text{ e} / Å^3$.