Chinese Chemical Letters Vol. 16, No. 12, pp 1577-1600, 2005 1577
http://www.imm.ac.cn/journal/ccl.html

Synthesis of Racemic Bis[2-(6-fluoro-2-chromanyl)-2-hydroxyethyl]-amine Methanesulfonic Acid Salt Using Lithium Aluminum Amide as a Promoter in Regioselective Ring Opening of Epoxide

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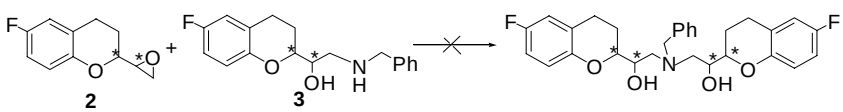
Abstract: Lithium aluminium amide [$LiAl(NHR)_4$] **5** obtained by treating the primary amine **4** with $LiAlH_4$ could promote the ring opening of epoxide **2** and led to high regioselective product of racemic bis[2-(6-fluoro-2-chromanyl)-2-hydroxyethyl]amine methanesulfonic acid salt **7**.

Keywords: Epoxide, lithium aluminium amide, bis[2-(6-fluoro-2-chromanyl)-2-hydroxyethyl]-amine.

Bis[2-(6-fluoro-2-chromanyl)-2-hydroxyethyl]amine **6** is one of a multitude β_1-adrenergic blocking agents bearing β-amino alcohol units. It is a *pseudo*symmetrical molecule with four asymmetric carbon atoms[1]. We report here a new synthesis method for racemic **6** as well as its methanesulfonic acid salt **7** by the regioselective ring opening reaction of racemic epoxide **2**. These reactions can be used as the "reaction model" in the synthesis of its optical isomers of **6**.

Regioselective ring opening of epoxides with amines is an important procedure for the synthesis of β-amino alcohols. This reaction is usually carried out directly with a large excess of amines at elevated temperatures and often fails because of steric hindrance or low nucleophilicity of amines. The regioselectivity of ring opening reaction can not be controlled well by direct heating epoxides in the presence of excess amine. Although several useful modifications of the classical procedures have been developed, the general utility of epoxides aminolysis is still limited[2]. Thus, more reactive nucleophilic metal amide reagents, such as alkali[3], lithium, aluminium, silicon-Lewis acid, stibium, lead, magnesium, tin, titanium[4] and halomagnesium alkylamides[5]

Scheme 1



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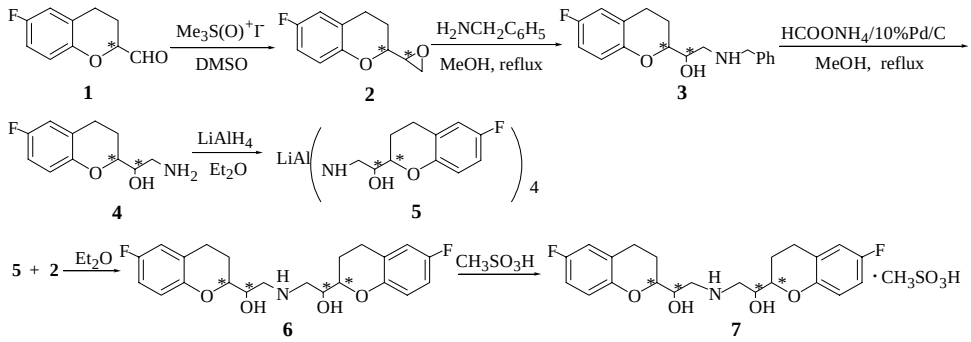
Scheme 2



have been developed. Furthermore, the reagents, such as trimethylsilyl, tetraphenylantimony, especially the dimethylaluminum amides, have also been reported that they can increase the regioselectivity in the synthesis of difunctional compounds of amine alcohols[6]. But all the reports only concern the simple substrates, which have no asymmetric carbon atoms adjacent to the epoxides ring. So, the effect of asymmetric carbon atoms adjacent to the oxirane rings on the regioselective epoxides ring opening reaction is not clear.

Initially, we investigated the ring opening reaction of epoxide **2** with benzylamine derivative **3** under a variety of reaction conditions, the reaction was proved to give a less regioselective inextricable mixture (**Scheme 1**). Therefore, the unmasked primary amine **4,** which reacted with $LiAlH_4$ to form the complex **5** was tested as a nucleophilic regent in the regioselective ring opening of epoxide **2**.

Compound **1**[11a] was employed as the starting material to synthesize the primary amine **4**. Epoxide **2** was prepared according to the standard Corey-Chaykovsky epoxide synthesis method from **1** and dimethylsulfoxonium methyllide[7,11b]. Benzylamine derivative **3** was obtained in 80 % yield by refluxing epoxide **2** directly with benzylamine in methanol[11c]. Due to the unhindrance of benzylamine, the ring opening reaction gave a slightly satisfactory regioselective yield of **3** without using any ring opening promoters in this reaction (**Scheme 2**).

Deprotection of the N-benzyl group to the corresponding primary amine, generally, was performed by catalytic hydrogenation[8]. We treated **3** by catalytic hydrogenation **(**hydrogen pressure 0.5 MPa, 40°C, 16 h, 10 % Pd/C, 5 % HCl in methanol) to obtained **4** in 80 % yield. This classical method is not satisfactory for the potential dangerous hydrogen and the long reaction time. We therefore tried to remove the N-benzyl group from **3** according to the reference[9] (0.5 hour, 10 % Pd/C as the heterogeneous catalyst, ammonium formate as hydrogen donor) and obtained **4**[11d] in 85% yield.

When **4** was refluxed with **2** in methanol for 4 h to prepare **6,** the product was very complicated (monitored by TLC). We think, in the prescence of large volume of the primary amine the asymmetric carbon centers neighbouring to the oxirane ring in **2** and the asymmetric carbon centers neighbouring to the amine group in **4** may affect the ring opening reactivity of oxirane **2** and the nucleophilicity of amine **4**.

As reported that $LiAlH_4$ has the high promoting regioselectivity for the ring opening of epoxides[10], we used lithium aluminum amide complex **5** as the ring opening promoter of epoxide **2** to prepare compound **6**. The best ratio of $LiAlH_4$ to **4** was 1:5. The ring opening reaction of epoxide **2** proceeded in nearly quantitative yield at 0˚C. **6** was converted to **7**[11e] in 90 % yield (based on **4**).

In conclusion, we have developed a new and an efficient method for preparation of **6** as well as its methanesulfonic acid salt **7** in satisfactory yield. Lithium aluminum amide **5** is easier to prepare and has the high regioselectivity in promoting the ring opening of epoxide **2**. The availability of primary amine **4** and the easy N-debenzylation of benzylamine derivative **3** by using CTH make this approach most attractive for the synthesis of other possible isomers and analogues.

Acknowledgments

We thank the National 863 Program (No.2003AA323030) and the National Natural Science Foundation of China (No.50272069 and No.20472090) for financial support.

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11. (a) The data of compound **1** obtained from an authentic sample were as follow: IR (KBr film, cm^{-1}): 3067, 2940, 2849, 2733, 1738, 1492, 1217, 812; ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): 9.81 (s, 1H, C*H*O), 6.76-6.92 (m, 3H, Ar*H*), 4.45-4.49 (dd, 1H, *J* = 8.7, 3.3 Hz, OC*H*CHO), 2.76-2.85 (m, 2H, ArCH_2CHH), 2.19-2.22 (m, 1H, C*H*HCHO), 2.02-2.07 (m, 1H, CH*H*CHO); MS EI, (*m/z*, %): 181 (M+H, 2.85), 180 (M^+, 30.3), 151(100).
(b) The data of **2**: IR (KBr film, cm^{-1}): 3061, 2998, 2931, 2853, 1492, 1434, 1261, 1217, 942, 901; ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): 6.74-6.81 (m, 3H, ArH), 3.81-3.87 (double, 1H, *J* = 9.9, 14.5, 2.4 Hz, CH_2CHO), 3.18-3.22 (m, 1H, *H*COCH_2), 2.79-2.90 (m, 4H, HCOCH_2, ArCH_2), 1.92-2.08 (m, 1H, C*H*HCHO), 1.91-1.97 (m, 1H, CH*H*CHO); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 117.6 (C_6H_3), 117.5 (C_6H_3), 115.4 (C_6H_3), 115.2 (C_6H_3), 114.2 (C_6H_3), 114.0 (C_6H_3), 75.6 (O*C*HCH$_2$), 53.4 (*C*HOCH$_2$), 52.9 (CHO*C*H$_2$), 45.7 (Ar*C*H$_2$), 24.2 (OCH*C*H$_2$). MS EI, (*m/z*, %): 195 (M+H, 7.76), 194 (M^+, 100), 149(42).
(c) The data of **3**: mp: 113-115 °C. IR (KBr, cm^{-1}): 3430, 3292, 2911, 2841, 1620, 1494, 1427, 1216, 877; ^1H NMR ($CDCl_3$, 300 MHz, δ ppm): 7.47-7.51 (m, 4H, Ar*H*), 7.41-7.45 (m, 1H, Ar*H*), 6.83-6.94 (m, 3H, F-Ar*H*), 3.91-4.04 (m, 4H, OCHCH$_2$, HOC*H*CH$_2$, ArCH_2NH),

2.91-3.18 (m, 4H, ArCH_2, HOCHCH_2), 1.97-2.31 (m, 4H, OCHCH_2, N*H*, O*H*); MS EI, (*m/z*, %): 302 (M+H, 3.1), 301 (M^+, 8.5), 283 (17.5), 119 (100).

(d) The data of **4**: (KBr, cm^{-1}): 3427, 3364, 3287, 2906, 2857, 2728, 1494, 1217, 884; ^{1}H NMR (CD_3SOCD_3, 400 MHz, δ ppm): 6.83-6.91 (m, 2H, Ar*H*), 6.69-6.75 (m, 1H, Ar*H*), 3.81-3.85 (m, 1H, OC*H*CH_2), 3.47-3.53 (m, 1H, OCHC*H*OH), 2.59-2.85 (m, 4H, ArCH_2, CH_2NH_2), 2.04-2.07 (m, 1H, OCHC*H*H), 1.61-1.76 (m, 1H, OCHCH*H*); MS EI, (*m/z*, %): 212 (M+H, 84.3), 211 (M^+, 100), 193 (30), 176 (54.4).

(e) The data of **7**: mp: 195-197 °C. IR (KBr, cm^{-1}): 3316, 3184, 3030, 2986, 2920, 2876, 1616, 1578, 1496, 1440, 1218, 1140, 1078, 864, 809; ^{1}H NMR (D_2O, 400 MHz, δ ppm): 6.75-6.87 (m, 6H, Ar*H*), 3.96-4.04 (m, 4H, OC*H*CH_2, OCHC*H*OH), 3.11-3.37 (m, 4H, CH_2NH), 2.77-2.82 (m, 7H, ArCH_2, O*H*, N*H*), 1.74-2.10 (m, 4H, OCHC*H*H, OCHCH*H*); ^{13}C NMR (D_2O, 100 MHz, δ ppm): 158.0 (C_6H_3), 155.7 (C_6H_3), 149.6 (C_6H_3), 124.2 (C_6H_3), 124.1 (C_6H_3), 117.3 (C_6H_3), 117.3 (C_6H_3), 115.6 (C_6H_3), 115.3 (C_6H_3), 114.0 (C_6H_3), 113.8 (C_6H_3), 77.2 (O*C*HCH_2), 76.8 (O*C*'HCH_2), 68.8 (HO*C*HCH_2), 68.8 (HO*C*'HCH_2), 41.9 (*C*H_2NH), 41.3 (*C*'H_2NH), 38.4 (*C*H_3SO_3H), 24.0 (Ar*C*H_2). 23.3 (Ar*C*'H_2), 22.9 (OCH*C*H_2), 22.4 (OCH*C*'H_2); MS EI, (*m/z*, %): $H_{25}F_4NO_4$ 406 (M+H, 10.22), 405 (M^+, 14), 254 (12.68), 224 (34.35), 114 (48.36), 117 (100).

Received 30 March, 2005