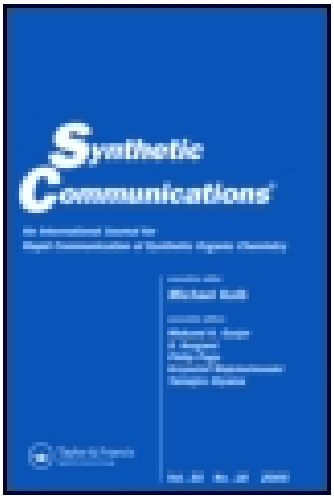

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Efficient Synthesis of β-Amino Alcohols Catalyzed by Niobium Pentachloride: Regioselective Ring Opening of Epoxides with Aromatic Amines

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Efficient Synthesis of β-Amino Alcohols Catalyzed by Niobium Pentachloride: Regioselective Ring Opening of Epoxides with Aromatic Amines

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Abstract: Epoxides undergo a rapid ring-opening reaction with aromatic amines catalyzed by niobium pentachloride under mild reaction conditions. All the reactions were carried out at room temperature to afford the corresponding β-amino alcohols in excellent yields and with high regioselectivity.

Keywords: Aromatic amines, β-amino alcohols, epoxides, niobium pentachloride

INTRODUCTION

The β-amino alcohols are versatile intermediates and major functional groups for the synthesis of various biologically active natural and synthetic products, synthetic amino acids, β-blockers, insecticidal agents, chiral auxiliaries, and oxazolines, which have been widely explored as protecting groups.[1] Because of remarkable synthetic demand, the development of an efficient and environmentally friendly method for the regioselective ring opening of epoxides constitutes an active area of investigation in organic synthesis. One of the most straightforward synthetic approaches for the preparation of β-amino alcohols involves heating an epoxide with an excess of amines at

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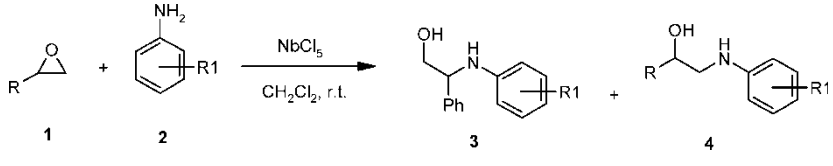
elevated temperatures. Because some functional groups may be susceptible to high temperature, and also to control the regioselectivity, A variety of activators or promoters such as metal amides, metal triflates, transition-metal halides,[2] microwaves, and ionic liquids[3] have been developed to perform the epoxide ring-opening reactions with amines under mild reaction conditions.[4] The introduction of a new and efficient method for this transformation under more convenient and general conditions is still in demand. Niobium pentachloride is well known in the literature as a mild and efficient catalyst for various organic transformations.[5]

RESULTS AND CONDITIONS

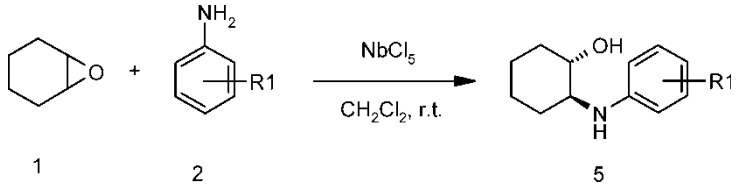
As part of our ongoing program into develop various new synthetic methodologies,[6] herein we report our results on regioselective ring opening of various oxiranes with aromatic amines using a catalytic amount (10 mol%) of niobium pentachloride under mild reaction conditions.

In a typical experiment, styrene oxide **1** (2 mmol) and aniline **2** (2 mmol) were stirred in the presence of niobium pentachloride (0.2 mmol) at room temperature in dichloromethane to obtain the corresponding β-amino alcohol **3a** in 95% yield (Scheme 1). The reaction was completed within 1 h, and the epoxide opening takes place in a regioselective manner preferentially at the benzylic position. Only a single product was obtained in all the styrene oxide reactions, and the structure of the product was confirmed by its ^{1}H NMR spectrum. In a similar manner, glycidyl aryl ethers and aliphatic alkyl oxiranes reacted smoothly with aryl amines to afford the corresponding β-amino alcohols (**4i**–**4p**) in very good yields with high regioselectivity. The epoxide opening takes place in a regioselective manner preferentially at the terminal opening. In these reactions also, only a single product was obtained, and the structure of the product was confirmed by its ^{1}H NMR spectrum. Furthermore, a cycloalkyl epoxide such as cyclohexene oxide reacted smoothly with different substituted aromatic amines to afford the corresponding β-amino alcohols (**5e**–**5h**) in excellent yields with high regioselectivity (Scheme 2).

The stereochemistry of the ring-opening products (Scheme 2) was found to be *trans* from the coupling constants. In the case of epichlorohydrin



Scheme 1.



Scheme 2.

(Table 1, entries **i**–**l**) the ring-opening reaction proceeds very well, with one product of β-amino alcohols but no side products. The four different epoxides underwent ring opening with various substituted aromatic amines to afford the corresponding β-amino alcohols in very good to excellent yields. We noticed that the present reaction in the absence of $NbCl_5$ could not progress. All the products were characterized by ^{1}H NMR, IR, and mass spectroscopic data. This method does not require any anhydrous solvents or stringent reaction conditions. No precautions need to be taken to exclude moisture from the reaction medium. The reactions are clean and highly regioselective, affording high yields of products in a short reaction time of 1–4 h. The scope and the generality of this process are illustrated with respect to various epoxides and different substituted anilines. The advantages of niobium pentachloride are its simplicity in handling and the easy workup procedure for the isolation of products.

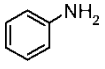
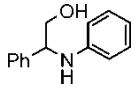
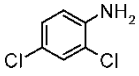
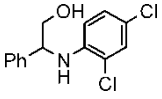
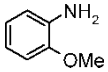
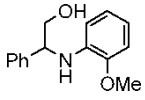
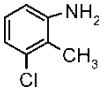
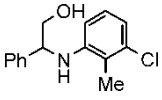
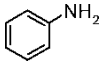
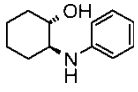
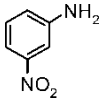
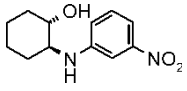
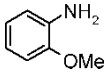
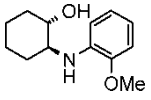
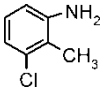
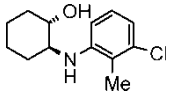
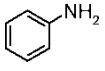
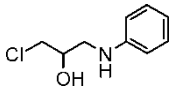
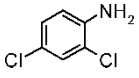
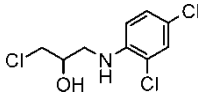
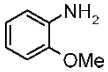
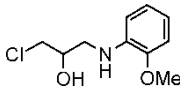
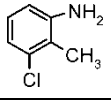
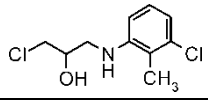
In conclusion, the present methodology describes a simple, convenient, and efficient procedure for the regioselective ring opening of epoxides with a variety of aromatic amines using a catalytic (10 mol) amount of niobium pentachloride. The notable features of this procedure are mild reaction conditions, excellent regioselectivity, cleaner reaction profiles, improved yields, enhanced reaction rates, and simplicity of operation, which makes it a useful and attractive process for the synthesis of β-amino alcohols of biological and synthetic importance.

GENERAL PROCEDURE

Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer. ^{1}H NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. All the products' physical and spectroscopic data were compared with those reported in the literature.

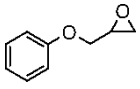
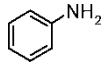
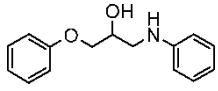
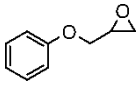
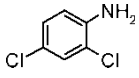
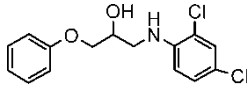
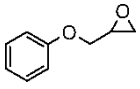
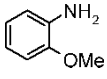
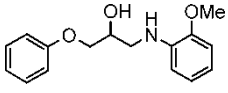
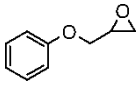
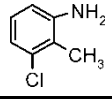
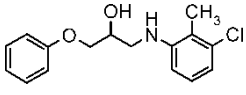
Niobium pentachloride (0.2 mmol) was added to a mixture of epoxide (2 mmol) and aniline (2 mmol) in dichloromethane (DCM, 10 mL). The resulting mixture was stirred at room temperature for a specified period

Table 1. Niobium(V) chloride–catalyzed ring opening of epoxides

Entry	Substrate **(1)**	Aniline **(2)**	Product[a]	Reaction time (h)	Yield (%)[b]
a				1.0	95
b				1.5	93
c				1.5	91
d				1.0	90
e				2.0	92
f				2.5	90
g				3.0	91
h				2.5	88
i				3.5	84
j				4.0	82
k				3.5	83
l				4.0	80

(*continued*)

Table 1. Continued

Entry	Substrate (**1**)	Aniline (**2**)	Product[a]	Reaction time (h)	Yield (%)[b]
m				2.5	92
n				3.0	90
o				3.0	87
p				3.5	85

[a]All the products characterized by ^{1}H NMR, IR, and mass spectroscopy.
[b]Yields were isolated and not optimized.

(Table 1). The progress of the reaction was monitored by thin-layer chromatography (TLC). After complete conversion of the starting material, the reaction mixture was diluted by adding dichloromethane (20 mL). The mixture was washed with water (2 × 20 mL) followed by brine solution. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to obtain the crude products, which were purified by column chromatography (silica gel 60–120 mesh) while eluting with ethyl acetate–petroleum ether (3 : 7).

Spectral Data of the Selected Products

2-(3-Chloro-2-methylphenylamino)-2-phenylethanol (3d): Brownish oil, IR (neat) ν 3412, 3326, 3068, 2942, 2851, 1605, 1554, 1436, 1372, 1251, 1128, 1049, 1018, 936, 847, 752 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 3.70–3.80 (m, 1H), 4.40–4.50 (m, 1H), 4.95 (t, 1H, $J = 6.5$ Hz), 6.18 (d, 1H, $J = 6.5$ Hz), 6.65–6.80 (m, 1H) 7.25–7.40 (m, 6H); EIMS m/z (%) 261 (m^+ 10), 230 (88), 156 (18), 125 (100), 103 (31), 91 (95), 77 (35), 61 (42), 57 (70), 43 (55). Calcd. for $C_{15}H_{16}ClNO$: C, 68.83; H, 6.16; N, 5.35. Found: C, 68.81; H, 6.13; N, 5.32.

1-*trans*-2-(2-Chloro-3-methylphenylamino)-cyclohexanol (5h): Light-colored solid, mp 49–50°C; IR (KBr) ν 3408, 3374, 3061, 2935, 2861, 1603, 1585, 1506, 1456, 1429, 1389, 1346, 1312, 1267, 1214, 1163, 1131,

1097, 1059, 946, 913, 854, 763, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94–1.15 (m, 1H), 1.23–1.40 (m, 3H), 1.68–1.79 (m, 2H), 2.02–2.20 (m, 2H), 2.40 (s, 3H), 2.85 (brs, NH), 3.15 (ddd, 1H, $J = 4.0$, 9.0 & 11.0 Hz), 3.38 (ddd, 1H, $J = 4.0$, 10.0 & 10.0 Hz), 6.50 (d, 1H, $J = 6.5$ Hz), 6.75 (d, 1H, $J = 6.5$ Hz), 7.05 (t, 1H, $J = 6.5$ Hz); EIMS m/z (%) 241 (m^+ 30), 204 (12), 189 (10), 127 (100), 114 (56), 90 (39), 75 (31), 65 (11), 51 (32). Calcd. for $C_{13}H_{18}ClNO$: C, 65.13; H, 7.57; N, 5.84. Found: C, 65.10; H, 7.55; N, 5.81.

1-Chloro-3-(3-chloro-2-methylphenyl)-aminopropan-2-ol (4l): Brown-colored syrup, IR (neat) ν 3403, 3386, 3072, 2941, 2837, 1605, 1518, 1461, 1404, 1346, 1286, 1231, 1203, 1172, 1134, 1108, 1031, 917, 846, 748 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.28 (s, 3H), 2.45 (brs, 1H), 3.25 (q, 1H, $J = 6.5$ Hz), 3.42 (dd, 1H, $J = 4.0$ & 9.5 Hz), 3.65–3.75 (m, 2H), 4.00 (brs, 1H), 4.15 (brs, 1H), 6.53 (d, 1H, $J = 7.0$ Hz), 6.80 (d, 1H, $J = 7.0$ Hz), 7.05 (t, 1H, $J = 7.0$ Hz); EIMS m/z (%) 234 (m^+ 10), 232 (15), 156 (41), 154 (100), 125 (15), 117 (10), 89 (20), 77 (12), 51 (10), 43 (12). Calcd. for $C_{10}H_{13}Cl_2NO$: C, 51.30; H, 5.60; N, 5.98. Found C, 51.27; H, 5.56; N, 5.95.

1-Phenoxy-3-(3-chloro-2-methylphenyl)-aminopropan-2-ol (4p): Light-yellow oil, IR (neat) ν 3403, 3371, 3065, 2943, 2849, 1636, 1606, 1541, 1508, 1431, 1362, 1308, 1256, 1137, 1046, 1012, 937, 851, 749 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.37 (s, 3H), 3.18 (dd, 1H, $J = 5.5$ & 10.5 Hz), 3.32 (dd, 1H, $J = 5.5$ & 10.5 Hz), 3.45–3.58 (m, 2H), 3.90–3.97 (m, 1H), 6.20 (d, 1H, $J = 7.0$ Hz), 6.70–6.85 (m, 1H) 7.30–7.40 (m, 6H); EIMS m/z (%) 291 (m^+ 21), 256 (18), 154 (21), 137 (100), 119 (56), 104 (11), 93 (15), 77 (25), 61 (412), 57 (37), 43 (51). Calcd. for $C_{16}H_{18}ClNO_2$: C, 65.86; H, 6.22; N, 4.80. Found C, 65.84; H, 6.19; N, 4.78.

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