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Microwave-Assisted Ring Opening of Epoxides in Solvent-Free Conditions

Wei Tan, Bao-Xiang Zhao, Lei Sha, Pei-Fu Jiao, and Mao-Sheng Wan
Institute of Organic Chemistry, School of Chemistry and Chemical Engineering, Shandong University, Jinan, China

Lei Su
Institute of Pesticide, Shandong, Jinan, China

Dong-Soo Shin
Department of Chemistry and Research Institute of Natural Sciences, Changwon National University, Changwon, Korea

Abstract: The reaction of aryloxymethyl epoxide with anilines under solvent-free conditions and microwave irradiation affords high yields of 1-arylamino-3-aryloxypropan-2-ols. The reaction was rapid and completely regioselective.

Keywords: β-Amino alcohols, epoxide, microwave irradiation, ring opening

INTRODUCTION

β-Amino alcohols are a very important class of organic compounds and have considerable application in medicinal chemistry.[1] The conventional route for the synthesis of these compounds involves ring opening of epoxides at elevated temperatures.[1,2] These reactions are usually carried out in a solvent, requiring a large excess of amines or anilines and many hours of reflux temperature, which is environmentally unfriendly. Furthermore, the

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Address correspondence to Bao-Xiang Zhao, Institute of Organic Chemistry, School of Chemistry and Chemical Engineering, Shandong University, Jinan 250100, China. E-mail: bxzhao@sdu.edu.cn

cleavage of epoxides by aniline to obtain *N*-aryl-β-aminoalcohol is much more difficult using classical procedures.

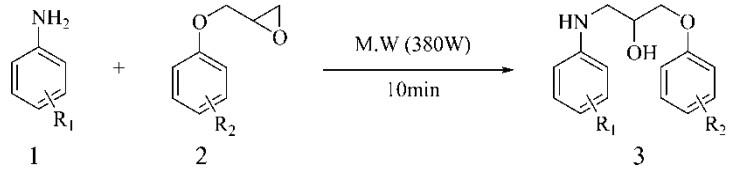
Recently, the use of catalysts to carry out these reactions under mild conditions has been developed, but this still needs expensive catalysts and large excess of anilines and solvents.[3–6] We have reported earlier regioselective ring opening of aryloxymethyl epoxide by anilines in the presence of alumina to afford *N*-aryl aminoalcohol in moderate to good yields.[7] However, the scope of the reaction is limited as it requires prolonged heating in a solvent, and the yield is much lower when deactivated aniline is used. Because of these reasons, further investigation was necessary to overcome these difficulties, and here we have chosen microwave as the energy source to carry out this reaction.

RESULTS AND DISCUSSION

The application of microwave-assisted reactions in organic synthesis is well documented in the literature.[8,9] Compared to conventional heating, microwave irradiation often gives greatly enhanced reaction rates and fewer by-products. In this article, we report a simple and fast procedure for ring opening of epoxides by anilines under microwave irradiation in solvent-free conditions. These reactions are performed in a domestic microwave oven because of its low cost and ready availability. Gratifyingly, we obtained the desired *N*-aryl-β-aminoalcohol in good yields in only 10 min using the microwave-assisted protocol. It is interesting that Kamal reported recently a similar reaction system, the cleavage of epoxides with aromatic amines by ultrasonic activated method.[10]

In a typical experiment aryloxymethyl epoxide **1** and anilines **2** were mixed in an open vessel and irradiated at 380 W for 10 min without any solvent; the complete reaction took place, leading to 1-arylamino-3-aryloxypropan-2-ols **3** (Scheme 1). The reaction was completely regioselective because no other isomer was detected. The different entries and isolated yields in comparison with earlier reports are given in Table 1.

As it can be seen from Table 1, the reaction was carried out using five different aromatic amines. This process worked well for all types of



1 2 3

Scheme 1.

Table 1. 1-Arylamino-3-aryloxypropan-2-ols prepared by the microwave-irradiation method

Entry	R_1	R_2	Major product	Yield[a] (%)	Yield[b] (%)
1	H	4-Cl	3a	49	43
2	4-OMe	4-Cl	3b	66	60
3	3-Cl	4-Cl	3c	46	—
4	2-OMe	4-Cl	3d	77	—
5	4-Cl	4-Cl	3e	67	50
6	H	4-NO_2	3f	50	61
7	4-OMe	4-NO_2	3g	74	51
8	3-Cl	4-NO_2	3h	69	—
9	2-OMe	4-NO_2	3i	57	—
10	4-Cl	4-NO_2	3j	54	50
11	H	2-OMe	3k	61	—
12	4-OMe	2-OMe	3l	82	—
13	3-Cl	2-OMe	3m	76	—
14	2-OMe	2-OMe	3n	76	—
15	4-Cl	2-OMe	3o	70	—

[a]Isolated yields of **3**.
[b]Yields reported in Ref.[7]

aromatic amines, regardless of their electronic and steric nature, giving the desired products with complete regioselectivity. The yields are better than or as good as our previously reported results.[7] The moderate yields of **3a**, **3c**, and **3f** may be partially due to the evaporation of the starting epoxide during microwave heating, because no epoxide was found in the product after microwave irradiation.

In summary, we have achieved an efficient microwave-assisted protocol for the regioselective ring-opening reaction of aryloxymethyl epoxides with anilines to afford 1-arylamino-3-aryloxypropan-2-ols. Compared to previous methods, this procedure uses more friendly reaction conditions and shorter reaction times, generally gives higher yields, and is applied to a larger set of substrates. We are currently engaged in investigating other nucleophiles for the ring-opening reactions of aryloxymethyl epoxides.

EXPERIMENTAL

General

IR spectra were recorded with an IR spectrophotometer Nicolet-20Sx FT-IR. ^{1}H NMR spectra were recorded on Bruker Avance 400 M spectrometer using

TMS as internal reference and $CDCl_3$ as solvent. The chemical shifts are expressed as δ ppm, and coupling constants are in Hz. MS spectra were obtained on an API4000 mass spectrograph. Elemental analyses were obtained on an Elementar VarioEL-3 elemental analyzer.

General Method for the Preparation of 1-Arylamino-3-aryloxypropan-2-ol

A mixture of aryloxymethyl epoxide (1 mmol) and aromatic amine (1.3 mmol) was placed in an open vessel. Then the mixture was irradiated with mid-power (380 W) in a conventional microwave oven for 10 min. After the mixture was cooled to room temperature, the residue was purified by flash-column chromatography using silica gel to afford compound **3**. The structures of all the newly synthesized compounds were assigned by IR, NMR, and mass spectral data.

Data

1-(4-Chlorophenoxy)-3-(phenylamino)propan-2-ol (3a): White solid; mp 75–78°C; ^{1}H NMR: $\delta = 3.30$ (dd, $J = 13.0$ and 7.2 Hz, 1H, CH_2-N), 3.45 (dd, $J = 13.0$ and 4.3 Hz, 1H, CH_2-N), 4.05 (m, 2H, CH_2-O), 4.28 (m, 1H, CH-OH), 6.72 (m, 2H, Ar), 6.78 (m, 1H, Ar), 6.85 (m, 2H, Ar), 7.23 (m, 4H, Ar); IR (KBr) υ: 3414, 3265, 2924, 1601, 1492, 1245, 1092 cm^{-1}; EI-MS (m/z): 278.1 ($M^+ + H$); anal. calcd. for $C_{15}H_{16}ClNO_2$: C, 64.87; H, 5.81; N, 5.04. Found C, 64.68; H, 5.98; N, 5.10.

1-(4-Chlorophenoxy)-3-(4-methoxyphenylamino)propan-2-ol (3b): White solid; mp 89–91°C; ^{1}H NMR: $\delta = 3.25$ (dd, $J = 12.9$ and 7.3 Hz, 1H, CH_2-N), 3.39 (dd, $J = 12.9$ and 4.1 Hz, 1H, CH_2-N), 3.75 (s, 3H, O-CH_3), 4.02 (m, 2H, CH_2-O), 4.25 (m, 1H, CH-OH), 6.70 (m, 2H, Ar), 6.80 (m, 2H, Ar), 6.85 (m, 2H, Ar), 7.24 (m, 2H, Ar); IR (KBr) υ: 3438, 3259, 2936, 1515, 1492, 1248, 1038 cm^{-1}; EI-MS (m/z): 308.2 ($M^+ + H$); anal. calcd. for $C_{16}H_{18}ClNO_3$: C, 62.44; H, 5.89; N, 4.55. Found C, 62.32; H, 5.98; N, 4.63.

1-(4-Chlorophenoxy)-3-(3-chlorophenylamino)propan-2-ol (3c): White solid; mp 76–77°C; ^{1}H NMR: $\delta = 3.28$ (dd, $J = 13.0$ and 7.2 Hz, 1H, CH_2-N), 3.41 (dd, $J = 13.0$ and 4.2 Hz, 1H, CH_2-N), 4.00 (dd, $J = 9.4$ and 6.1 Hz, 1H, CH_2-O), 4.03 (dd, $J = 9.4$ and 4.2 Hz, 1H, CH_2-O), 4.25 (m, 1H, CH-OH), 6.58 (m, 1H, Ar), 6.68 (t, $J = 2.0$, 1H, Ar), 6.73 (m, 1H, Ar), 6.85 (m, 2H, Ar), 7.10 (t, $J = 8.0$, 1H, Ar), 7.30 (m, 2H, Ar); IR (KBr) υ: 3414, 3289, 2927, 1598, 1490, 1246, 1088 cm^{-1}; EI-MS (m/z): 313.1 ($M^+ + H$); anal. calcd. for $C_{15}H_{15}C_{l2}NO_2$: C, 57.71; H, 4.84; N, 4.49. Found C, 57.86; H, 4.79; N, 4.43.

1-(4-Chlorophenoxy)-3-(2-methoxyphenylamino)propan-2-ol (3d): Oil; ^{1}H NMR: $\delta = 3.30$ (dd, $J = 13.1$ and 7.3 Hz, 1H, CH_2-N), 3.45 (dd, $J = 13.1$ and 4.3 Hz, 1H, CH_2-N), 3.85 (s, 3H, O-CH_3), 4.05 (m, 2H, CH_2-O), 4.28 (m, 1H, CH-OH), 6.73 (m, 2H, Ar), 6.80 (m, 1H, Ar), 6.87 (m, 3H, Ar), 7.25 (m, 2H, Ar); IR (film) υ: 3414, 2935, 1601, 1492, 1246 1028 cm^{-1}; EI-MS (m/z): 308.7 ($M^+ + H$); anal. calcd. for $C_{16}H_{18}ClNO_3$: C, 62.44; H, 5.89; N, 4.55. Found C, 62.49; H, 5.76; N, 4.61.

1-(4-Chlorophenoxy)-3-(4-chlorophenylamino)propan-2-ol (3e): White solid; mp 83–84°C; ^{1}H NMR: $\delta = 3.25$ (dd, $J = 12.9$ and 7.2 Hz, 1H, CH_2-N), 3.40 (dd, $J = 12.9$ and 4.3 Hz, 1H, CH_2-N), 4.05 (m, 2H, CH_2-O), 4.20 (m, 1H, CH-OH), 6.58 (m, 2H, Ar), 6.90 (m, 2H, Ar), 7.10 (m, 2H, Ar), 7.30 (m, 2H, Ar); IR (KBr) υ: 3551, 3381, 2927, 1599, 1495, 1243, 1092, 755, 692 cm^{-1}; EI-MS (m/z): 313.1 ($M^+ + H$); anal. calcd. for $C_{15}H_{15}C_{l2}NO_2$: C, 57.71; H, 4.84; N, 4.49. Found C, 57.76; H, 4.90; N, 4.42.

1-(4-Nitrophenoxy)-3-(phenylamino)propan-2-ol (3f): White solid; mp 125–127°C; ^{1}H NMR: $\delta = 3.35$ (dd, $J = 13.2$ and 7.1 Hz, 1H, CH_2-N), 3.47 (dd, $J = 13.2$ and 4.3 Hz, 1H, CH_2-N), 4.15 (m, 2H, CH_2-O), 4.33 (m, 1H, CH-OH), 6.72 (m, 2H, Ar), 6.80 (m, 1H, Ar), 7.00 (m, 2H, Ar), 7.20 (m, 2H, Ar), 8.20 (m, 2H, Ar); IR (KBr) υ: 3438, 3268, 2926, 1593, 1501, 1349, 1265, 1114, 1016, 751, 698 cm^{-1}; EI-MS (m/z): 289.4 ($M^+ + H$); anal. calcd. for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found C, 62.28; H, 5.68; N, 9.79.

1-(4-Methoxyphenylamino)-3-(4-nitrophenoxy)propan-2-ol (3g): White solid; mp 123–124°C; ^{1}H NMR: $\delta = 3.25$ (dd, $J = 12.9$ and 7.4 Hz, 1H, CH_2-N), 3.40 (dd, $J = 12.9$ and 4.0 Hz, 1H, CH_2-N), 3.75 (s, 3H, O-CH_3), 4.15 (m, 2H, CH_2-O), 4.30 (m, 1H, CH-OH), 6.80 (m, 4H, Ar), 6.97 (m, 2H, Ar), 8.20 (m, 2H, Ar); IR (KBr) υ: 3440, 3263, 2931, 1594, 1507, 1352, 1274, 1030, 751, 665 cm^{-1}; EI-MS (m/z): 319.3 ($M^+ + H$); anal. calcd. for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found C, 60.28; H, 5.69; N, 8.71.

1-(3-Chlorophenylamino)-3-(4-nitrophenoxy)propan-2-ol (3h): White solid; mp 95–97°C; ^{1}H NMR: $\delta = 3.33$ (dd, $J = 12.9$ and 6.7 Hz, 1H, CH_2-N), 3.42 (dd, $J = 12.9$ and 3.1 Hz, 1H, CH_2-N), 4.15 (m, 2H, CH_2-O), 4.32 (m, 1H, CH-OH), 6.58 (d, $J = 8.2$ Hz, 1H, Ar), 6.66 (s, 1H, Ar), 6.74 (d, $J = 7.9$ Hz, 1H, Ar), 7.00 (d, $J = 8.9$ Hz, 2H, Ar), 7.10 (t, $J = 7.9$ Hz, 1H, Ar), 8.21 (d, $J = 8.7$ Hz, 2H, Ar); IR (KBr) υ: 3439, 3278, 2923, 1592, 1509, 1340, 1264, 1109, 752, 666 cm^{-1}; EI-MS (m/z): 295.7 ($M^+ + H$); anal. calcd. for $C_{15}H_{15}ClN_2O_4$: C, 55.82; H, 4.68; N, 8.68. Found C, 55.98; H, 4.59; N, 8.63.

1-(2-Methoxyphenylamino)-3-(4-nitrophenoxy)propan-2-ol (3i): Oil; ^{1}H NMR: $\delta = 3.38$ (dd, $J = 13.2$ and 7.0 Hz, 1H, CH_2-N), 3.48 (dd, $J = 13.2$

and 4.6 Hz, 1H, CH_2-N), 3.87 (s, 3H, O-CH_3), 4.18 (m, 2H, CH_2-O), 4.35 (m, 1H, CH-OH), 6.78 (m, 3H, Ar), 6.89 (m, 1H, Ar), 7.0 (m, 2H, Ar), 8.21 (m, 2H, Ar); IR (film) υ: 3410, 2936, 1592, 1510, 1341, 1261, 1111, 741 cm^{-1}; EI-MS (m/z): 319.2 ($M^+ + H$); anal. calcd. for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found C, 60.21; H, 5.83; N, 8.83.

1-(4-Chlorophenylamino)-3-(4-nitrophenoxy)propan-2-ol (3j): White solid; mp 100–102°C; ^{1}H NMR: δ = 3.30 (dd, J = 13.1 and 7.1 Hz, 1H, CH_2-N), 3.42 (dd, J = 13.1 and 4.3 Hz, 1H, CH_2-N), 4.15 (m, 2H, CH_2-O), 4.31 (m, 1H, CH-OH), 6.62 (m, 2H, Ar), 6.98 (m, 2H, Ar), 7.15 (m, 2H, Ar), 8.20 (m, 2H, Ar); IR (KBr) υ: 3415, 3304, 2923, 1592, 1509, 1268, 1111, 819, 752 cm^{-1}; EI-MS (m/z): 323.5 ($M^+ + H$); anal. calcd. for $C_{15}H_{15}ClN_2O_4$: C, 55.82; H, 4.68; N, 8.68. Found C, 55.99; H, 4.63; N, 8.60.

1-(2-Methoxyphenoxy)-3-(phenylamino)propan-2-ol (3k): White solid; mp 64–66°C; ^{1}H NMR: δ = 3.34 (dd, J = 12.7 and 6.4 Hz, 1H, CH_2-N), 3.50 (dd, J = 12.7 and 4.3 Hz, 1H, CH_2-N), 4.15 (m, 2H, CH_2-O), 4.31 (m, 1H, CH-OH), 6.52 (m, 1H, Ar), 6.60 (m, 2H, Ar), 6.94 (m, 4H, Ar), 7.07 (m, 2H, Ar); IR (KBr) υ: 3414, 3301, 2923, 1592, 1509, 1268, 1085, 821, 749 cm^{-1}; EI-MS (m/z): 274.4 ($M^+ + H$); anal. calcd. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found C, 70.26; H, 7.03; N, 5.16.

1-(2-Methoxyphenoxy)-3-(4-methoxyphenylamino)propan-2-ol (3l): White solid; mp 66–68°C; ^{1}H NMR: δ = 3.26 (dd, J = 12.6 and 6.4 Hz, 1H, CH_2-N), 3.42 (dd, J = 12.6 and 4.4 Hz, 1H, CH_2-N), 3.76 (s, 3H, O-CH_3), 3.88 (s, 3H, O-CH_3), 4.08 (dd, J = 9.8 and 6.3 Hz, 1H, CH_2-O), 4.16 (dd, J = 9.8 and 3.6 Hz, 1H, CH_2-O), 4.28 (m, 1H, CH—OH), 6.72 (m, 2H, Ar), 6.81 (m, 2H, Ar), 6.95 (m, 4H, Ar); IR (KBr) υ: 3435, 3379, 2933, 1593, 1514, 1253, 1124, 822, 746 cm^{-1};EI-MS (m/z): 304.2 ($M^+ + H$); anal. calcd. for $C_{17}H_{21}NO_4$. C, 67.31; H, 6.98; N, 4.62. Found C, 67.19; H, 7.03; N, 4.68.

1-(3-Chlorophenylamino)-3-(2-methoxyphenoxy)propan-2-ol (3m): White solid; mp 53–54°C; ^{1}H NMR: δ = 3.24 (dd, J = 12.7 and 6.4 Hz, 1H, CH_2-N), 3.42 (dd, J = 12.7 and 4.5 Hz, 1H, CH_2-N), 3.88 (s, 3H, O-CH_3), 4.05 (dd, J = 9.8 and 6.3 Hz, 1H, CH_2-O), 4.16 (dd, J = 9.8 and 3.6 Hz, 1H, CH_2-O), 4.23 (m, 1H, CH-OH), 6.52 (m, 1H, Ar), 6.66 (m, 2H, Ar), 6.91 (m, 3H, Ar), 6.99 (m, 1H, Ar), 7.07 (m, 1H, Ar); IR (KBr) υ: 3421, 3300, 2912, 1601, 1508, 1256, 1127, 822, 738 cm^{-1}; EI-MS (m/z): 308.8 ($M^+ + H$); anal. calcd. for $C_{16}H_{18}ClNO_3$: C, 62.44; H, 5.89; N, 4.55. Found C, 62.29; H, 5.95; N, 4.61.

1-(2-Methoxyphenoxy)-3-(2-methoxyphenylamino)propan-2-ol (3n): Oil; ^{1}HNMR: δ = 3.50 (dd, J = 12.6 and 7.1 Hz, 1H, CH_2-N), 3.65 (dd, J = 12.6 and 3.7 Hz, 1H, CH_2-N), 3.85 (s, 3H, O-CH_3), 4.10 (m, 2H, CH_2-O), 4.50 (m, 1H, CH—OH), 6.95 (m, 4H, Ar), 7.13 (m, 1H, Ar), 7.29

(m, 1H, Ar), 7.38 (m, 1H, Ar), 7.50 (m, 1H, Ar); IR (film) υ: 3438, 3396, 2935, 1594, 1505, 1254, 826, 746 cm^{-1}; EI-MS (m/z): 304.3 ($M^+ + H$); anal. calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found C, 67.19; H, 7.26; N, 4.61.

1-(4-Chlorophenylamino)-3-(2-methoxyphenoxy)propan-2-ol (3o): White solid; mp 70–72°C; ^{1}HNMR: $\delta = 3.25$ (dd, $J = 12.7$ and 6.4 Hz, 1H, CH_2-N), 3.40 (dd, $J = 12.7$ and 4.4 Hz, 1H, CH_2-N), 3.89 (s, 3H, O-CH_3), 4.07 (dd, $J = 9.8$ and 6.4 Hz, 1H, CH_2-O), 4.15 (dd, $J = 9.8$ and 3.5 Hz, 1H, CH-OH), 4.24 (m, 1H, CH-OH), 6.62 (m, 2H, Ar), 6.92 (m, 3H, Ar), 7.00 (m, 1H, Ar), 7.13 (m, 2H, Ar); IR (KBr) υ: 3433, 3387, 2931, 1599, 1505, 1253, 1125, 744 cm^{-1}; EI-MS (m/z): 308.8 ($M^+ + H$); anal. calcd. for $C_{16}H_{18}ClNO_3$: C, 62.44; H, 5.89; N, 4.55. Found C, 62.58; H, 5.83; N, 4.39.

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