Microwave-enhanced catalyst-free aminolysis of epoxides with anilines in aqueous phase: efficient synthesis of β-amino secondary alcohols

Zhengyin Du,* Wenwen Zhang, Yuanmin Zhang and Xiaohong Wei

Key Laboratory of Eco-Environment Related Polymer Materials of Ministry of Education, Key Laboratory of Polymer Materials of Gansu Province & College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou 730070, P. R. China

β-Amino secondary alcohols were formed by aminolysis of epichlorohydrin and styrene oxide with aromatic amines using aqueous ethanol (1:1) as the solvent in conjunction with microwave irradiation without a catalyst. The methodology is fast, efficient, highly regioselective, chemoselective and environmentally benign.

Keywords: amination, epoxides, ring opening, aqueous phase reaction, microwave irradiation, green chemistry

Epoxides play an important role in organic synthesis because their highly strained three-membered ring makes them sensitive to various nucleophiles. Apart from alcohols and thiols, amines are also effective nucleophiles. The ring-opening of epoxides with amines is an atom-economical reaction and an important route for the preparation of β-amino alcohols that are key intermediates in the synthesis of biologically active natural products and pharmaceuticals.[1] It is also used in the synthesis of unnatural amino acids and chiral auxiliaries.[2] This reaction shows a regioselectivity based on the electronic properties of the substituents on the substrates and the reaction conditions (Scheme 1).

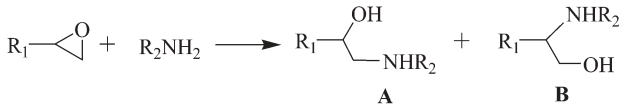
Recently, the reaction has been studied in order to improve the selectivity of the products and reaction conditions. Lautens and Fagnou[3] reported that the rhodium-catalysed ring opening of vinyl epoxides with alcohols and aromatic amines possessed excellent diastereo- and regioselectivity. As a strong Lewis acid, stoichiometric amounts of indium tribromide were reported to promote the ring opening of epoxides with aromatic amines to form β-amino secondary alcohols exclusively in CH_2Cl_2 at room temperature.[4] The synthesis of β-amino alcohols by the regioselective ring opening of styrylepoxides with anilines catalysed by cobalt chloride gave the corresponding primary alcohols as the main product.[5] The enantioselective ring opening of meso-epoxides by aromatic amines catalysed by lanthanide iodobinaphtholates,[6] $Sc(OSO_3C_{12}H_{25})_3$/chiral bipyridine ligand[7] and Zn(II)/Cu(II) surfactant-type catalysts[8] has also been studied and good to excellent enantioselectivities have been achieved with enantiomeric excesses up to 96%. Some environmental friendly reagents and reaction procedures have been investigated in the context of green chemistry. Three-dimensional mesoporous aluminosilicate[9] and nanoporous aluminosilicate materials[10] as structure- directing agents and solid acids were prepared and found to be highly selective and recyclable heterogeneous catalysts for the synthesis of β-amino alcohols in good yields with high selectivity for the Markovnikov addition product. Silica chloride nanoparticles have also been described as catalysts for this reaction.[11] Tertiary amines, such as DABCO and triethylamine are highly efficient catalysts in the ring-opening reactions of epoxides with amines in water under mild conditions.[12] The zinc (II) perchlorate hexahydrate catalysed opening of epoxide ring by amines, introduced by Chakraborti *et al*. under solvent-free conditions,[13] showed excellent chemo-, regio-, and stereoselectivities. A thiourea derivative was also reported by Chimni's group as a highly efficient catalyst for aminolysis of epoxides under solvent-free conditions.[14] In addition, a few examples of the ring opening of epoxides without the use of any catalyst have been disclosed. Highly chemoselective addition of amines to epoxides in water was introduced by Saidi and Azizi in 2005.[15] Qu *et al.*[16] found that hot water of 60–100 °C acted as a mild acidic catalyst and solvent to promote the ring-opening of epoxides by aniline without any additive. Although the microwave-assisted ring opening of epoxides by amines in absolute ethanol in the absence of activators proceeded rapidly and efficiently, the nucleophilic reagents were limited to aliphatic amines and not aromatic amines.[17] However, the above-mentioned procedures suffer from some disadvantages.

The aminolysis of asymmetric epoxides by aromatic amines described previously gave the corresponding β-amino primary alcohols **B** as main products, except in one case[4] in which the products were β-amino secondary alcohols **A**. In order to overcome these shortcomings and based on our investigation about green organic synthesis,[18–20] we have developed a practical, rapid and efficient method for the aminolysis of epoxides with aromatic amines.

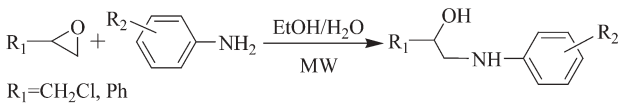
Results and discussion

We report here a catalyst-free ring-opening reaction of epoxides with anilines using microwave irradiation in aqueous alcohol. We obtained the corresponding β-amino secondary alcohols exclusively in high yields, unlike the previous reports (Scheme 2).

The ring-opening of epichlorohydrin (**C**) with aniline (**D**) was used as the model reaction to examine the selectivity and yield with respect to the solvent, the microwave power, the molar ratio of the two substrates, and the reaction time. The results are listed in Table 1. First, we surveyed the effects of different solvents on the reaction with the molar ratio of **C/D**=2/1 (Table 1, entries 1–16) and irradiating at 264 W for 10 min. A yield of 78% of the corresponding product was observed in aqueous ethanol (1:1 in volume) (Table 1, entry 13). Then we explored the optimal power of microwave irradiation (Table 1, entries 13 and 17–19) and found that the optimal is 264 W. The ratio of the two substrates were also examinedshowing that a molar ratio of **C/D** = 3:1 gave a yield of 84% (Table 1, entry 21). Finally, the irradiation time was studied revealing that 8 minutes was the most effective (Table 1, entry 25).



Scheme 1 Ring-opening of epoxides with amines.



Scheme 2 Ring-opening of epoxides with anilines.

* Correspondent. E-mail: clinton_du@126.com

Table 1 Ring-opening reaction of epichlorohydrin **C** with aniline **D** in different conditions[a]

Entry	Solvent (V/V)	Molar ratio of **C**/**D**	Power /W	Time /min	Yield /%[b]
1	THF	2:1	264	10	21
2	THF/H_2O (1:1)	2:1	264	10	59
3	THF/H_2O (2:1)	2:1	264	10	12
4	THF/H_2O (4:1)	2:1	264	10	7
5	CH_2Cl_2	2:1	264	10	17
6	CH_3CN	2:1	264	10	20
7	CH_3CN/H_2O (1:1)	2:1	264	10	38
8	CH_3OH	2:1	264	10	16
9	CH_3OH/H_2O (1:1)	2:1	264	10	77
10	PEG-400/H_2O (1:1)	2:1	264	10	30
11	Toluene	2:1	264	10	3
12	EtOH	2:1	264	10	39
13	EtOH/H_2O (1:1)	2:1	264	10	78
14	EtOH/H_2O (1:2)	2:1	264	10	56
15	EtOH/H_2O (2:1)	2:1	264	10	47
16	H_2O	2:1	264	10	68
17	EtOH/H_2O (1:1)	2:1	136	10	51
18	EtOH/H_2O (1:1)	2:1	440	10	63
19	EtOH/H_2O (1:1)	2:1	616	10	61
20	EtOH/H_2O (1:1)	1:1	264	10	70
21	EtOH/H_2O (1:1)	3:1	264	10	84
22	EtOH/H_2O (1:1)	4:1	264	10	66
23	EtOH/H_2O (1:1)	1:2	264	10	61
24	EtOH/H_2O (1:1)	3:1	264	5	82
25	EtOH/H_2O (1:1)	3:1	264	8	87
26	EtOH/H_2O (1:1)	3:1	264	12	81
27	EtOH/H_2O (1:1)	3:1	264	15	85
28	EtOH/H_2O (1:1)	3:1	264	20	77

[a] The scale of aniline was 0.5 mmol and the total volume of solvents was 4 mL.
[b] Isolated yield after column chromatography.

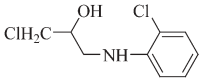
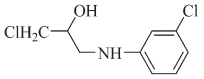
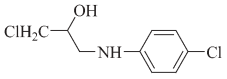
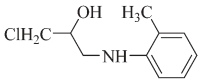
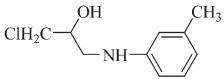
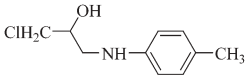
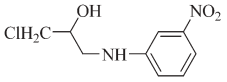
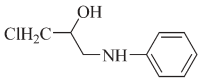
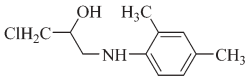
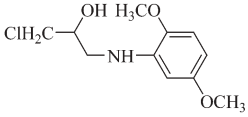
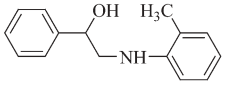
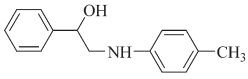
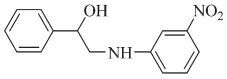
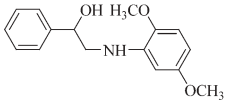
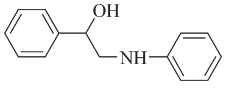
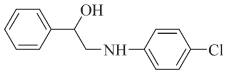
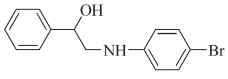
After optimisation of the reaction conditions, we investigated the scope and limitation of the ring-opening reaction. Epichlorohydrin and styrene oxide, as representatives of aliphatic and aromatic epoxide respectively, were examined in this reaction. The results shown in Table 2 reveal that epoxides reacted with a number of aromatic amines with different substituents to form the corresponding β-amino alcohols in good to excellent yields. The reaction was completely regioselective and chemoselective since the only products isolated were β-amino secondary alcohol isomers arising from attack of the amine at the less substituted carbon of epoxides. No diols of hydrolysis of epoxides were observed. This selectivity was observed even for styrene oxide (Table 2, entries 11–17), unlike most previously reports.[5,9–11,13–16] In comparison with electron-withdrawing groups, electron-donating groups attached to the aromatic ring of amines gave higher yields in the ring-opening of epichlorohydrin to form β-amino alcohols (Table 2, entries 1–10). Styrene oxide showed the same pattern under these conditions (Table 2, entries 11–17). For the same aniline, the reaction of styrene oxide resulted in a lower yield than epichlorohydrin. This may be explained by greater steric hindrance and conjugative effects of benzene ring of styrene oxide.

In conclusion, we have developed a new methodology for C–N bond-formation via aminolysis of epoxides with aromatic amines without catalysts in aqueous alcohol under microwave irradiation. It is a simple, high efficient, completely regioselective and chemoselective procedure for the synthesis of β-amino secondary alcohols.

Experimental

All reagents were used as obtained from commercial sources without further purification. The ^1H and ^{13}C NMR spectra were recorded on a

Table 2 Ring-opening reaction of epoxides with various aromatic amines[a]

Entry	R^1	R^2	Product		Yield /%[b]
1	$ClCH_2$	2-Cl		**a**[21,22]	48
2	$ClCH_2$	3-Cl		**b**[21]	57
3	$ClCH_2$	4-Cl		**c**[21,23]	68
4	$ClCH_2$	2-CH_3		**d**[23]	82
5	$ClCH_2$	3-CH_3		**e**[24]	89
6	$ClCH_2$	4-CH_3		**f**[21,23]	93
7	$ClCH_2$	3-NO_2		**g**[23]	73
8	$ClCH_2$	H		**h**[21,22]	87
9	$ClCH_2$	2,4-$(CH_3)_2$		**i**	100
10	$ClCH_2$	2,5-$(CH_3O)_2$		**j**[21]	95
11	Ph	2-CH_3		**k**[23]	81
12	Ph	4-CH_3		**l**[23]	89
13	Ph	3-NO_2		**m**[23]	70
14	Ph	2,5-$(CH_3O)_2$		**n**	91
15	Ph	H		**o**[22,23]	85
16	Ph	4-Cl		**p**[23]	66
17	Ph	4-Br		**q**[23]	69

[a] Reaction conditions: amines (0.5 mmol), epoxides (1.5 mmol), EtOH (2 mL), water (2mL), MW 264 W, 8 minutes.
[b] Isolated yields after column chromatography; all known products were characterised by ^1H and ^{13}C NMR, which were consistent with literature data.

Bruker MERCURY-PLUS 400 MHz NMR spectrometer. Chemical shifts were reported in parts per million (ppm, δ). IR spectra were measured on an Alpha Centauri FT-IR spectrometer. Melting points were determined on an XT-4 electrothermal micromelting-point apparatus. Microwave irradiation was carried out with a modified Midea MM823ESJ-PA domestic microwave oven. In order to avoid the unreliable and un-reproducible results by using this microwave oven, all experiments were conducted at least twice under parallel conditions to obtain coincident yield.

Caution: the use of a domestic microwave oven for chemical purposes has been found to be potentially hazardous.

Synthesis of β-amino alcohols

A mixture of the amine (0.5 mmol), epoxide (1.5 mmol), EtOH (2.0 mL) and H_2O (2.0 mL) were added to a 50 mL round-bottomed flask. The flask was placed into the domestic microwave oven at 264 W for 8 minutes. After cooling the reaction mixture to room temperature, the contents were extracted with ethyl acetate (4 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$. The solvent was removed by evaporation under reduced pressure to afford the crude products, which were further purified by column chromatography on silica gel using petroleum ether and ethyl acetate as eluents.

Physical spectroscopic data of new products

1-Chloro-3-(2,4-dimethylphenylamino)propan-2-ol (**i**): A light red solid, m.p. 34–35 °C. ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): δ = 6.91–6.84 (m, 2H, ArH), 6.55–6.51 (m, 1H, ArH), 4.04–3.98 (m, 1H, NH), 3.62–3.52 (m, 2H, CH_2), 3.33–3.29 (m, 3H, CH_2 & OH), 3.20–3.12 (m, 1H, CH), 2.26 (s, 3H, CH_3), 2.10 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): δ = 143.1, 131.1, 127.3, 127.0, 122.8, 110.4 (all unsaturated CH), 69.5 (C-O), 47.6 (CH_2), 47.2 (CH_2), 20.2 (CH_3), 17.3 (CH_3); IR (KBr, υ/cm^{-1}): 3404 (NH), 1618 (benzene ring), 1514 (benzene ring), 1378 (CH_3), 749 (C-Cl); Anal. Calcd for $C_{11}H_{16}ClNO$ (213.09): C, 61.82; H, 7.55; N, 6.55. Found: C, 61.63; H, 7.61; N, 6.51%.

2-(2,5-Dimethoxyphenyl-amino)-1-phenylethanol (**n**): A light green liquid. ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): δ = 7.36–7.30 (m, 4H, ArH), 7.26–7.22 (m, 1H, ArH), 6.67 (d, *J* = 8.4 Hz, 1H, ArH), 6.14–6.11 (m, 1H, ArH), 6.02 (d, *J* = 2.8 Hz, 1H, ArH), 5.04 (s, 1H, NH), 4.50–4.47 (m, 1H, CH), 3.95–3.76 (m, 2H, CH_2), 3.89 (s, 3H, OCH_3), 3.62 (s,3H, OCH_3), 1.81 (s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): δ = 154.4, 141.8, 140.0, 138.1, 128.8, 127.6, 126.7, 109.8, 99.7, 99.4 (all unsaturated CH), 67.4 (C-O), 59.7 (CH_2), 56.0 (OCH_3), 55.3 (OCH_3); IR (liquid film, υ/cm^{-1}): 3420 (NH), 1610 (benzene ring), 1519 (benzene ring), 1216 (OCH_3); Anal. Calcd for $C_{16}H_{19}NO_3$ (273.14): C, 70.31; H, 7.01; N, 5.12. Found: C, 70.68; H, 7.06; N, 5.09%.

Electron Supplementary Information

Electron Supplementary Information includes spectroscopic data and ^{1}H NMR, ^{13}C NMR spectra of all products and is available online via http://www.ingentaconnect.com/content/stl/jcr.

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