Silica Perchloric Acid Matrix Supported Ring Opening of Epoxide Under Microwave Radiation[†]

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Abstract: An efficient and economically feasible microwave-assisted eco-friendly reaction was developed for the preparation of β-amino alcohols from aminolysis of epoxides. The reaction was executed on the reusable perchloric acid supported silica matrix ($HClO_4$–SiO_2) surface in a microwave. The yields of β-amino alcohols are uniformly good. The applicability of the catalyst was studied in the synthesis of propranolol, a cardiovascular drug. The results were presented.

Keywords: Microwave irradiation, Epoxides, Reusable catalyst, Silica perchloric acid, Propranolol

Introduction

Now-a-days, it is a big challenge in the field of chemistry, to develop new synthetic processes which are having reduced amount of jeopardy to humans and environment, than the conventional processes. In the industrial sector, economically viable and recyclable catalyst supported reactions are playing a significant role. The use of microwave-assisted reactions could be a prominent protocol for the synthesis of organic molecules in industrial sector with eco pleasant manner[1-4]. The concept of utilizing catalysts in microwave-assisted reactions is a vital task to develop better reaction conditions. In such reactions catalysts often have the advantages *viz.*, mild reaction conditions, ease of setup and work-up, increased yield and greater selectivity. In the present study, perchloric acid supported silica matrix ($HClO_4$–SiO_2) was chosen for nucleophilic ring opening of epoxides by amines (aminolysis), because of its easy preparation, reusability and inexpensive. The $HClO_4$-SiO_2 has been proven recently that it is a mild, sensible heterogeneous catalyst, which is efficiently and selectively catalyzes the various organic transformations[5-7]. Thus, microwave-assisted $HClO_4$–SiO_2 supported system is more advantageous for the development of efficient and cost-effective synthetic protocols for the preparation of organic molecules.

β-Amino alcohols are the attractive intermediates for many organic compounds, particularly biologically active compounds of natural and synthetic origin[8,9]. They have been widely used as β-blockers, insecticidal agents and chiral auxiliaries[10]. The most frequently used method for the preparation of β-amino alcohols is the aminolysis of epoxides which is carried out in excess of amines at high temperatures. These high temperature reaction conditions may not be appropriate for certain functional groups and for the control of regioselectivity[11]. A range of various promoters or activators have been used for this process such as metal halides[12-16], metal salts[17], metal amides[18-20], metal alkoxides[21], metal triflates[22-25], alumina[26,27] and montmorillonite under microwave conditions[28]. The core limitations such as the requirement of overindulgence of amines, elevated temperature, poor reactivity of less nucleophilic and sterically hindered amines, lack of appreciable regioselectivity, undesired side reactions such as rearrangement or polymerization with sensitive epoxides, *etc.* associated with the classical approach of heating the mixture of epoxide and amine guided to the development of various catalytic procedures. Hence, it necessitates a demand to develop cost-effective and efficient synthetic procedures for the ring opening of epoxides by amines. A microwave-assisted $HClO_4$–SiO_2 supported system for the aminolysis of epoxides has been developed in order to overcome above mentioned limitations. In continuation of our investigation on the microwave-assisted organic synthesis[29], here the present report describes an efficient and economically feasible microwave-promoted solid supported procedure for aminolysis of epoxides. Using epoxides and amines as substrates, the reaction was carried out in presence of $HClO_4$–SiO_2 to yield corresponding enantio pure β-amino alcohols with an advantage of catalyst recyclability (Scheme 1). Ten different substituted amines were taken up and the final products (β-amino alcohol) were prepared, purified and characterized by spectroscopic data. Besides the above, a cardiovascular drug molecule *viz.* (*RS*)-propranolol was prepared in good yields and characterized.
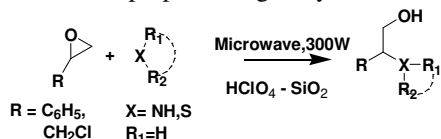
R_1=H, R_2= 2substiturte aryls, R_1=R_2=Piperidine & Morpholine

Scheme 1. Ring opening of epoxides by amines/thiols employing silicaperchloric acid matrix under microwave irradiation

Experimental

Preparation of $HClO_4$–SiO_2 matrix[30]

$HClO_4$ (1.25 g, 12.5 mmol), as a 70% aqueous solution was added to the suspension of silica gel (23.75 g, 230-400 mesh) in Et_2O. The mixture was concentrated and the residue was heated at 100 °C for 72 h under vacuum to afford $HClO_4$-SiO_2 (0.5 m mol g^{-1}) as a free flowing powder.

General synthesis of β-amino alcohols

In a typical experimental procedure, a mixture of epoxide (1 m mol), amine (1.2 m mol) and catalyst (15 mol %) were grinded in mortar and pestle and irradiated in a microwave (Panasonic inverter, 300 W) for different time intervals which were tabulated (Table 1 & 3.) After completion of the reaction, 10 mL of diethyl ether was added to the reaction mixture to filter the catalyst and triturated with water (5 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The obtained crude product was purified by column chromatography.

Typical procedure for the preparation of 1-naphthylglycidic ether

To a magnetically stirred solution of 1-naphthol (360 mg, 2.5 mmol) in anhydrous MeCN (10 mL) and K_2CO_3 (690 mg, 5 mmol), (*RS*)-epichlorohydrin (0.29 mL, 3.75 mmol) were added and the reaction mixture was heated under reflux for 16. The cooled (rt) reaction mixture was filtered, the filtrate was concentrated under vacuum and the residue was purified by passing through a column chromatography of silica gel (60-120 mesh) and eluting with EtOAc:Hexane (2:8) to aforded (*RS*)- 1-naphthylglycidic ether.

Typical procedure for the preparation of (RS)-propranolol

A mixture of *RS*- naphthylglycidic ether (200 mg, 1 mmol), isopropyl amine (58 mg, 1 mmol) were grinded by silicaperchloric acid catalyst (20 mol %) and was kept under microwave irradiation for 10 min. After completion of the reaction (18 min, TLC, GCMS), the reaction mixture was diluted with Et_2O (15 mL), was quenched with water (5 mL), was dried over $MgSO_4$ and was concentrated under vacuum to afford (*RS*)-propranolol.

Spectral data for the selected compounds

1-Chloro-3-(2, 6-diisopropyl-phenylamino)-propan-2-ol

Liquid IR (cm^{-1}): 3412, 3070, 2964, 1620, 1460, 1263,1089; ^{1}H NMR (90MHz, CDCl$_3$): 7.21 - 6.99 (m, 3H), 4.90 (br s, 1H,), 3.74 (m, 1H), 3.19 - 3.12 (m, 4H), 3.04 – 2.97 (m, 2H), 1.51-1.21 (br m, 6H);^{13}C NMR (22.5MHz, CDCl$_3$): 142.65, 132.41, 124.41, 123.56, 122.64, 118.64, 70.39, 54.29, 47.30, 27.62, 24.21, 22.42. GC-MS: 269[*m/e*].

1-Chloro-3-(2-chloro-phenylamino)-propan-2-ol

Liquid IR (cm^{-1}): 3468, 3370, 3010, 2964, 1620, 1496, 1263,1095; ^{1}H NMR (90MHz, CDCl$_3$): 7.06-6.43 (m, ArH), 3.98 (t, 1H,), 3.59 (m, 1H), 3.24-3.19 (m, 2H), 3.12 (m, 2H), 2.12 (br s, 1H); ^{13}C NMR (22.5MHz, CDCl$_3$): 149.07, 135.07, 130.46, 118.24, 117.74, 115.47, 114.91, 113.24, 112.68, 111.95, 111.38,70.26,69.36,48.35,47.55,46.91. GC-MS: 219[*m/e*].

1-Phenyl-2-p-tolylamino-ethanol

Liquid, IR (cm^{-1}): 3610, 3417, 2877, 1620, 1519, 1265; ^{1}H NMR (90MHz, CDCl$_3$): 2.22(s,3H), 3.63-3.80 (m,1H), 4.16 (brs,1H), 4.37 (m,1H), 4.53 (m,2H), 6.36-7.54 (br m, ArH); ^{13}C NMR (22.5MHz,CDCl$_3$): 149.96 ,144.94, 140.37, 129.59, 128.69, 127.48, 127.10, 126.74, 113.78, 20.47. GC-MS: 227[*m/e*].

2-(2-Methoxyphenylamino)-2-phenylethanol

^{1}H NMR (CDCl$_3$, 400 MHz): δ 2.07 (bs, 1 H), 3.76 (dd, 1 H, J = 10.8, 7.3 Hz), 3.87 (s, 3 H), 3.89_3.93 (m, 1 H), 4.50 (dd, 1 H, J = 7.9, 4.7 Hz), 5.0 (bs, 1 H), 6.45 (dd, 1 H, *J* = 8.1, 1.48 Hz), 6.61-6.78 (m, 3 H),7.22-7.35 (m, 5 H). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 55.4, 59.8, 67.4, 109.4, 111.5, 117.1, 121.1, 126.7, 127.5, 128.7, 137.0, 140.2, 147.1. GC-MS: 243 (*m/e*)[31a].

2-(4-Methoxyphenylamino)-2-phenylethanol

Liquid, IR (cm^{-1}): 3610, 3394, 3016, 2939, 1620, 1512, 1219, 1035; ^{1}H NMR (CDCl$_3$, 400 MHz): δ 3.68 (s, 3 H), 3.70 (dd, 1 H), 3.89 (dd, 1 H), 4.41 (dd, 1 H), 6.52 (d, 2 H), 6.79 (d, 2 H), 7.23-7.35 (m, 5 H). ^{13}C NMR (CDCl$_3$, 100 MHz): δ 55.7, 60.8, 67.3, 114.7, 115.3, 126.7, 127.5, 128.8, 140.3, 141.3, 152.3. GC-MS: 243 (*m/z*)[31b].

1-Phenyl-4-chlorophenylamino-ethanol

Liqiud IR (cm^{-1}): 3479, 3394, 3016, 1620, 1496, 1280,1095; ^{1}H NMR (90MHz, CDCl$_3$): 7.32-6.82 (m, ArH),6.58-6.49 (d, 2ArH,), 5.00-4.92 (m, 1H), 4.16 (br s, 1H), 3.43 (br s, 1H), 3.18-3.15(m,2H); ^{13}C NMR (22.5 MHz , CDCl$_3$): 144.92,139.14, 135.71, 131.26, 129.61, 128.67, 128.20, 128.02, 127.12,126.31,126.03,125.71,12.34,116.06,115.69.GC-MS:247[*m/e*][31c].

2-Phenyl-2-phenylsulfanyl-ethanol

^{1}H NMR (90MHz, CDCl$_3$): 7.32 (brm, ArH), 5.20 (brs, 1H), 4.70-4.40 (brm, 2H), 3.28-3.20 (brm, 1H); ^{13}C NMR (22.5 MHz, CDCl$_3$): 139.74, 138.05, 134, 46,132.87, 131.08, 130.05, 129.51, 129.00, 128.58, 128.39, 128.21, 127.82, 126.92, 126.49, 125.66, 59.09.

1-Naphthylglycidic ether

^{1}H NMR (400 MHz, CDCl$_3$): 2.84-2.87 (m, 1 H), 2.95- 2.98 (m, 1 H), 3.48-3.49 (m, 1 H), 4.15 (dd, 1 H; *J* = 5.5, 11.0 Hz), 4.40 (dd, 1 H; *J* = 3.0, 11.0 Hz), 6.81 (d, 1 H; *J* = 7.5 Hz),7.36 (t, 1 H; *J* = 8.0 Hz), 7.43-7.52 (m, 3 H), 7.78-7.81 (m, 1 H), 8.28-8.31 (m, 1 H) identical with those reported in the literature[32]. ^{13}C NMR: 154.04, 134.43, 134.27, 127.31, 126.36, 125.52, 125.20, 122.90, 121.74, 120.72, 70.31, 50.91, 44.48.
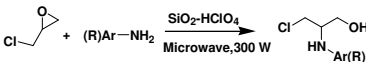
(RS)-Propranolol

^{1}H NMR (400 MHz, CDCl$_3$):1.14 (s, 3 H), 2.60 (bs, 1 H, OH), 2.90-3.02 (m, 3 H), 4.19 (m, 3 H), 6.82 (d, 1 H; *J*=6.6 Hz), 7.25-7.46 (m, 5 H), 7.78 (m, 1 H), 8.22 (m, 1 H), identical with the authentic sample.

Results and Discussion

Initially, the efforts were taken up to optimize the finest reaction conditions for the synthesis of β-amino alcohols. A variety of aryl amines, epoxides and catalyst were mixed and placed in a microwave oven for specific time intervals as shown in Table 1. The reaction was monitored by TLC and the completion of the reaction was confirmed by the complete disappearance of the starting materials. After treating the mixture with diethyl ether and water crude product was obtained, this was purified by column chromatography. The regioselectivity of the products was identified by GCMS. The obtained products were characterized by comparing with literature reports[33].

Table 1. Ring opening of epichlorohydrin by various amines

Entry	Amine	Time, min	Product	Yield, %
1	X=H	3	X=H	92
2	X=2-CH$_3$	4	X=2CH$_3$	93
3	X=4-CH$_3$	4	X=4CH$_3$	92
4	X=2,6-CH(CH$_3$)$_2$	3	X=2,6 CH(CH$_3$)$_2$	82
5	X=2-OCH$_3$	5	X=2OCH$_3$	90
6	X=4-OCH$_3$	7	X=4OCH$_3$	92
7	X=2-Cl	6	X=2Cl	61
8	X=4-Cl	7	X=4Cl	63
9	X=4-F	6	X=4F	68
10	X=H, N,N-2CH$_3$	N.R		

[a]*Yields corresponds to isolated products after usual workup; No Reaction(N.R)*

To evaluate generality of the catalyst; various substituted amines were used in ring opening of epoxides. The substituent/functional group present in the aromatic amine was found to have significant influence on the reaction. In general, electron-rich aromatic amines required lesser reaction times compared to others. On the basis of these results, we corroborate

that catalyst enhanced the rate of the reaction and yield of products. *N, N*-dimethyl aniline could not react with epichlorohydrin and styrene oxide (Table 1, entriy 10 and table 2 entry 10); confirming the cleavage of epoxide rings could not occur by tertiary amines. The presence of electron withdrawing groups at ortho and para in aniline decreases the yield of the *β*-amino alcohols. This happens due to the decrease of nucleophilc nature of anilines by presence of electron withdrawing groups at ortho and para positions.

The amino alcohols derived from nucleophilic attack at the less substituted carbon atom of the epoxide rings were obtained as the exclusive/major products (GCMS). The reaction with epichlorohydrin provided an example of excellent chemoselectivity and no product from nucleophilic substitution of the chlorine atom was formed (GCMS).

The regioselectivity of the microwave-assisted $HClO_4$–SiO_2 supported reaction was evaluated by the reaction of styrene oxide with various amines and the data confirmed by GCMS analysis. The regioisomer formed by the reaction of the amine at the benzylic carbon atom of the epoxide ring showed the characteristic ion peak at *m/z* [M+ - 31] due to the loss of the CH_2OH in the GC-MS[34]. The reaction of styrene oxide with various amines was best catalysed by silicaperchloric acid matrix to afford 96% conversion to the amino alcohols with preferential nucleophilic attack at the benzylic carbon of the epoxide ring obtaining the major product with 99% regioselectivity (Table 2).

Table 2. Silicaperchloric acid matrix catalyzed ring opening of styreneoxide by various amines

Entry	Amine	Time, min	Product	Yield, %
	X (NH$_2$ aniline)		X (product)	
1	X=H	5	X=H	92
2	X=2-CH$_3$	12	X=2-CH$_3$	88
3	X=4-CH$_3$	9	X=4-CH$_3$	92
4	X=2-OCH$_3$	10	X=2-OCH$_3$	90
5	X=4-OCH$_3$	7	X=4-OCH$_3$	92
6	X=2-Cl	6	X=2-Cl	61
7	X=4-Cl	5	X=4-Cl	58
8	O_NH (morpholine)	18	NH (piperidine)	70[b]
9	O_NH (morpholine)	15	NH (piperidine)	73[b]
10	X=H, N,N-2CH$_3$	N.R		

[a]Yields corresponds to isolated products after usual workup;[b] The isomers cannot be separated and the yields corresponds to mixture of isomers. No Reactio(N.R)

Further it was anticipated to examine the reusability of the catalyst. After completion of the reaction, the catalyst was recovered by filtering the reaction mixture with the addition of diethyl ether (10 mL), which was activated at 150 $^{\circ}$C for 5 hours and used again in the reactions. The catalyst reactivity was preserved in the subsequent five test runs under the optimized reaction conditions and the results were tabulated in Table 3.

Table 3. Recyclability of the catalyst

| S.No	Catalyst recovery[*], %	Yield, %
1	-	92
2	95	88
3	93	85
4	95	82
5	90	80

* Catalyst recovered after washing with diethyl ether.

The formation of *β*-amino alcohols by the reaction of styrene oxide with various amines can be explained by carbocationinc character at benzylic carbon of the epoxide ring. Thus, aromatic amines react selectively at the benzylic carbon of the styrene oxide with anti-Markovnikov addition due to less nucleophilicity. The carbocationic character at the benzylic position of the epoxide ring is demonstrated that an increase in polarity of the reaction medium by the use of fluoro alcohols[35] and ionic liquids[10] leads to selective nucleophilic attack in the absence of metal catalyst.

Further studies were extended to the ring opening of styrene oxide by thiophenol emplyoing $HClO_4$–SiO_2 matrix under the said optimized conditions (Scheme 2). The product obtained according to anti-Markovnikov addition and it was confirmed by GCMS (*m/e*: 230) and was characterised by spectroscopic data.
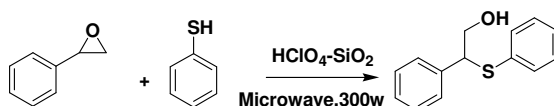
Scheme 2. Ring opening of epoxides employing thiophenol under microwave conditions

The applicability of this methodology is further investigated in the synthesis of cardiovascular drugs such as propranolol as racemic mixture. The synthetic approach involved in the nucleophilic ring opening of the of 1-naphthyl glycidyl ether with isopropyl amine (Scheme 3). The key starting material (*RS*) – naphthyl glycidic ether was prepared in 80% yield by the reaction of 1-naphthol with (*RS*)-epichlorohydrin, in the presence of K_2CO_3 in MeCN under reflux by modification of the reported procedure[30]. The treatment of (*RS*)- naphthyl glycidic ether with $iPrNH_2$ (1 equiv) for 10 min in the presence of $HClO_4$–SiO_2 under microwave conditions afforded (*RS*)-propranolol in 70% yield.
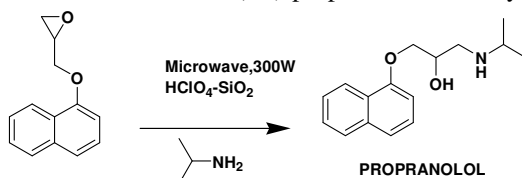
Scheme 3. Synthesis of (*RS*)-propranolol employing silicaperchloric acid catalyst

A possible mechanism for the ring opening of epoxide under the solid supported microwave conditions occurred through the weak interaction between Lewis acid catalyst ($HClO_4$–SiO_2)[5] was proposed and the oxygen atom of epoxide (Scheme 4). The formation of products A and B were attributed by nucleophilic attack of aniline nitrogen atom either on terminal carbon of epoxide to form product A or internal carbon of epoxide to produce product B. After thorough study the formation of product B in enantiomeric pure form is envisaged. However, to establish the detailed mechanism for the aminolysis of epoxide employing $HClO_4$–SiO_2 catalyst under microwave conditions need further investigation.
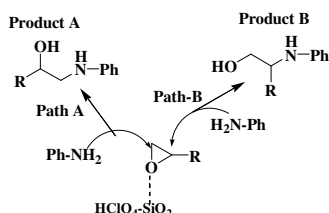
Scheme 4. Plausible mechanism for the ring opening of epoxides employing $HClO_4$-SiO_2 matrix under microwave conditions

Conclusions

In conculsion, $HClO_4$-SiO_2 catalyst effectively promotes the ring opening reaction of epoxides under microwave conditions. The ring opening of terminal epoxides such as styrene oxide produces secondary alcohols in good yields. The notable advantages of this procedure are: (a) reasonably good yields; (b) shorter reaction times; (c) mild reaction conditions; (e) in tune with green synthesis avoiding solvents; (f) reusability of catalyst.

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