

Regioselective ring opening of epoxides with amines using monodispersed silica nanoparticles in water

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Abstract

Monodispersed silica nanoparticles were synthesized and used as catalyst for the regioselective synthesis of β -amino alcohols in water via nucleophilic ring opening of epoxides with amines under ambient conditions in shorter reaction times. The use of water as 'green' solvent allows easy recycling of the catalyst.

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1. Introduction

β -Amino alcohols are versatile organic compounds with pharmaceutical and biological importance [1–5]. The classical method for the synthesis of these compounds involves heating of epoxides in the presence of excess amine at elevated temperature [6,7]. Recently, various methods have been reported using metal amides, metal salts, metal alkoxides, metal triflates, metal halides [8–19]. Some heterogeneous catalysts such as alumina [20], zirconium sulfophenyl phosphonate [21], silica gel [22], clays [23], ionic liquids [24] and polymer supported copper sulphate [25] and rare earth metals [26] were reported for this reaction. The catalyzed as well as uncatalyzed [27,28] aminolysis of epoxides have improved the scope of the reaction considerably; however, there are some limitations such as prolonged reaction times, use of expensive reagents in stoichiometric quantities and hazardous organic solvents.

In recent years, silica nanoparticles have gained importance in scientific research due to their easy preparation and wide applicability as thermal insulators, humidity sensors and also in the field of catalysis. The high surface area of the nanoparticles is responsible for their catalytic activity [29–34].

In view of the great attention paid to the development of organic reactions in aqueous medium [35,36], herein, we report

the synthetic applicability of monodispersed silica nanoparticles for regioselective ring opening of epoxides with amines in water to afford the corresponding β -amino alcohols in good yields with high regioselectivities and in shorter reaction times (Scheme 1).

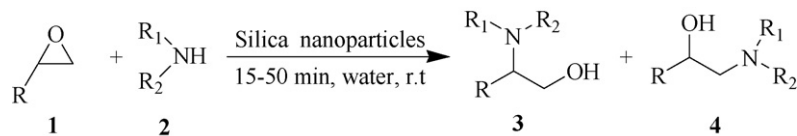
2. Experimental

Styrene oxide, tetraethylorthosilicate (TEOS), cyclohexene oxide and *cis*-dimethyl oxirane were purchased from Aldrich or Fluka and used without further purification. Amines were purchased from S.D. Fine Chemicals Ltd., Mumbai. ACME silica gel (100–200 mesh) was used for column chromatography and thin-layer chromatography (TLC) was performed on Merck-precoated silica gel 60-F₂₅₄ plates. All the other solvents and chemicals were obtained from commercial sources and purified using standard methods.

2.1. Synthesis of monodispersed silica nanoparticles

Monodispersed silica nanoparticles were synthesized according to the procedure reported by Stober et al. [30] Different silica nanoparticles (S1 and S2) were prepared by adjusting the concentrations of ethanol:water:ammonium hydroxide:TEOS and the time for which they react. As the reaction time increases, the particles of silica grow from tens of nanometers to hundreds of nanometers in size. TEOS, ethanol, water and ammonium hydroxide were mixed in molar ratio 1:75:31:4 and 1:75:31:8,

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Scheme 1. Ring opening of epoxides with amines.

respectively and stirred for 3 h till the solution turned milky with time. The silica particles were collected by centrifugation and washed with water for three times.

2.2. Typical procedure for the ring opening of epoxides with amines

In the typical procedure, epoxide (1 mmol), amine (1 mmol) and catalyst (40 mg) were taken in water and stirred at room temperature for the appropriate time. After completion of the reaction, as indicated by TLC, the product was extracted with ethyl acetate (3 mL \times 10 mL). The aqueous layer containing the catalyst was preserved for the next run. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuum and purified by column chromatography on silica gel with ethyl acetate and *n*-hexane as eluent to afford the pure β -amino alcohol. The products were identified by comparing the spectral data with those reported in the literature [15,16,20–22,24].

2.2.1. The spectral data for unknown compounds

3-Phenylamino-butan-2-ol (Table 2, entry 5) ^1H NMR (CDCl_3): δ 7.09–7.14 (m, 3H, phenyl), 6.60–6.70 (m, 2H, phenyl), 3.55–3.64 (q, 1H, CH), 3.27–3.34 (q, 1H, CH), 1.14–1.16 (d, $J=6.79$ Hz, 3H, CH_3), 1.23–1.25 (d, $J=6.04$ Hz, 3H, CH_3). MS (EI) m/z 165 (M^+ peak), 120, 77.

3-Morpholin-4-yl-butan-2-ol (Table 2, entry 6) ^1H NMR (CDCl_3): δ 3.64–3.76 (m, 4H, CH_2), 3.37–3.46 (q, 1H, CH), 2.62–2.66 (m, 2H, CH_2), 2.35–2.42 (m, 2H, CH_2), 2.20–2.31 (q, 1H, CH), 1.12–1.14 (d, $J=6.05$ Hz, 3H, CH_3), 0.92–0.94 (d, $J=6.76$ Hz, 3H, CH_3). MS (EI) m/z (159 M^+ peak), 141, 114, 57.

3. Results and discussion

Although, silica gel was found to be an effective solid catalyst for the ring opening of epoxides with amines [22], in order to study the influence of the size and surface area of the silica particles for the reaction, different monodispersed silica nanoparticles (S1 and S2) of varied sizes and surface area were synthesized according to the procedure reported by Stober et al. [30] and studied for the ring opening reactions.

Transmission electron micrograph (TEM) images of samples S1 and S2 are given in Fig. 1 and as can be noticed the particles are uniformly distributed and are of 60–70 nm and 350 nm size respectively. The BET surface areas of the prepared S1 and S2 particles have been found to be 243.6 and 19.9 m^2/g , respectively.

These particles were employed as catalyst for the ring opening reaction of styrene oxide with aniline in aqueous medium

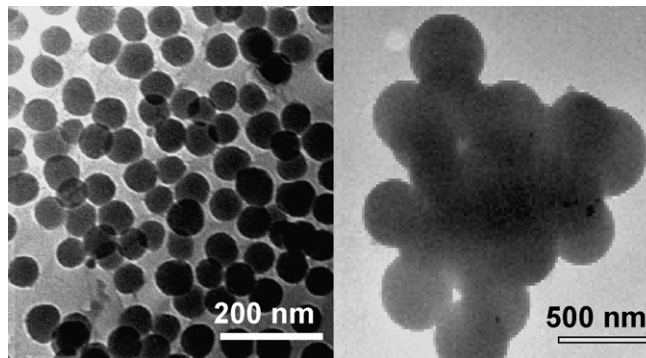


Fig. 1. TEM photographs of S1 and S2 particles.

(Table 1, entry 1). The desired product was obtained in good yields in very short reaction time. Whereas, the same reaction in the presence of silica gel (60–120 mesh), routinely used for column chromatography gave the ring-opening product in 20% yield only. These observations clearly indicate that the synthesized monodispersed silica nanoparticles exhibit higher activity due to an increase in the surface area with reduced size when compared to their micron sized counterparts.

Further, the ring opening reactions of styrene oxide with various primary and secondary aliphatic amines were investigated in water in the presence of silica particles and the results are presented in Table 1. The corresponding β -amino alcohols were

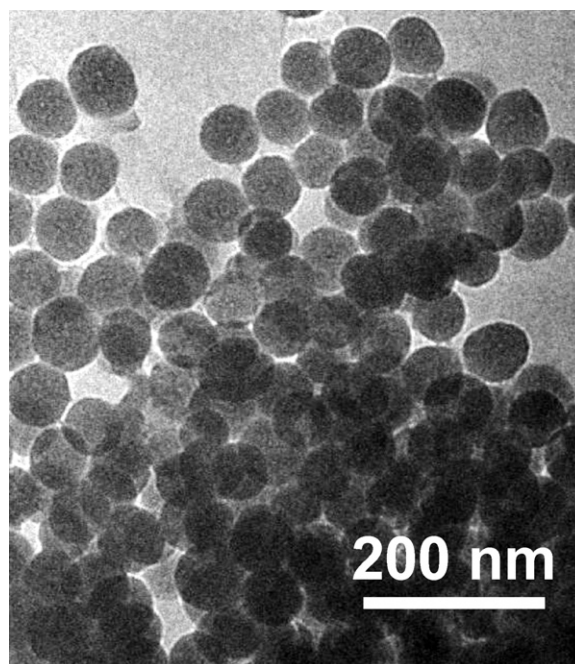
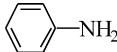
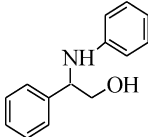
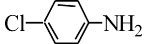
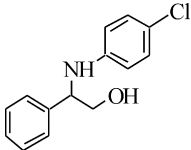
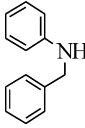
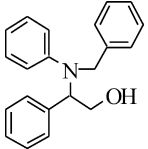
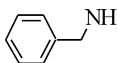
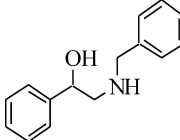

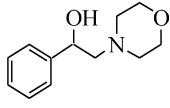

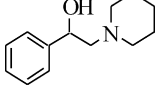

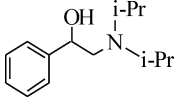

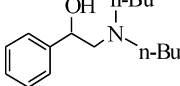

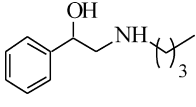

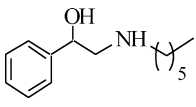
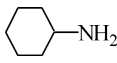
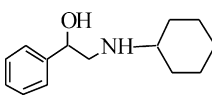


Fig. 2. TEM photograph of used catalyst (S1).

Table 1
 Ring opening of styrene oxide with various amines at room temperature using silica particles in water

Entry	Amine	Product	Time (min)	Ratio (3:4) ^a	Yield (%) ^b
1			15	100:0	90 ^c , 70 ^d , 20 ^e , 85 ^f
2			50	100:0	75
3			35	90:10	84
4			50	10:90	88
5			30	15:85	85
6			25	20:80	70
7			35	10:90	80
8			25	10:90	80
9			30	35:65	75
10			25	30:70	77
11			25	10:90	80

Reaction conditions: silica nanoparticles (S1) (40 mg); epoxide (1 mmol); amine (1 mmol); water (3 mL) at room temperature.

^a Regioselectivities were obtained using GC/¹H NMR.

^b Isolated yields.


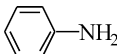
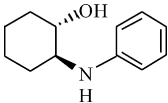

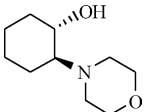

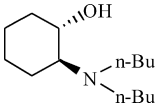
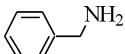
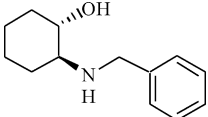

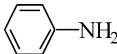
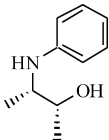

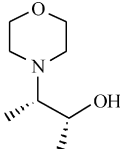
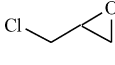
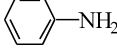
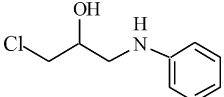
^c Reaction using nanosilica particles (S1).

^d Reaction using nanosilica particles (S2).

^e Reaction using silica gel.

^f Yield after fifth cycle.

Table 2
Ring opening of different epoxides with amines using silica particles

Entry	Epoxide	Amine	Product	Time (min)	Yield (%) ^a
1	 1b			15	88
2	1b			25	85
3	1b			40	82
4	1b			50	88
5	 1c			25	90
6	1c			25	92
7	 1d			20	88 ^b

Reaction conditions: silica nanoparticles (S1) (40 mg); epoxide (1 mmol); amine (1 mmol); water (3 mL) at room temperature.

^a Isolated yields.

^b Only one regioisomer is obtained.

obtained in good yields with high regioselectivities in shorter reaction times. Substituted anilines and benzyl amine required longer reaction times when compared to aniline (Table 1, entries 2–4). Aryl amines underwent the reaction with styrene oxide in a regioselective manner to give the corresponding β -amino alcohols (**3**) with preferential nucleophilic attack at benzylic position (Table 1, entries 1–3). Aliphatic amines on reaction with styrene oxide gave the product in good yields with preferential attack at the non-benzylic terminal carbon (Table 1, entries 4–11). Thus, less nucleophilic aromatic amines react selectively at the benzylic carbon of styrene oxide whereas; increased nucleophilicity of aliphatic amines favors the reaction at the terminal carbon following S_N^2 mechanism.

The use of water as a solvent not only is advantageous being the most 'green' solvent available but also allows a simple, efficient and robust system for the reuse of the catalyst. In fact, after the completion of reaction, the aqueous solution containing the catalyst was extracted with organic solvent. To the remaining aqueous solution containing the monodispersed silica nanopar-

ticles, fresh substrates were added and the process was repeated for five cycles with consistent activity (Table 1, entry 1). In order to know the influence of the reactants on the monodispersed particles, the catalyst after the fifth cycle was analyzed by TEM. The TEM image of the used catalyst was found to be similar to that of the fresh catalyst suggesting that after the reaction, there is no agglomeration of the particles (Fig. 2) and from the recycling experiments it is evident that the catalyst shows consistent activity for several cycles.

To study the generality and scope of the reactions, aliphatic epoxides were allowed to react with different amines and the results are presented in Table 2. Cyclohexene oxide on reaction with amines gave stereoselectively *trans*-product (Table 2, entries 1–4). The reaction of *cis*-dimethyl oxirane with aniline and morpholine afforded the corresponding amino alcohols in good yields (Table 2, entry 5–6). Excellent regioselectivity was achieved with epichlorohydrin resulting in 88% yield of the amino alcohol corresponding to nucleophilic attack at the terminal carbon of the epoxide (Table 2, entry 7). Therefore, the

attack of nucleophile is governed by the nature of epoxide used for the reaction.

4. Conclusions

In conclusion, a simple, rapid, efficient and recyclable protocol for the synthesis of β -amino alcohols via regioselective ring opening of epoxides with amines using catalytic amount of monodispersed silica nanoparticles in water has been described in shorter reaction times.

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