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ORIGINAL ARTICLE

Facile Amberlyst A-21 catalyzed access of β-hydroxynitriles *via* epoxide opening in water

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Abstract β-Hydroxynitriles are essential intermediates in the synthesis of diverse bioactive compounds and clinical drugs. One of the precursor reactions to these intermediates is the opening of an epoxide ring with a cyanide nucleophile. In the present study, we report a milder and safer route to β-hydroxynitriles employing recyclable, Amberlyst A-21 resin in the ring-opening of epoxides with acetone cyanohydrin in water. A diverse range of substrates (fifteen), including aromatic epoxides, phenoxy epoxides, non-terminal, and terminal aliphatic epoxides, are investigated under the optimized conditions to afford the desired β-hydroxynitriles in good to excellent yield. In addition to this, the recyclability of the Amberlyst A-21 resin is also successfully demonstrated. This relatively safer methodology has the potential to be explored in other organic transformations.

1. Introduction

In recent decades, the development of environmentally less hazardous methods in organic synthesis has become critical because of the increased environmental regulations and awareness. The use of water as reaction media and recyclable reagents/catalysts in organic synthesis are two of the most promising approaches. The epoxide ring-opening reaction is one of the most versatile reactions in organic synthesis. It generates a diverse range of functionalities with controlled regiospecificity and stereospecificity. A broad range of

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nucleophiles such as alkoxides, Grignard's reagent, hydroxides, hydrides, cyanides, azides, etc., are employed in epoxide ring-opening reaction. This results in the generation of various key intermediates that are further exploited in the synthesis of bioactive compounds, chiral auxiliaries, active pharmaceutical ingredients, and other useful compounds (Pastor and Yus, 2005; Schneider, 2006). One of such nucleophiles is cyanide ion that provides access to β-hydroxynitriles, a useful intermediate in the synthesis of other chiral intermediates, bioactive compounds and clinical drugs like fluoxetine, duloxetine, GABOB, orlistat, levamisole, β-adrenergic blocking agents etc, (Fig. 1) (Gregory, 1999; Kamal and Ramu, 2002; Kamal et al., 2003, 2006; Kamal et al., 2005a, 2005b; Kim et al., 2012). The cyanide ion, which acts as a nucleophile, is an inhibitor of the enzyme cytochrome *c* oxidase and is highly toxic (Hamel, 2011). In general, to generate a cyanide nucleophile for the epoxide opening reaction, three approaches are employed, as shown in Fig. 1. Primarily, the epoxide ring opening to access β-hydroxynitriles is carried out by using highly toxic inorganic salts such as NaCN, KCN, LiCN, and volatile HCN (Fülöp et al., 1991; Ciaccio et al., 1992; Jin and Weinreb, 1997; Kamal and Ramu, 2002, 2014). These cyanide-based salts are also studied in combination with additives such as metal complexes such as triflates, perchlorate salts, $Yb(CN)_3$, cyanide ion exchange resin etc, to increase the efficiency of the reaction (Chini et al., 1991; Yamasaki et al., 2001; Iranpoor et al., 2003; Tamami et al., 2003; Naeimi and Karshenas, 2013).

In the second approach, trimethylsilyl cyanide was developed as a cyanide source in the ring-opening of epoxide to avoid the use of more toxic cyanide-based salts; however, it resulted in the formation of undesired isonitriles as the main product. To overcome this problem, additives are required to obtain the desired hydroxynitriles as the main product. (Matsubara et al., 1990; Konno et al., 2003, 2014). Moreover, trimethylsilyl cyanide and its hydrolyzed products are also toxic. In addition to inorganic salts and trimethylsilyl cyanide, acetone cyanohydrin is an interesting cyanating agent that provides a steady source of cyanide ion. In these reactions, the cyanide ions are produced from acetone cyanohydrin in the presence of base along with the formation of acetone (Van Leeuwen (2014). However, the reported reactions with this reagent were carried out under reflux conditions and in the presence of lanthanide alkoxide, lithium hydride, methyl lithium, and triethylamine to generate the *in-situ* cyanide ion (Mitchell and Koenig, 1992; Hiroshi et al., 1993; Tsuruoka et al., 1997; Ciaccio et al., 2004). Therefore, there is a need for milder and environmentally safer methodologies that provides access to β-hydroxynitriles. In the present study, we report a milder and safer alternative methodology that allows access to β-hydroxynitriles via ring opening of the epoxide employing acetone cyanohydrin by introducing two crucial

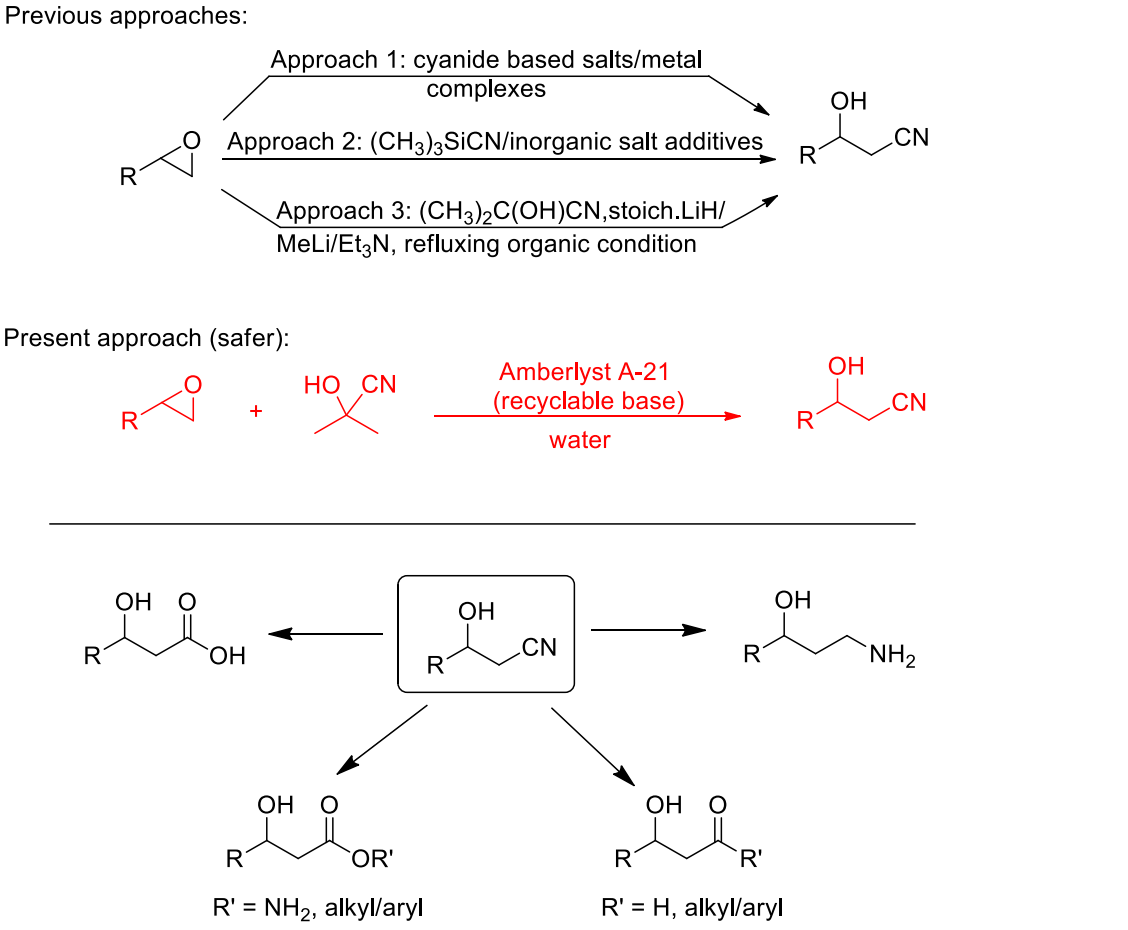


Fig. 1 Epoxide opening approaches to β-hydroxynitriles and their versatility.

greener aspects. The first is the use of a recyclable Amberlyst A-21 resin, which acts as a base by abstracting the proton of acetone cyanohydrin thus facilitating the release of cyanide ion required for epoxide ring-opening. The second important aspect is avoiding the use of organic solvents as reaction medium, and all the reactions are successfully carried out in the water with excellent results.

2. Experimental

2.1. General

Reactions were monitored by thin layer chromatography (silica gel glass plates containing 60 F-254) and visualization was achieved by UV light or iodine indicator. Column chromatography was performed with Merck (Navi Mumbai, India) 60–120 mesh silica gel. Infrared (IR) spectra are recorded on Perkin-Elmer model 683 or 1310 spectrometers with sodium chloride optics. ^{1}H NMR spectra were recorded on Gemini (200 MHz) (Varian Inc, Palo Alto, CA, USA) and chemical shifts (d) are reported in ppm, downfield from internal TMS standard. ESI spectra were recorded on Micro mass, Quattro LC using ESIñ software with capillary voltage of 3.98 kV and ESI mode positive ion trap detector. Elemental analyses were performed on an elemental analyzer (Model: VARIO EL, Elementar, Hanau, Germany). Starting materials and reagents were either commercially available or purchased from, Sigma Aldrich (St Louis, MO, USA), Lancaster (Alfa Aesar, Johnson Matthey Co, Ward Hill, MA, USA) and Spectrochem Pvt Ltd (Mumbai, India). The glycidyl phenyl ether substrates **3a-10a** and **15a** were prepared by following standard literature procedure (Zhu et al., 2019).

2.2. General procedure for the synthesis of β-hydroxynitriles (*1b–12b*)

To a mixture of substituted epoxides (**1a-12a**) (3 mmol) and acetone cyanohydrin (5 mmol) in 15 mL of deionized water in a 25 mL pressure flask, 1.5 gm of Amberlyst A-21 was added. The reaction was incubated at 45–48 °C in a shaker, and the progress of the reaction is monitored on thin layer chromatography with a solvent system of 25–30% ethyl acetate in hexane. After the completion of the reaction in 6–8 h, the reaction mixture is filtered under vacuum to separate Amberlyst A-21. The catalyst was washed thoroughly with ethyl acetate and also stirred in a small quantity of organic solvent. The water-based reaction mixture was extracted with ethylacetate (twice), and the combined organic layer was washed with brine solution and dried over with and. Na_2SO_4. The solvent was evaporated under pressure, and the obtained crude residues was purified by 60–120 silica-gel column chromatography with 20–25% ethylacetate in hexane to provide pure β-hydroxynitriles (**1b-12b**).

2.2.1. 3-Hydroxy-3-phenylpropanenitrile (*1b*)

Following the general procedure, the reaction was carried out by employing epoxide **1a** (0.36 g, 3 mmol), acetone cyanohydrin (0.45 mL, 5 mmol), 1.5 g Amberlyst A-21 in 25 mL deionized water to provide compound **1b** (0.37 g, 85% yield) as yellow liquid. IR (Neat) 3438, 3046, 2954, 2923, 2238, 1092 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.67 (d, 2H, J = 5.8 Hz), 3.15 (br s, 1H), 4.94 (t, 1H, J = 5.8), 7.35 (s, 5H) [lit. (Yang et al., 2018): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.58 (d, 2H, J = 6.0 Hz), 3.28 (br s, 1H), 4.85 (t, 1H, J = 6.2), 7.20–7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 27.8, 69.7, 117.6, 125.6, 128.6, 128.8, 144.1]; EIMS (m/z): 147 (M^+); Anal. Calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.28; H, 6.03; N, 9.45%.

2.2.2. 3-(4-Chlorophenyl)-3-hydroxypropanenitrile (*2b*)

Following the general procedure, the reaction was carried out by employing epoxide **2a** (0.46 g, 3 mmol), acetone cyanohydrin (0.45 mL, 5 mmol), 1.5 g Amberlyst A-21 in 25 mL deionized water to provide compound **2b** (0.45 g, 83% yield) as yellow liquid. IR (KBr) 3444, 3074, 2936, 2904, 2234, 1069 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.73 (d, 2H, J = 5.8 Hz), 3.19 (br s, 1H) 5.00 (t, 1H, J = 5.8 Hz), 7.32–7.39 (m, 4H); [lit. (Coady et al., 2015): ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.74 (d, 2H, J = 6.4 Hz), 5.04 (t, 1H, J = 6.4), 7.35 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 28.01, 69.9, 114.4, 126.9 (2Cs), 133.6 (2Cs), 160.2]; EIMS (m/z): 181 (M^+); Anal. Calcd for for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71. Found C, 59.72; H, 4.42; N, 7.68%.

2.2.3. 3-Hydroxy-4-phenoxybutanenitrile (*3b*)

Following the general procedure, the reaction was carried out by employing epoxide **3a** (0.45 g, 3 mmol), acetone cyanohydrin (0.45 mL, 5 mmol), 1.5 g Amberlyst A-21 in 25 mL deionized water to provide compound **3b** (0.48 g, 90% yield) as pale solid, mp 69–72 °C. IR (KBr) 3397, 3024, 2932, 2267, 1244, 1099 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.62–2.79 (m, 2H), 3.01–3.06 (m, 1H), 3.99–4.09 (m, 2H), 4.27–4.36 (m, 1H), 6.84–6.99 (m, 3H); 7.25–7.31 (m, 2H); [lit. (Azizi et al., 2015): ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 2.69–2.81 (m, 2H), 2.92 (m, 1H), 4.12–4.17 (m, 2H), 4.39 (br.s, 1H), 7.02–7.13 (m, 3H), 7.31–7.39 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 26.8, 28.7, 29.6, 31.2, 60.8, 116.1, 117.4, 119.2, 159.1]; EIMS (m/z): 177 (M^+); Anal. Calcd for for $C_{10}H_{11}NO_2$: C, 67.79; H, 6.21; N, 7.90. Found C, 67.75; H, 6.17; N, 7.82%.

2.2.4. 3-Hydroxy-4-(o-tolyloxy)butanenitrile (*4b*)

Following the general procedure, the reaction was carried out by employing epoxide **4a** (0.49 g, 3 mmol), acetone cyanohydrin (0.45 mL, 5 mmol), 1.5 g Amberlyst A-21 in 25 mL deionized water to provide compound **4b** (0.49 g, 86% yield) as gummy solid. IR (KBr) 3401, 3022, 2930, 2269, 1242, 1095 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.22 (s, 3H) 2.62–2.88 (m, 3H), 3.97–4.08 (m, 2H), 4.28–4.39 (m, 1H), 6.75–6.90 (m, 2H); 7.08–7.15 (m, 2H); [lit. (Kamal and Khanna, 2001): ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.22 (s, 3H), 2.60–2.84 (m, 2H), 3.16 (d, J = 4.76 Hz, 2H), 3.93–4.10 (m, 2H), 4.23–4.40 (m, 1H), 6.73–6.94 (m, 2H), 7.06–7.19 (m, 2H)]; EIMS (m/z): 191 (M^+); Anal. Calcd for for $C_{11}H_{13}NO_2$: C, 69.11; H, 6.80; N, 7.33. Found C, 68.93; H, 6.76; N, 7.19%.

2.2.5. 3-Hydroxy-4-(m-tolyloxy)butanenitrile (*5b*)

Following the general procedure, the reaction was carried out by employing epoxide **5a** (0.49 g, 3 mmol), acetone cyanohydrin (0.45 mL, 5 mmol), 1.5 g Amberlyst A-21 in 25 mL

deionized water to provide compound **5b** (0.52 g, 92% yield) as gummy solid. IR (KBr) 3398, 3024, 2926, 2258, 1238, 1088 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.25 (s, 3H) 2.64–2.82 (m, 3H), 3.97–4.08 (m, 2H), 4.26–4.36 (m, 1H), 6.79–7.19 (m, 4H); EIMS (*m*/*z*): 191 (M^+); Anal. Calcd for for $C_{11}H_{13}NO_2$: C, 69.11; H, 6.80; N, 7.33. Found C, 68.94; H, 6.75; N, 7.19%.

2.2.6. 3-Hydroxy-4-(p-tolyloxy)butanenitrile (*6b*)

Following the general procedure, the reaction was carried out by employing epoxide 6**a** (0.49 g, 3 mmol), acetone cyanohydrin (0.45 mL, 5 mmol), 1.5 g Amberlyst A-21 in 25 mL deionized water to provide compound **6b** (0.48 g, 85% yield) as white solid, mp 59–62 °C. IR (KBr) 3401, 3028, 2928, 2260, 1239, 1089 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.29 (s, 3H) 2.61–2.80 (m, 3H), 3.98–4.09 (m, 2H), 4.25–4.35 (m, 1H), 6.79 (d, 2H); 7.06 (d, 2H); [lit. (Azizi et al., 2015): ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 2.31 (s, 3H), 2.78–2.86 (m, 2H), 3.71–3.85 (m, 2H), 4.13 (m, 1H), 4.41 (br.s, 1H), 6.87 (m, 2H), 7.24 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 21.2, 23.1, 65.8, 71.2, 114.9, 117.8, 131.2, 132.4, 156.5]; EIMS (*m*/*z*): 191 (M^+); Anal. Calcd for for $C_{11}H_{13}NO_2$: C, 69.11; H, 6.80; N, 7.33. Found C, 68.92; H, 6.76; N, 7.11%.

2.2.7. 4-(4-Chlorophenoxy)-3-hydroxybutanenitrile (*7b*)

Following the general procedure, the reaction was carried out by employing epoxide **7a** (0.55 g, 3 mmol), acetone cyanohydrin (0.45 mL, 5 mmol), 1.5 g Amberlyst A-21 in 25 mL deionized water to provide compound **7b** (0.58 g, 92% yield) as yellowish solid. IR (KBr) 3404, 3025, 2933, 2258, 1245, 1089 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.63–2.81 (m, 3H), 3.96–4.05 (m, 2H), 4.21–4.32 (m, 1H), 6.82 (d, 2H); 7.15 (d, 2H); [lit. (Kamal and Khanna, 2001): ^1H NMR (200 MHz, $CDCl_3$): 2.63 (dd, 1H), 2.79 (dd, 1H), 3.19 (br.s, 1H), 3.99 (d, 2H), 4.24–4.34 (m, 1H), 6.84 (d, 2H), 7.24 (d, 2H)]; EIMS (*m*/*z*): 211 (M^+); Anal. Calcd for for $C_{10}H_{10}NO_2$-Cl: C, 56.87; H, 4.74; N, 6.64. Found C, 56.78; H, 4.70; N, 6.61%.

2.2.8. 4-(4-Bromophenoxy)-3-hydroxybutanenitrile (*8b*)

Following the general procedure, the reaction was carried out by employing epoxide **8a** (0.68 g, 3 mmol), acetone cyanohydrin (0.45 mL, 5 mmol), 1.5 g Amberlyst A-21 in 25 mL deionized water to provide compound **8b** (0.68 g, 90% yield) as pale solid, mp 80–82 °C. IR (KBr) 3395, 3028, 2938, 2259, 1242, 1092 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.60–2. 77 (m, 3H), 3.98–4.11 (m, 2H), 4.20–4.31 (m, 1H), 6.81 (d, 2H); 7.18 (d, 2H); [lit. (Kamal and Khanna, 2001): ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 22.61 (dd, 1H), 2.74 (dd, 1H), 3.99 (d, 2H), 4.20–4.33 (m, 1H), 6.76 (d, 2H), 7.35 (d, 2H)]; EIMS (*m*/*z*): 255 (M^+); Anal. Calcd for for $C_{10}H_{10}NO_2Br$: C, 47.05; H, 3.92; N, 5.49. Found C, 47.01; H, 3.88; N, 5.53%.

2.2.9. 3-Hydroxy-4-(naphthalen-1-yloxy)butanenitrile (*9b*)

Following the general procedure, the reaction was carried out by employing epoxide **9a** (0.6 g, 3 mmol), acetone cyanohydrin (0.45 mL, 5 mmol), 1.5 g Amberlyst A-21 in 25 mL deionized water to provide compound **9b** (0.63 g, 93% yield) as white solid, mp 88-92 °C. IR (KBr) 3401, 3025, 2933, 2261, 1242, 1096 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.68–2.89 (m, 3H), 3.88–4.03 (m, 2H), 4.05–4.29 (m, 1H), 6.68–6.81 (m, 1H); 7.52–8.2 (m, 6H); [lit. (Kamal and Khanna, 2001): ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.70–2.91 (m, 2H), 4.21 (d, 2H), 4.39–4.50 (m, 1H), 6.8 (d, 1H), 7.25–7.51 (m, 4H), 7.76–7.81 (m,1H)]; EIMS (*m*/*z*): 227 (M^+); Anal. Calcd for for $C_{14}H_{13}NO_2$: C, 74.00; H, 5.72; N, 6.16. Found C, 73.85; H, 5.68; N, 6.19%.

2.2.10. 3-Hydroxy-4-(naphthalen-2-yloxy)butanenitrile (*10b*)

Following the general procedure, the reaction was carried out by employing epoxide **10a** (0.6 g, 3 mmol), acetone cyanohydrin (0.45 mL, 5 mmol), 1.5 g Amberlyst A-21 in 25 mL deionized water to provide compound **10b** (0.61 g, 90% yield) as white solid, mp 130–133 °C. IR (KBr) 3395, 3031, 2928, 2264, 1248, 1098 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.26–2.85 (m, 3H), 3.81–4.02 (m, 2H), 4.03–4.25 (m, 1H), 7.19–8.03 (m, 7H); [lit. (Kamal and Khanna, 2001): ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.69 (dd, 1H), 2.84 (dd, 1H), 3.99–4.33 (m, 3H), 7.14–7.20 (m, 2H), 7.26–7.55 (m, 2H), 7.66–7.78 (m, 3H)]; EIMS (*m*/*z*): 227 (M^+); Anal. Calcd for for $C_{14}H_{13}NO_2$: C, 74.00; H, 5.72; N, 6.16. Found C, 73.78; H, 5.64; N, 6.10%.

2.2.11. 2-Hydroxycyclohexanecarbonitrile (*11b*)

Following the general procedure, the reaction was carried out by employing epoxide **11a** (0.29 g, 3 mmol), acetone cyanohydrin (0.45 mL, 5 mmol), 1.5 g Amberlyst A-21 in 25 mL deionized water to provide compound **11b** (0.29 g, 78% yield) as oily liquid. IR (KBr) 3420, 2970, 2256, 1060 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.15–1.40 (m, 3H), 1.52–1.83 (m, 3H), 1.96–2.16 (m, 2H), 2.36–2.47 (m, 1H); 3.48 (s, 1H); 3.63–3.75 (m, 1H); [lit. (Rocha et al., 2017): ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.25 (m, 3H), 1.56 (m, 1H), 1.71 (m, 1H), 2.06 (m, 2H), 2.41 (m, 1H), 2.85 (bs, 1H), 3.70 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 23.5, 24.0, 28.2, 33.8, 37.6, 70.6, 121.6]; EIMS (*m*/*z*): 125 (M^+); Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found C, 67.20; H, 8.89; N, 10.99%.

2.2.12. 3-Hydroxyheptanenitrile (*12b*)

Following the general procedure, the reaction was carried out by employing epoxide **12a** (0.3 g, 3 mmol), acetone cyanohydrin (0.45 mL, 5 mmol), 1.5 g Amberlyst A-21 in 25 mL deionized water to provide compound **12b** (0.3 g, 80% yield) as oily liquid. IR (KBr) 3598, 3019, 2259, 1065 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.91 (t, 3H), 1.30 (m, 4H), 1.60 (m, 2H) 2.53 (m, 2H), 3.14 (bs, 1H); 3.82 (q, 1H); [lit. (Pollock et al., 2007): ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.93 (t, 1H), 1.25–1.5 (m, 4H), 1.55–1.70 (m, 2H), 2.1 (bs, 1H), 2.46 (dd, 1H), 2.52 (dd, 1H), 3.96 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.9, 22.4, 26.1, 27.5, 36.2, 67.7, 117.7]; EIMS (*m*/*z*): 127 (M^+); Anal. Calcd for $C_7H_{13}NO$: C, 66.10; H, 10.30; N, 11.01. Found C, 65.81; H, 10.05; N, 10.95%0.

2.2.13. 3-Hydroxypentanenitrile (*13b*)

Following the general procedure, the reaction was carried out by employing epoxide **13a** (0.21 g, 3 mmol), acetone cyanohydrin (0.45 mL, 5 mmol), 1.5 g Amberlyst A-21 in 25 mL

Table 1 Optimization of ring-opening of styrene epoxide employing Amberlyst A-21.[a]

Entry	Solvent	Temperature	Time (h)	Yield (%)
1.	Water	rt	12	41
2.	Water	45 °C	8	85 (70)[b]
3.	Dichloromethane	45 °C	8	55
4.	Acetonitrile	45 °C	8	45
5.	Ethanol	45 °C	8	80

[a] 1 equiv of styrene epoxide **1a** (3 mmol), 1.6 equiv of acetone cyanohydrin (5 mmol), 1.5 g of Amberlyst A-21 beads (active sites concentration, 4.8 meq/gm) in 15 mL of deionized water.
[b] 1 g of Amberlyst A-21 was used.

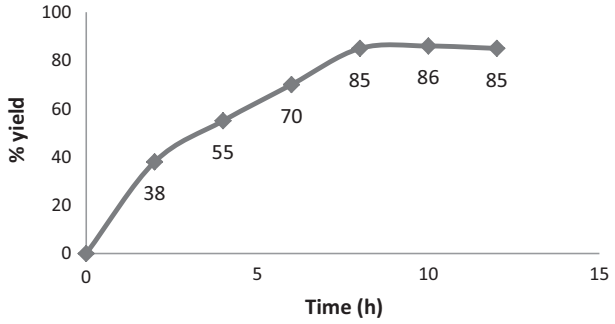


Fig. 2 Reaction progress curve of epoxide opening of **1a**[a].

deionized water to provide compound **13b** (0.22 g, 76% yield) as oily liquid. IR (KBr) 3485, 2989, 2285, 1071 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 0.96 (t, 3H), 1.51 (m, 2H), 2.58 (m, 2H), 3.29 (bs, 1H); 3.69 (q, 1H); EIMS (*m*/*z*): 99 (M^+); Anal. Calcd for C_5H_9NO: C, 60.58; H, 9.15; N, 14.13. Found C, 60.53; H, 9.18; N, 14.10%.

*2.2.14. 4-Chloro-3-hydroxybutanenitrile (**14b**)*

Following the general procedure, the reaction was carried out by employing epoxide **14a** (0.27 g, 3 mmol), acetone cyanohydrin (0.45 mL, 5 mmol), 1.5 g Amberlyst A-21 in 25 mL deionized water to provide compound **14b** (0.29 g, 84% yield) as oily liquid. IR (KBr) 3458, 2985, 2289, 1058 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 2.68–2.71 (m, 2H), 3.60–3.71 (m, 3H); [lit. (Wan et al., 2015): ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 2.74–2.71 (t, 2H), 3.67–3.69 (dd, 2H), 4.22 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 25.9, 50.1, 70.0, 119.1]. EIMS (*m*/*z*): 119 (M^+); Anal. Calcd for C_4H_6ClNO: C, 40.19; H, 5.06; N, 11.72. Found C, 39.2; H, 5.02; N, 11.59%.

*2.2.15. 4-(tert-butoxy)-3-hydroxybutanenitrile (**15b**)*

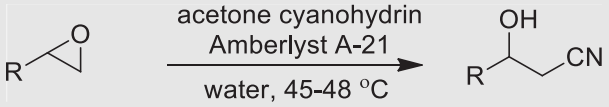
Following the general procedure, the reaction was carried out by employing epoxide **15a** (0.39 g, 3 mmol), acetone cyanohydrin (0.45 mL, 5 mmol), 1.5 g Amberlyst A-21 in 25 mL deionized water to provide compound **15b** (0.39 g, 83% yield) as oily liquid. IR (KBr) 3419, 2985, 2252, 1062 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 1.20 (s, 9H), 2.39–2.68 (m, 2H), 3.25–3.42 (m, 2H), 3.72–3.91 (m, 1H); [lit. (Naeimi and Moradian, 2006) ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.14 (s, 9H), 2.36–2.4 8 (m, 2H), 3.14 (m, 2H), 3.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 22.1, 27.4, 36.2, 66.5, 68.5, 73.2, 117.8]; EIMS (*m*/*z*): 157 (M^+); Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found C, 61.08; H, 9.58; N, 8.88%.

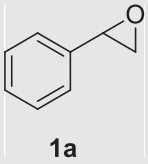
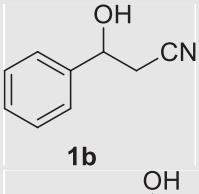
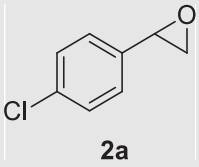
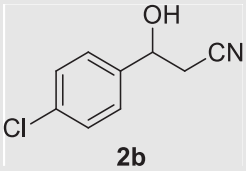
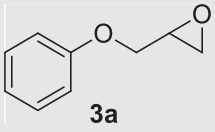
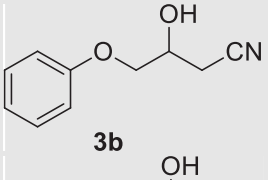
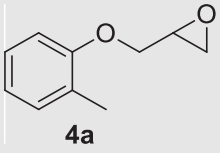
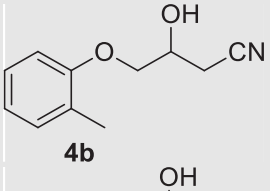
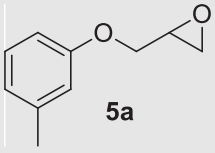
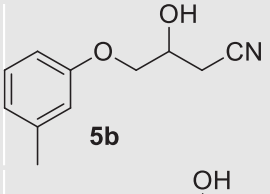
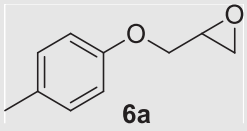
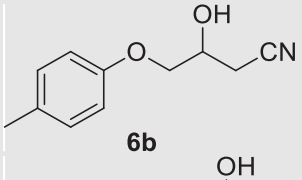
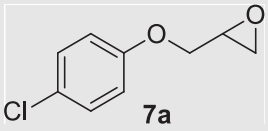
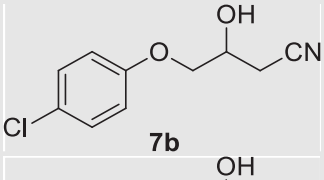
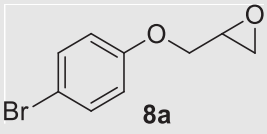
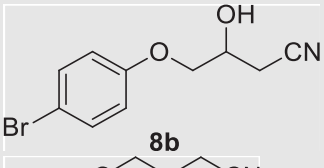
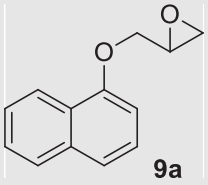
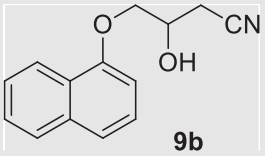
3. Results and discussion

Heterogeneous reactions employing ion exchange resins offer promising advantages over their homogenous counterparts. Environmental compatibility, simpler operating conditions, recyclability, non-corrosiveness, etc., are some of the advantages involving the use of ion exchange resins (Barbaro and Liguori, 2009). Amberlyst A-21 is a weakly basic ion exchange resin, which was primarily developed to remove acidic materials from a range of product streams. It is used as a recyclable base in the synthesis of diverse heterocyclic compounds such as substituted pyrans, chromenes, furans, indazolones etc, that avoids the use of hazardous solvents in chromatographic separation (Yadav et al., 2007; Palmieri et al., 2010; Bihani et al., 2013; Rao et al., 2014). Additionally, Amberlyst A-21 is utilized in different organic transformations such as the conversion of the carbonyl group to oximes, deprotection of *N*-Boc amines and Henry reaction (Ballini et al., 1996, 1997; Srinivasan et al., 2005). Amberlyst A-21 supported with copper iodide is also exploited in catalyzing Huisgen's reaction, KA^2 coupling reaction, and reaction involving the synthesis of propargyl amines (Girard et al., 2006; Bosica and Gabarretta, 2015; Bosica and Abdilla, 2017). Keeping in view the versatility of Amberlyst A-21, we investigated its efficiency as a recyclable base in the epoxide ring-opening reaction to obtain the useful key intermediates, β-hydroxynitriles.

In the present study, macro-reticular, commercially available Amberlyst A-21 resin in bead form was used without any further conditioning or purification for epoxide ring-opening by a cyanide nucleophile provided by acetone cyanohydrin. Amberlyst A-21 has a macroporous matrix, comprised of styrene divinylbenzene, with a moisture content of 56–62%. It is weakly basic with tertiary alkylamine functionality as a free base form with an added advantage of recyclability. The use of organic solvent as the reaction medium was completely circumvented, and the reaction was carried out in water, the most environmentally compatible solvent. To optimize the reaction, initially, the epoxide ring-opening reaction was carried out with styrene oxide as a model substrate.

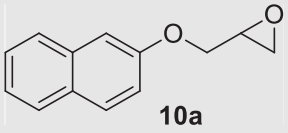
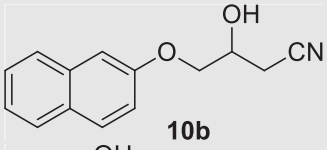
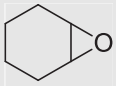
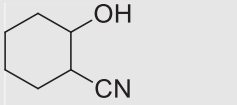
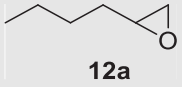
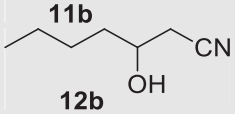
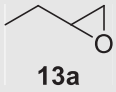
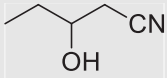
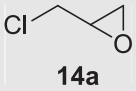
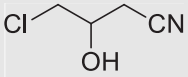
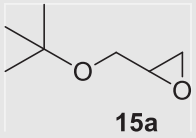
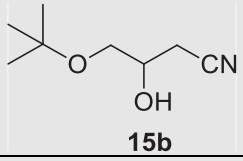
Table 2 Amberlyst A-21 catalyzed epoxide ring-opening with acetone cyanohydrin.[a]



Entry	Substrate	Product	Yield (%)[b]	Yield (%)[c]
1.	 **1a**	 **1b**	85	79[d] 80[e,f]
2.	 **2a**	 **2b**	83	78[f]
3.	 **3a**	 **3b**	90	88[d] 80[g] 72[f]
4.	 **4a**	 **4b**	86	86[g]
5.	 **5a**	 **5b**	90	–
6.	 **6a**	 **6b**	85	87[g] 78[f]
7.	 **7a**	 **7b**	92	90[g]
8.	 **8a**	 **8b**	90	82[g]
9.	 **9a**	 **9b**	93	70[g]

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	Product	Yield (%)[b]	Yield (%)[c]
10.	 10a	 10b	90	55[g]
11.	 11a	 11b	78	89[d] 85[h]
12.	 12a	 12b	80	78[d] 70[h]
13.	 13a	 13b	76	–
14.	 14a	 14b	84	85[d,h]
15.	 15a	 15b	83	85[d]

[a] 1 equiv (3 mmol) of epoxide, 1.6 equiv (5 mmol) of acetone cyanohydrin, 1.5 g of Amberlyst A-21 beads (active sites concentration, 4.8 meq/gm) in 15 mL of deionized water at 45–48 °C.
[b] Isolated yields after 6–8 h of reaction time.
[c] Reported yields of earlier methods.
[d] (Iranpoor and Shekarize, 1999).
[e] (Kamal and Ramu, 2002).
[f] (Azizi et al., 2015).
[g] (Kamal and Khanna, 2001).
[h] (Iranpoor et al., 2003).

Table 3 Recyclability of Amberlyst A-21 with epoxide **3a.**[a]

Entry	Cycle	Yield (%)
1.	First	90
2.	Second	90
3.	Third	88
4.	Fourth	86
5.	Fifth	78

[a] Conditions as mentioned in Table 2, reaction time 6 h.

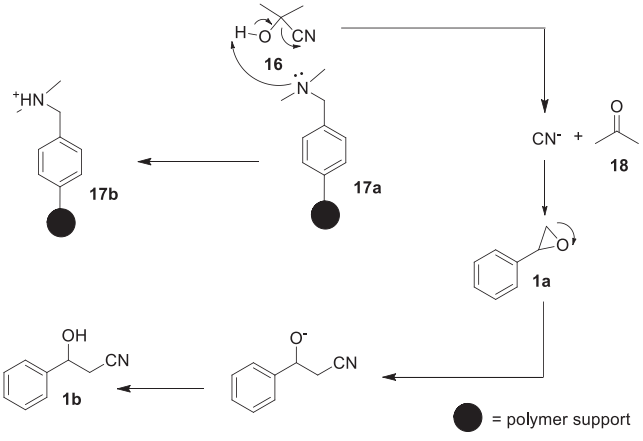


Fig. 3 Plausible mechanism of β-hydroxynitrile formation.

Acetone cyanohydrin was employed as a cyanide source in the presence of Amberlyst A-21 with water as the reaction medium (Table 1). The preliminary results showed that the progress of the reaction was promising, and the desired hydroxynitrile was formed with over 40% yield after 12 h at room temperature.

In subsequent optimization, the temperature was increased to 45–48 °C, which resulted in higher yield (over 85% in 8 h). However, there was no remarkable increase in the yield with a further rise in temperature. In addition to this, three different organic solvents were studied and compared with the water. The yields of the reactions in organic media were comparatively lower than water, and in this case, the use of an

environmentally compatible water-based reaction medium was desired. The Amberlyst A-21 resin amount was also investigated, and the use of 1 g and 1.5 g of resin provided 70% and 85% of yields, respectively. However, a further increase in the amount of resin did not lead to any substantial increase in yield. In addition to this, the reaction progress was also studied under the optimized conditions with styrene oxide **1a** as a model substrate (Fig. 2). The results showed that the reaction proceeded with 38% and 70% after 2 h and 6 h, respectively. After 8 h of reaction time, 85% yield of the product was obtained, and a further increase in reaction time resulted in no improvement in reaction yield.

Finally, the Amberlyst A-21 mediated nucleophilic opening of different epoxides was carried out in the presence of acetone cyanohydrin at 45–48 °C with water as solvent (table 2). In this investigation, the aromatic epoxides acted as better substrates for nucleophilic opening with acetone cyanohydrin than the aliphatic epoxides. The styrene-based epoxides provided the corresponding β-hydroxynitriles in around 85% yields under the optimized conditions. The aromatic glycidyl phenyl ethers were comparatively more reactive than the styrene epoxides, and the glycidyl phenyl ethers afforded the desired products in 86–92% yields. The parent glycidyl phenyl ether **3a** resulted in 90% of corresponding product **3b,** and subsequently, the electronic effect of some selected electron-donating and withdrawing groups and their positions on **3a** was studied. The substrate **5a** with electron-donating methyl substitution on meta-position provided the best result with 92% yield compared to other isomeric substrates (**4a** and **6a**). The glycidyl phenyl ether with electron-withdrawing groups like bromo and chloro substituents on *para*-position (**7a** and **8a**) also provided excellent results. The glycidyl ethers with bulkier napthyl group were employed as substrates, and 1-substituted ether **9a** produced slightly better yield than 2-substituted ether **10a**. In addition to the aromatic substrate, some selected aliphatic epoxides were also investigated to establish the versatility of the methodology. Among the aliphatic substrates, the non-terminal cyclohexene oxide **11a** afforded the desired product **11b** in 78% yield. On the other hand, the terminal aliphatic epoxide, 1,2-epoxyhexane **12a** and 1,2-epoxybutane **13a** proceeded with 80% and 76% yield, respectively. The glycidyl based aliphatic substrates with chloride and *tert*-butoxy groups (**14a** and **15a**) were also investigated affording the desire products in good yields. In these ring-opening reactions, the nucleophilic cyanide attacked the epoxide from the least hindered side, resulting in a single product. The formation of the products was confirmed with the characteristic IR stretching vibration bands around 3400 and 2200 cm^{-1} corresponding to hydroxyl and cyanide groups, respectively, in addition to other spectroscopic characterization.

The recyclability of the Amberlyst A-21 resin was demonstrated with glycidyl phenyl ether **3a** as a model substrate. After the completion of the first run under the studied conditions, Amberlyst A-21 resin was recovered by simple filtration. It was washed with ethanol, followed by drying at 80 °C under reduced pressure (1 h) for subsequent use. The results showed that the efficiency of the resin was retained in the second run, and from the third run, the yields started to decrease marginally (table 3). After the fifth cycle, the resin was required to be reactivated to obtain the desired high yields. Amberlyst A-21 resin catalyzed the ring-opening of epoxide by the mechanism outlined in Fig. 3. The tertiary alkylamine functionality in the free base form of Amberlyst A-21 **17a** abstracts the active proton from acetone cyanohydrin **16**, thereby releasing the cyanide ion besides the formation of acetone **18**. The released cyanide ion than attacks the epoxide **1a** from sterically unhindered side to provide the desired β-hydroxynitriles **1b**. This recyclable Amberlyst A-21 offers a steady source of cyanide nucleophile in a minimal amount required for ring-opening of the epoxide.

4. Conclusion

The synthetic utility of β-hydroxynitriles necessitates the development of safer methodologies. Toxic cyanide salts or trimethylsilyl cyanide are primarily used as a source of cyanide ion in the ring-opening of epoxide to access β-hydroxynitriles. An alternate route to produce a cyanide nucleophile is the use of acetone cyanohydrin in the presence of a base. In the present investigation, a weakly basic, recyclable, ion exchange resin, Amberlyst A-21 is utilized for the opening of different aromatic and aliphatic oxiranes to access β-hydroxynitriles. To further enhance the environmental compatibility of the method, the reactions are performed in water with excellent results. The results showed that aromatic phenoxy epoxides were more susceptible to ring-opening than the aliphatic epoxides, and the aromatic epoxides with electron-withdrawing groups provided relatively better yields under the studied conditions. The present methodology offers a relatively greener alternative to the reported methods, which employs toxic cyanide sources, mostly in organic solvents. It has the potential to be explored in other organic transformations like ring-opening of azirines.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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