Synthesis of β-amino alcohols using MgO as a new catalyst under solvent-free conditions

Mona Hosseini-Sarvari

Abstract: MgO catalyzed efficiently the ring opening of epoxides with a range of aromatic and aliphatic amines to produce β-substituted alcohols in high yields under solvent-free conditions. Exclusive trans stereoselectivity is observed for cyclic epoxide.

Key words: MgO, β-amino alcohols, solvent-free, epoxide, amine.

Résumé : Dans des conditions n'impliquant aucun solvant, l'oxyde de magnésium, MgO, catalyse d'une façon efficace l'ouverture du cycle des époxydes avec une grande variété d'amines aliphatiques et aromatiques pour conduire avec des rendements élevés aux alcools β-substitués correspondants. On observe exclusivement l'ouverture stéréosélective *trans* avec les époxydes cycliques.

Mots-clés : MgO, β-aminoalcools, sans solvant, époxyde, amine.

[Traduit par la Rédaction]

Introduction

The formation of β-amino alcohols from epoxides and amines is an important reaction in medicinal and organic chemistry, as they are useful synthetic intermediates for the preparation of β-amino acids, natural products, and chiral auxiliaries (1). Opening of epoxides with amines developed in the past few years, and many catalysts (reagents) were used, such as metal triflates (2), metal halides (3), polymer supported (4), montmorillonite K10 (5), and metal salt (6). Different reaction media, such as ionic liquids (7), ultrasound (8), microwave irradiation (9), solvent-free conditions (SFC), and water (10) were also employed. These processes are useful; however, they suffer from disadvantages, such as the use of expensive or air-sensitive reagents, extended reaction times, and the requirement for protracted work-up procedures, or are limited in the range of amines specially aliphatic amines.

MgO is an environmentally safe, non-volatile, non hygroscopic, odourless, and white powder with outstanding physical properties and stability. It is commercially available and is a very cheap chemical. Recently, it was shown that MgO has the prospect to be used as a substitute for conventional basic catalytic materials. It has been used as an efficient heterogeneous catalyst in many important organic reactions (11).

In this pursuit, and during the course of the studies aimed at developing solvent-free procedures (12), for the first time, MgO-catalyzed ring opening of epoxides by amines in solvent-free conditions is reported in this paper (Scheme 1).

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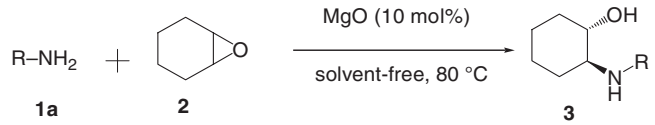
Scheme 1. Synthesis of β-amino alcohols catalyzed by MgO.



1a 2 3

R = alkyl and aryl

Results and discussion

The condensation between an amine and an epoxide leading to the formation of a β-amino alcohol should be a facile reaction due to the good electrophilic and nucleophilic properties of the epoxide and amine groups, respectively. This reaction may not require any catalytic assistance in the absence of electronic/steric factors that might decrease the electrophilicity/nucleophilicity of the epoxide/amine groups. Thus, the condensation of cyclohexene oxide with 4-methylaniline, 4-methoxyaniline, and 4-bromoaniline afforded 70%–90% yields, in 6–8 h, under neat conditions at 80 °C without the requirement of any additional reagent/catalyst. The treatment of cyclohexene oxide with aniline afforded the corresponding β–aminol alcohols in 60% yields in 12 h. However, no significant β-amino alcohol formation was observed (^{1}H NMR) when cyclohexene oxide was treated with 4-nitroaniline at 100 °C under neat conditions.

The presence of the strong electron-withdrawing property of the nitro group in 4-nitroaniline decreases the nucleophilicity of the amine group. Thus, the combination of this substrate with cyclohexene oxide constitutes a model reaction for evaluating the efficiency of a catalyst. Hence, cyclohexene oxide was treated with 4-nitroaniline under various conditions (Table 1). Clearly, the best results were reached with MgO under solvent-free conditions (Table 1, entry 1).

To evaluate the generality, reaction of various epoxides were carried out with various aromatic, aliphatic, primary,

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Table 1. Reaction between cyclohexene oxide (**2d**) and 4-nitroaniline (**1l**) in the presence of various catalysts and conditions

Entry	Catalyst/conditions	Time (h)	Yield[a] (%)
1	MgO (10 mol%)/neat	12	65
2	MgO (10 mol%)/CH_2Cl_2	24	Trace
3	MgO (10 mol%)/PhMe	24	Trace
4	MgO (10 mol%)/THF	24	Trace
5	No catalyst/neat	No reaction	
6	Mesoporous aluminizilicate (13)	No reaction	
7	$H_3PW_{12}O_{40}$ (14)	24	35
8	Sulfamic acid (15)	No reaction	
9	CaO (10 mol%)/neat	24	Trace
10	K_2CO_3 (10 mol%)/neat	24	43
11	CuO (10 mol%)/neat	24	Trace

[a]Yields are for the isolated compounds.

and secondary amines under the catalytic influence of MgO, and excellent results were obtained (Table 2). The reaction protocol is simple and does not require dry glassware and reagents. This is very important for scaling-up the process. The final amino alcohol was isolated in >99% purity in 50%–98% yield.

The results summarized in Table 2 reveal that excellent yields were obtained with aromatic and aliphatic amines. In the case of cyclohexene oxide, in each occasion, the resultant racemic 2-aryl/alkylaminocyclohexanol was obtained with exclusive trans diastereoselectivity as detected by ^{1}H NMR spectroscopic analysis (Table2, entries 5–26). The reactions are remarkably clean, and no chromatographic separation is necessary to get the spectra-pure compounds except in a few cases (Table 2, entries 16–20) where some starting materials remained; the conversion being less than 100%. Primary and secondary amines react very rapidly. Aniline and its derivatives with electron-donating substitutes also react quite fast. However, anilines with electron-accepting substitutes, as well as satirically hindered anilines, react very slowly, and aminolysis required prolonged reaction times. The reaction of diamines showed good results without any significant influence of their structures on the product yields; these products can be used for preparation of macrocyclic compounds. The conversion of aniline into 2-aryl/alkylaminocyclohexanol on a 100 mmol scale proceeded just as well as the 1 mmol reaction.

The ratio of the two regioisomeric products was determined by GC–MS and ^{1}H NMR (based on the methane and methylene proton signals). In the MS the regioisomer of α-product exhibited a daughter ion at *m*/*z* ($M^+ - 31$) due to the CH_2OH, and the diagnostic feature in the mass spectra of the β-product (**3a**) was the ion peak at *m*/*z* ($M^+ - 106$) arising from the loss of PhCHO. The GC–MS revealed the product to be a mixture of β-product (**3a**) and α-product in a ratio of 95:5 on the basis of the daughter ions at *m*/*z* 228–106 and 228–31, corresponding to β-product (**3a**) and α-product, respectively. Also, a 95:5 ratio could be determined for β-product (**3a**): α-product, taking into consideration the integral values of the corresponding benzyl protons.

Excellent chemo selectivity was achieved with epichlorohydrin (Table 2, entry 4) resulting in 93% yield of the amino alcohol corresponding to nucleophilic attack at the terminal carbon of the epoxide moiety. No product arising from nucleophilic displacement of the chlorine could be detected through MS analysis of the reaction mixture.

The reuse ability and catalytic activity of MgO was studied in this system. The catalyst was recovered by centrifugation after diluting the reaction mixture with Et_2O and dried in an oven at 100 °C for 3 h and was reused repeatedly without any significant loss of catalytic activities. As shown in Table 3, the yields of 2-(2-picolylamine)cyclohexanol (**3d**) only decreases a little after the reuse of MgO for three times.

In conclusion, the results demonstrated that MgO efficiently catalyze the formation of β-amino alcohols from amines and epoxides in high yields under mild and solvent-free reaction conditions. The facile synthesis of these materials, their benign nature, the ease of handling, and the simplified reaction and isolation procedures make them a highly attractive alternative to current methodologies.

Experimental

Chemicals were purchased from Fluka, Merck, B. D. H., and Aldrich Chemical Companies. Progress of the reactions was followed by TLC using silica-gel polygrams SIL G/UV 254 plates. NMR spectra were recorded on a Bruker DPX 250 MHz instrument. Mass spectra were recorded on a Shimadzu GC MS-QP 1000 EX apparatus. Microanalyses were performed on a PerkinElmer 240-B microanalyzer.

General procedure

A mixture of MgO (10 mol%, 0.004 g), amine (1 mmol), and 1,2-epoxide (1 mmol) was heated in an oil bath at 80 °C and stirred with a magnetic stirrer. The progress of the reaction was monitored by TLC. After the reaction was complete, the obtained product was poured into water, stirred well to dissolve the MgO, and then extracted with ethyl acetate. The organic solvent was then evaporated, and the pure product was obtained. This was further purified by recrystallization with a suitable solvent (ether). The regioisomers were separated after silica-gel column chromatography (20% Hexane/EtOAc). The structures of the products were confirmed by GC–MS, ^{1}H NMR, ^{13}C NMR, and comparison with authentic samples obtained commercially or prepared by reported methods.

Table 2. Synthesis of β-amino alcohols.

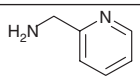
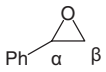
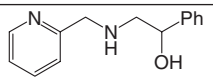
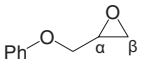
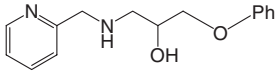
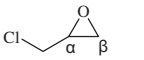
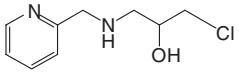
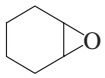
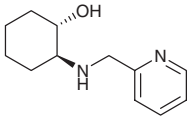
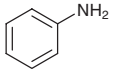
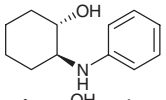
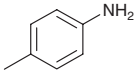
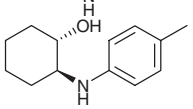
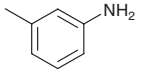
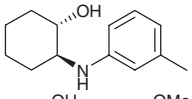
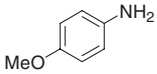
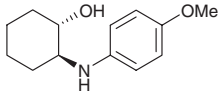
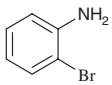
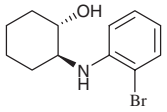
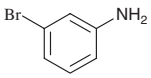
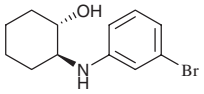
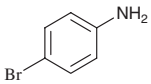
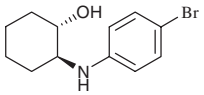
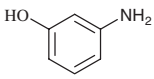
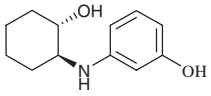
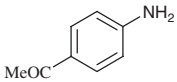
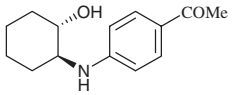
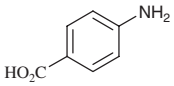
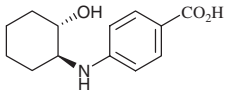
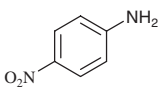
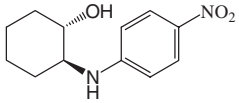
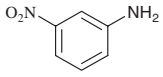
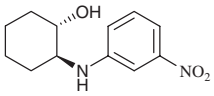
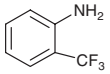
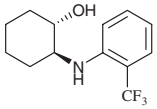
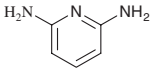
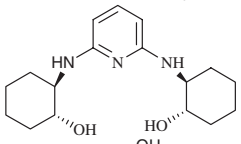
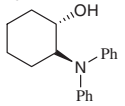
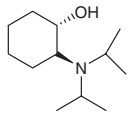
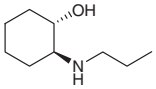
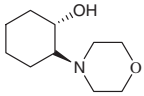
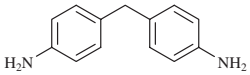
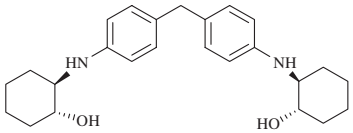
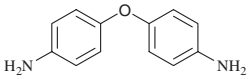
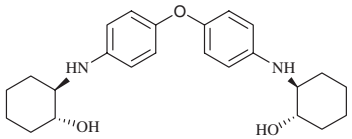
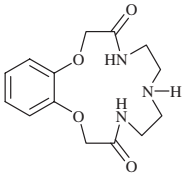
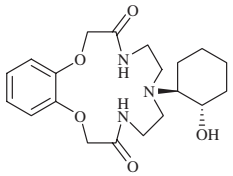
Entry	Amine (**1**)		1,2-Epoxide (**2**)		Product (**3**)		Time (h)	Yields[a] %
1		**1a**		**2a**		**3a**	2	90[b]
2	**1a**		**2a**		**3a**		12	33[c]
3	**1a**			**2b**		**3b**	3	95[b]
4	**1a**			**2c**		**3c**	1	93[b]
5	**1a**			**2d**		**3d**	1	98
6		**1b**	**2d**			**3e**	3	95
7		**1c**	**2d**			**3f**	2	98
8		**1d**	**2d**			**3g**	1	98
9		**1e**	**2d**			**3h**	1	97
10		**1f**	**2d**			**3i**	3	90
11		**1g**	**2d**			**3j**	3	95
12		**1h**	**2d**			**3k**	0.5	90
13		**1i**	**2d**			**3l**	1	95
14		**1j**	**2d**			**3m**	2	98
15		**1k**	**2d**			**3n**	3	94
16		**1l**	**2d**			**3o**	12	65
17		**1m**	**2d**			**3p**	18	63

Table 2 (*concluded*).

Entry	Amine (**1**)	1,2-Epoxide (**2**)	Product (**3**)	Time (h)	Yields[a] %
18		**1n** **2d**		**3q** 4	78
19		**1o** **2d**		**3r** 3	73
20	PhNHPh	**1p** **2d**		**3s** 24	50
21	$(CH_3)_2CHNHCH(CH_3)_2$	**1q** **2d**		**3t** 2	86
22	$CH_3CH_2CH_2NH_2$	**1r** **2d**		**3u** 3	94
23		**1s** **2d**		**3v** 1	95
24		**1t** **2d**		**3w** 2	93
25		**1u** **2d**		**3x** 2	90
26		**1v** **2d**		**3y** 3	82

[a] Yields of isolated pure product after silica-gel column chromatography (20% Hexane/EtOAc).
[b] Products isolated in a 95:5 ratio of regioisomers. The major product was shown.
[c] The reaction was carried out under catalyst-free conditions. Products isolated in 50:50 ratio of regioisomers.

Table 3. Reuse of MgO.

Number of use	Yield (%)	Recovery of MgO
1	98	96% (3.8×10^{-3} g)
2	94	95% (3.6×10^{-3} g)
3	92	95% (3.4×10^{-3} g)

1-Phenyl-2- ((pyridin-2-yl)methylamino)ethanol (3a)

Oily liquid. R_f = 0.13 (EtOAc/MeOH/Et_3N, 90/7/3). ^1H NMR ($CDCl_3$, ppm) δ: 8.34 (1H, d, J = 4.9), 7.49 (1H, m), 7.02–7.21 (7H, m), 4.72 (1H, d, J = 3.4), 4.62 (2H, dd, J = 2.8, 2.8), 3.90 (1H, –NH), 3.82 (1H, –OH), 2.64–2.76 (2H, m). ^{13}C NMR ($CDCl_3$) δ: 54.1, 56.8, 72.1, 122.5, 125.9, 127.3, 128.2, 136.6, 137.1, 149.0, 159.4. MS *m/z*: 228 [M+]. Anal. calcd. for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; found: C, 73.34; H, 6.98.

1-Phenoxy-3-(pyridin-2-ylmethylamino)propan-2-ol (3b)

Oily liquid. R_f = 0.38 (EtOAc/MeOH/Et_3N, 90/7/3). ^1H NMR ($CDCl_3$, ppm) δ: 8.43 (1H, m), 7.50 (1H, m), 7.03–7.16 (4H, m), 6.71–6.84 (3H, m), 5.60 (2H, br s, –NH, –OH), 3.78–4.05 (5H, m). ^{13}C NMR ($CDCl_3$) δ: 53.2, 59.0, 114.5, 115.6, 121.0, 129.3, 137.0, 148.9, 158.4. MS *m/z:* 244 [M^+]. Anal. calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; found: C, 68.65; H, 6.43.

1-Chloro-3-(pyridin-2-ylmethylamino)propan-2-ol (3c)

Oily liquid. R_f = 0.52 (EtOAc/MeOH/Et_3N, 90/7/3). ^1H NMR ($CDCl_3$, ppm) δ: 9.07 (1H, d, J = 5.1), 7.7 (1H, d, J = 5.9), 7.27 (2H, m), 5.61 (2H, br s, –NH, –OH), 3.97

(2H, m), 3.54 (2H, s), 2.76–3.01 (3H, m). ^{13}C NMR ($CDCl_3$) δ: 46.5, 54.2, 54.3, 122.7, 135.0, 148.6, 169.1. MS *m/z*: 200 [M^+]. Anal. calcd. for $C_9H_{13}ClN_2O$: C, 53.87; H, 6.53; found: C, 53.66; H, 6.22.

2-(Pyridin-2-ylmethylamino)cyclohexanol (3d)

Solid; mp 87 °C (lit. 87–88 °C) (2*d*). ^{1}H NMR ($CDCl_3$, ppm) δ: 8.55 (1H, d, *J* = 4.8), 7.76 (1H, t, *J* = 5.8), 7.40 (1H, d, *J* = 2.9), 7.26 (1H, m), 5.20 (2H, br s, –NH, –OH), 4.34 (1H, d, *J* = 14.5), 4.10 (1H, d, *J* = 14.5), 3.62 (1H, m), 2.57 (1H, m), 2.01–2.08 (2H, m), 1.67–1.74 (2H, m), 1.18–1.43 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 24.0, 24.6, 28.8, 33.7, 50.0, 63.3, 72.0, 122.9, 137.1, 149.2, 156.0. MS *m/z*: 206 [M^+]. Anal. calcd. for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; found: C, 69.76; H, 8.66.

2-(Phenylamino)cyclohexanol (3e)

Solid; mp 58 °C (lit. 58–59 °C) (3*c*). ^{1}H NMR ($CDCl_3$, ppm) δ: 7.13 (2H, t, *J* = 7.5), 6.65–6.89 (3H, m), 3.45 (2H, br s, NH, OH), 3.30–3.39 (1H, m), 3.10–3.14 (1H, m), 2.05–2.10 (2H, m), 1.66–1.76 (2H, m), 1.05–1.35 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 23.9, 24.2, 31.3, 33.2, 60.3, 74.2, 115.2, 121.9, 129.3, 147.2. MS *m/z*: 191 [M^+]. Anal. calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; Found: C, 75.00; H, 8.56.

2-(*p*-Toluidino)cyclohexanol (3f)

Oily liquid. ^{1}H NMR ($CDCl_3$, ppm) δ: 6.78 (2H, d, *J* = 2.27), 6.48 (2H, d, *J* = 2.50), 3.09–3.14 (1H, m), 3.98 (2H, br s, NH, OH), 2.87–2.93 (1H, m), 3.89 (3H, s), 1.89 (2H, m), 1.56 (2H, m), 1.06–1.18 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 20.4, 24.5, 25.0, 31.5, 33.1, 60.5, 74.3, 115.3, 127.5, 129.3, 145.5. MS *m/z:* 205 [M^+]. Anal. calcd. for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; found: C, 75.98; H, 9.02.

2-(*m*-Toluidino)cyclohexanol (3g)

Oily liquid. ^{1}H NMR ($CDCl_3$, ppm) δ: 7.02 (1H, s), 6.39–6.60 (3H, m), 3.46 (2H, br s, NH, OH), 3.23 (1H, m), 3.03 (1H, m), 2.21 (3H, s), 2.00 (2H, m), 1.61–1.69 (2H, m), 1.17–1.35(4H, m). ^{13}C NMR ($CDCl_3$) δ: 21.5, 23.7, 25.0, 31.0, 33.4, 59.9, 75.6, 111.5, 115.6, 118.5, 128.7, 139.0, 148.0. MS *m/z*: 205 [M^+]. Anal. calcd. for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; found: C, 76.00; H, 9.30.

2-(4-Methoxyphenylamino)cyclohexanol (3h)

Solid; m.p. 53 °C. ^{1}H NMR ($CDCl_3$, ppm) δ: 7.01 (2H, d, *J* = 2.27), 6.84 (2H, d, *J* = 2.50), 3.29–3.21 (1H, m), 4.01 (2H, br s, NH, OH), 2.87–2.93 (1H, m), 3.91 (3H, s), 2.18 (2H, m), 1.86 (2H, m), 1.36–1.48 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 21.4, 25.5, 25.8, 32.5, 34.1, 61.5, 75.7, 115.8, 127.1, 129.9, 145.1. MS *m/z*: 221 [M^+]. Anal. calcd. for $C_{13}H_{19}NO_2$: C, 70.56; H,8.65; found: C, 70.32; H, 8.62.

2-(2-Bromophenylamino)cyclohexanol (3i)

Oily liquid. ^{1}H NMR ($CDCl_3$, ppm) δ: 7.40–7.46 (1H, m), 7.16–7.18 (1H, m), 6.74–6.85 (1H, m), 6.56–6.60 (1H, m) 3.20 (2H, br s, NH, OH), 4.35 (1H, m), 3.38 (1H, m), 2.04–2.10 (2H, m), 1.67–1.74 (2H, m), 1.13–1.43 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 24.0, 24.4, 31.5, 32.7, 59.7, 74.1, 112.9, 118.3, 128.3, 132.5, 144.9. MS *m/z*: 270 [M^+]. Anal. calcd. for $C_{12}H_{16}BrNO$: C, 53.35; H, 5.97; found: C, 53.01; H, 5.67.

2-(3-Bromophenylamino)cyclohexanol (3j)

Oily liquid. ^{1}H NMR ($CDCl_3$, ppm) δ: 6.93–6.99 (1H, m), 6.75–6.79 (2H, m), 6.53–6.58 (1H, m), 4.15 (2H, br s, NH, OH), 3.42 (1H, m), 3.10 (1H, m), 2.05 (2H, m), 1.64–1.73 (2H, m), 1.01–1.31 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 24.4, 24.6, 31.6, 33.1, 56.9, 73.9, 115.7, 117.8, 120.4, 129.8, 148.4. MS *m/z*: 270 [M^+]. Anal. calcd. for $C_{12}H_{16}BrNO$: C, 53.35; H, 5.97; found: C, 53.01; H, 5.67.

2-(4-Bromophenylamino)cyclohexanol (3k)

Solid; mp 67 °C. ^{1}H NMR ($CDCl_3$, ppm) δ: 7.11 (2H, m), 6.45 (2H, m), 3.45 (2H, br s, NH, OH), 3.18–3.25 (1H, m), 2.93–2.99 (1H, m), 1.94 (2H, m), 1.58–1.67 (2H, m), 1.09–1.25 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 24.4, 24.8, 31.4, 33.4, 59.9, 74.3, 115.7, 116.7, 131.8, 147.0. MS *m/z*: 269 [M^+]. Anal. calcd. for $C_{12}H_{16}BrNO$: C, 53.35; H, 5.97; found: C, 53.04; H, 5.86.

2-(3-Hydroxphenylamino)cyclohexanol (3l)

Oily liquid. ^{1}H NMR ($CDCl_3$, ppm) δ: 7.06 (1H, s), 6.18–6.27 (3H, m), 4.68 (2H, br s, NH, OH), 3.28 (1H, m), 3.03 (1H, m), 1.99–2.02 (2H, m), 1.61 (2H, m), 1.18–1.26 (4H, m). MS *m/z*: 206 [M^+]. Anal. calcd. for $C_{12}H_{18}NO_2$: C, 69.87; H, 8.79; found: C, 69.60; H, 8.70.

1-(4-(2-Hydroxycyclohexylamino)phenyl-ethenone (3m)

Solid; mp 79 °C. ^{1}H NMR ($CDCl_3$, ppm) δ: 7.76 (2H, d, *J* = 2.07), 6.56 (2H, d, *J* = 3.10), 4.30 (2H, br s, NH, OH), 3.43 (1H, m), 3.25 (1H, m), 2.48 (3H, s), 2.12 (2H, m), 1.69–1.79 (2H, m), 1.18–1.34 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 23.9, 24.2, 24.6, 31.4, 33.5, 58.9, 74.2, 112.1, 113.6, 130.6, 130.8, 152.3, 196.6. MS *m/z*: 233 [M^+]. Anal. calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; found: C, 71.89; H, 7.98.

4-(2-Hydroxycyclohexylamino)benzoic acid (3n)

Solid; mp 167 °C. ^{1}H NMR ($CDCl_3$, ppm) δ: 7.85 (2H, d, *J* = 2.32), 6.62 (2H, d, *J* = 2.12), 4.94 (2H, br s, NH, OH), 3.23–3.43 (2H, m), 2.10 (2H, m), 1.69 (2H, m), 1.02–1.47 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 24.2, 24.4, 30.3, 32.9, 74.2, 113.7, 118.3, 132.2, 151.5, 171.1. MS *m/z*: 235 [M^+]. Anal. calcd. for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; found: C, 66.02; H, 6.98.

2-(4-Nitrophenylamino)cyclohexanol (3o)

Solid; mp 143 °C. ^{1}H NMR ($CDCl_3$, ppm) δ: 7.21 (2H, m), 6.64 (2H, m), 3.54 (2H, br s, NH, OH), 3.28–3.35 (1H, m), 3.00–3.12 (1H, m), 2.02 (2H, m), 1.68–1.77 (2H, m), 1.10–1.35 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 24.8, 24.3, 32.4, 33.8, 60.15, 75.3, 115.9, 116.1, 131.6, 147.9. MS *m/z*: 236 [M^+]. Anal. calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; found: C, 61.04; H, 6.86.

2-(3-Nitrophenylamino)cyclohexanol (3p)

Solid; mp 157 °C. ^{1}H NMR ($CDCl_3$, ppm) δ: 7.48–7.54 (2H, m), 7.27 (1H, t, *J* = 8.04), 6.95 (1H, d, *J* = 5.04), 3.41 (2H, br s, NH, OH), 3.25 (1H, m), 3.20 (1H, m), 2.14 (2H, m), 1.73–1.82 (2H, m), 1.13–1.42 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 24.1, 24.7, 31.4, 33.5, 59.7, 74.5, 107.5, 112.5, 119.7, 129.8, 148.8. MS *m/z*: 236 [M^+]. Anal. calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; found: C, 60.97; H, 6.561.

2-(2-Trifluorophenylamino)cyclohexanol (3q)

Oily liquid. ^{1}H NMR ($CDCl_3$, ppm) δ: 7.16–7.35 (2H, m), 6.52–6.81 (2H, m) 4.27 (1H, m), 3.23–3.30 (1H, m), 3.19 (2H, br s, –NH, –OH), 1.92 (2H, m), 1.52 (2H, m), 1.07–1.15 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 24.2, 24.5, 33.4, 55.9, 59.5, 112.4, 113.0, 113.6, 114.6, 115.7, 116.5, 116.8, 117.0, 117.2, 126.2, 126.4, 126.5, 132.9, 144.9, 145.8. MS *m/z*: 259 [M^+]. Anal. calcd. for $C_{13}H_{16}F_3NO$: C, 60.22; H, 6.22; found: C, 60.00; H, 6.02.

2-(6-(2-Hydroxycyclohexylamino)pyridin-2-ylamino) cyclohexanol (3r)

Oily liquid. ^{1}H NMR (DMSO, ppm) δ: 7.41 (2H, m), 6.97 (1H, t, *J* = 1.45), 5.50–5.70 (4H, m), 5.36 (4H, br s, NH, OH), 2.30 (4H, m), 1.55 (4H, m), 104–1.27 (8H, m). ^{13}C NMR (DMSO) δ: 23.7, 24.2, 31.1, 34.1, 56.0, 73.3, 95.1, 138.4, 158.3. MS *m/z*: 305 [M^+]. Anal. calcd. for $C_{17}H_{27}N_3O_2$: C, 66.85; H, 8.91; found: C, 66.78; H, 8.56.

2-(Diphenylamino)cyclohexanol (3s)

Oily liquid. ^{1}H NMR ($CDCl_3$, ppm) δ: 6.67–7.32 (10H, m), 4.13–4.54 (1H, m), 3.02–3.23 (1H, m), 3.01 (2H, br s, –NH, –OH), 2.34 (2H, m), 1.84 (2H, m), 1.12–1.34 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 24.4, 25.9, 32.1, 33.4, 60.2, 74.1, 119.2, 120.6, 126.2, 146.4. MS *m/z*: 267 [M^+]. Anal. calcd. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; found: C, 80.45; H, 7.79.

2-(Diisopropylamino)cyclohexanol (3t)

Oily liquid. ^{1}H NMR ($CDCl_3$, ppm) δ: 3.73 (1H, m), 3.60 (2H, m), 3.39 (1H, m), 3.37 (2H, br s, –NH, –OH), 1.14–2.25 (20H, m). ^{13}C NMR ($CDCl_3$) δ: 19.3, 23.7, 23.8, 29.9, 32.9, 46.5, 67.5, 72.8. MS *m/z*: 199 [M^+]. Anal. calcd. for $C_{12}H_{25}NO$:, 72.31; H, 12.64; found: C, 72.01; H, 12.54.

2-(Propylamino)cyclohexanol (3u)

Oily liquid. ^{1}H NMR ($CDCl_3$, ppm) δ: 4.56 (2H, br s, –NH, –OH), 4.33 (1H, m), 4.13 (2H, dd, *J* = 7.15, 7.15), 3.61 (1H, m), 2.27 (2H, m), 2.08 (3H, s), 1.22–1.33 (6H, m). ^{13}C NMR ($CDCl_3$) δ: 14.1, 21.0, 24.1, 24.5, 30.9, 33.1, 60.4, 72.7, 87.0. MS *m/z*: 157 [M^+]. Anal. calcd. for $C_9H_{19}NO$: C, 68.74; H, 12.18; found: C, 68.65; H, 12.01.

2-Morpholinocyclohexanol (3v)

Oily liquid. ^{1}H NMR ($CDCl_3$, ppm) δ: 3.72 (4H, t, *J* = 4.9), 3.37 (1H, m), 2.72 (2H, t, *J* = 5.4), 2.41 (2H, t, *J* = 4.0), 2.15 (1H, m), 1.83 (2H, m), 1.71 (2H, m), 1.08–1.27 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 22.2, 23.9, 25.4, 33.1, 48.7, 67.4, 68.3, 70.5. MS *m/z*: 185 [M^+]. Anal. calcd. for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34 ; found: C, 64.66; H, 10.02.

2-(4-(4-(2-Hydroxycyclohexylamino)benzyl)phenyl amino)cyclohexanol (3w)

Oily liquid. ^{1}H NMR ($CDCl_3$, ppm) δ: 6.80 (4H, d, *J* = 5.85), 6.43 (4H, d, *J* = 4.36), 3.90–3.98 (2H, m), 3.59 (2H, s), 3.44 (4H, br s, NH, OH), 2.88–3.15 (2H, m), 0.84–1.87 (16H, m). ^{13}C NMR ($CDCl_3$) δ: 20.8, 24.2, 30.8, 31.3, 40.0, 60.3, 73.8, 114.2, 129.4, 146.0. MS *m/z*: 392 [M^+]. Anal. calcd. for $C_{25}H_{32}N_2O_2$: C, 76.49; H, 8.22; found: C, 76.33; H, 8.12.

2-(4-(4-(2-Hydroxycyclohexylamino) phenoxy)phenylamino)cyclohexanol (3x)

Oily liquid. ^{1}H NMR ($CDCl_3$, ppm) δ: 6.78 (4H, d, *J* = 8.77), 6.59 (4H, d, *J* = 8.85), 3.44 (4H, brs, NH, OH), 3.29 (2H, ddd, *J*= 9.20, 3.57, 9.77), 2.99 (2H, ddd, 8.95, 3.60, 8.97), 2.01–2.03 (4H, m), 1.68–1.80 (4H, m), 1.00–1.36 (8H, m). ^{13}C NMR ($CDCl_3$, ppm) δ: 24.3, 24.8, 32.4, 33.3, 60.8, 74.0, 115.0, 119.0, 143.4, 150.2. MS *m/z*: 396 [M^+]. Anal. calcd. for $C_{25}H_{32}N_2O_2$: C, 72.70; H, 8.13; found: C, 72.63; H, 8.03.

7-(2-Hydroxycyclohexyl)-5,6,7,8,9,10-hexahydro-2-*H*-1,13,4,7,10-benzadioxatriazacyclopentadecine-3,11, (4*H*,12*H*)-dione (3y)

Oily liquid. ^{1}H NMR ($CDCl_3$, ppm) δ: 8.03 (1H, s, NH), 6.96–7.01 (2H, m), 6.85–6.91 (2H, m), 4.51 (4H, s), 3.49 (4H, t, *J* = 5.37), 3.36 (1H, m), 3.20 (1H, m), 2.94 (4H, t, *J* = 5.35), 2.0 (2H, m), 1.69 (2H, m), 1.26 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 24.0, 24.8, 32.1, 32.7, 38.0, 47.3, 66.8, 73.2, 120.0, 122.0, 165.0, 168.1, 168.6. MS *m/z:* 391 [M^+]. Anal. calcd. for $C_{20}H_{29}N_3O_5$: C, 61.36; H, 7.47; found: C, 61.23; H, 7.43.

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References

1. (*a*) I. Cepanec, M. Litvic, H. Mikuldas, A. Bartolincic, and V. Vinkovic. Tetrahedron, **59**, 2435 (2003); (*b*) D.J. Ager, I. Prakash, and D.R. Schaad. Chem. Rev. **96**, 835 (1996); (*c*) P. O'Brien. Angew. Chem. Int. Ed. **38**, 326 (1999); (*d*) G. Li, H.T. Chang, and K.B. Sharpless. Angew. Chem. Int. Ed. **35**, 451 (1996); (*e*) J. Joossens, P. van der Veken, A.M. Lambeir, K. Augustyns, and A.J. Haemers. Med. Chem. **47**, 2411 (2004); (*f*) P.G. Williams, W.Y. Yoshida, R.E. Moore, and V.J. Paul. J. Nat. Prod. **65**, 29 (2002); (*g*) G.A. Rogers, S.M. Parsons, D.C. Anderson, L.M. Nilsson, B. Bahr, W.D. Kornreich, R. Kaufman, R.S. Jacobs, and B. Kirtman. J. Med. Chem. **32**, 1217 (1989).
2. (*a*) G. Sekar and V.K. Singh. J. Org. Chem, **64**, 287 (1999); (*b*) T. Ollevier and G. Lavie-Compin. Tetrahedron Lett. **45**, 49 (2004); (*c*) I. Cepanec, M. Litvic, H. Mikuldas, A. Bartolincic, and V. Vinkovie. Tetrahedron Lett. **44**, 2435 (2003); (*d*) F. Fringuelli, F. Pizzo, S. Tortoioli, and L. Vaccaro. J. Org. Chem. **69**, 7745 (2004).
3. (*a*) L.R. Reddy, M.A. Reddy, N. Bhanumathi, and K.R. Rao. New J. Chem. **25**, 221 (2001); (*b*) L. Duran Pachon, P. Gamez, J.J.M. Van Brussel, and J. Reedijk. Tetrahedron Lett. **44**, 6025 (2003); (*c*) A. Chakraborti and A. Kondaskar. Tetrahedron Lett. **44**, 8315 (2003); (*d*) J.R. Rodriguez and A. Navarro. Tetrahedron Lett. **45**, 7495 (2004); (*e*) S. Chandrasekhar, T. Ramachandar, and J.S. Prakash. Synthesis, 1817 (2000); (*f*) G. Sundarajan, K. Vijayakrishna, and B. Varghese. Tetrahedron Lett. **45**, 8253 (2004).
4. V.R. Yarapathy, S. Mekala, B.V. Rao, and S. Tammishetti. Catal. Commun. **7**, 466 (2006).
5. A.K. Chakraborti, A. Kondskar, and S. Rudrawar. Tetrahedron, **60**, 9085 (2004).

6. (*a*) P.-Q. Zhao, L.-W. Xu, and C.-G. Xia. Synlett, **5**, 846 (2004); (*b*) M. Curini, F. Epifano, M.C. Marcotullio, and O. Rosati. Eur. J. Org. Chem. **21**, 4149 (2001).
7. (*a*) U. Das, B. Crousse, V. Kesavan, D. Bonnet-Delpon, and J.-P. Begue. J. Org. Chem. **65**, 6749 (2000); (*b*) J.S. Yadav, B.V.S. Reddy, A.K. Basak, and A. Venkat Narsaiah. Tetrahedron Lett. **44**, 1047 (2003); (*c*) F.-S. Liang, A. Brik, Y.-C. Lin, J.H. Elder, and C.-H Wong. Bioorg. Med. Chem. **14**, 1058 (2006).
8. A. Kamal, S.F. Adil, and M. Arifuddin. Ultrason. Sonochem. **12**, 429 (2005).
9. R.I. Kureshy, S. Singh, N.H. Khan, S.H.R. Abdi, S. Agrawal, V.J. Mayani, and R.V. Jasra. Tetrahedron Lett. **47**, 5277 (2006).
10. (*a*) H. Eshghi, M. Rahimizadeh, and A. Shoryabi. J. Iran. Chem. Soc. **2**, 155 (2005); (*b*) N. Azizi and M.R. Saidi. Org. Lett. **7**, 3649 (2005).
11. (*a*) T. Seki, H. Kabashima, K. Akutsu, H. Tachikawa, and H. Hattori. J. Catal. **204**, 393 (2001); (*b*) B. Kaboudin and M. Karimi. Bioorg. Med. Chem. Lett. **16**, 5324 (2006); (*c*) A. Shockravi, H. Valizadeh, and M.M. Heravi. Phosphorus Sulfur Silicon Relat. Elem. 501 (2003).
12. (*a*) M. Hosseini Sarvari and H. Sharghi. J. Org. Chem. **69**, 6953 (2004); (*b*) H. Sharghi and M. Hosseini Sarvari. Synthesis, **8**, 1057 (2002); (*c*) M.Hosseini Sarvari. Synthesis, **5**, 787 (2005); (*d*) M. Hosseini Sarvari and H. Sharghi. Tetrahedron, **61**, 10903 (2005); (*e*) Y.J. Kim and R.S. Varma. Tetrahedron Lett. **45**, 7205 (2004); (*f*) M. Hosseini Sarvari and H. Sharghi. J. Org. Chem. **71**, 6652 (2006).
13. M.W.C. Robinson, D.A. Timms, S.M. Williams, and A.E. Graham. Tetrahedron Lett. **48**, 6249 (2007).
14. N. Azizi and M.R. Saidi. Tetrahedron, **63**, 888 (2006).
15. M. Hosseini-Sarvari and H. Sharghi. J. Iran. Chem. Soc. In press (2008).