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Cleaner and Efficient Green Chemistry Synthesis of *N,N*′-Dibenzyl or *N,N*′-(2-Hydroxybenzyl)-Ethane-1,2-Diamine,-Propane-1,3-Diamine and -1,3-Diamino-2-Propanol

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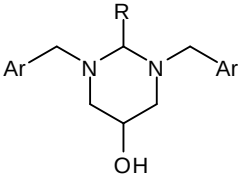
Abstract

An efficient and highly eco-friendly protocol for the preparation of *N,N*′-dibenzyl or *N,N*′-(2-hydroxybenzyl)diamines via the reduction of the corresponding di-Schiff bases that produces a good yield using water as a solvent without the need for catalysis or the azeotropic removal of water has been developed. These symmetric diimines have been reduced to their corresponding diamines with sodium borohydride using a catalyst- and solvent-free protocol with excellent yield. Mild conditions, high yields, and a simple work-up procedure are the primary benefits of this protocol.

Keywords: aqueous medium, catalyst free, green chemistry, reductive amination, di-Schiff bases, solvent-free

1. Introduction

The synthesis of cyclic amines from a carbonyl compound (aldehyde or ketone) and a diamine (or derivative) is currently the method of choice for the preparation of these compounds. In the framework of a program intended to develop 1,2,3-trisubstituted hexahydropyrimidin-5-ols (**1**) with conformational properties, we have been interested in the preparation of N,N′-bis(2-arylmethyl)-diamine compounds. In addition to interest in the stereochemical properties of these compounds and interest in their application in the asymmetric synthesis of ligands in catalysis, *N,N*′-bis(2-hydroxybenzyl) (**2**) and *N,N*′-dibenzyl (**3**) derivatives of 1,2, and 1,3-diamines are of biological importance because their derivatives with related structures act as analgesics, antiparasitics, antifungals, and antibacterials (Bisceglia, Díaz, Torres, & Orelli, 2011). Different methods have been developed to prepare 1,n diamines but the reduction of the corresponding diimines (e.g., **4** and **5**) offers the possibility to produce a wide range of such diamines (Saeed & Musad, 2009). Given our interest in the development of greener synthetic pathways, our synthesis started with the preparation of imines **10e-p** using a simple water-mediated procedure that require neither a catalyst nor any additive (Koteswara Rao et al., 2010) and the products were isolated simply by filtration. Respective di-Schiff bases **10e-p** obtained from this process were further successfully reduced with sodium borohydride under catalyst-free and solvent-free conditions (Wang, Tang, Pan, Yang, & Zhang, 2015), producing the corresponding tetrahydro-di-Schiff bases **11e-p** (Scheme 1). Two primary reduction procedures can be used to reduce C=N compounds: reduction via catalytic hydrogenation and reduction with metal hydrides. Sodium borohydride is one of the most-used reagents for the reduction of imines because of its effectiveness and its ease of handling. Most conventional imine reaction methods described to date involve treatment with reducing agents such as $NaBH_4$ in an organic solvent, such as ethanol or methanol, with the use of catalysts during reflux (Abdel-Magid, 2014). Many reactions proceed efficiently in the solid state. Indeed, in many cases, solid-state organic reactions occur more efficiently and more selectively than do their counterparts in solution; furthermore, solvent-free reactions have many advantages: reduced pollution, low cost, and simple processing and handling (Tanaka & Toda, 2000). In recent years, environmentally benign synthetic methods have received significant attention and some solvent-free protocols for imine reduction have been reported (Mohammadi & Setamdideh, 2015; Hasanloie & Setamdideh, 2014; Setamdideh & Sepehraddin, 2014; Alinezhad & Tollabian, 2010; Alinezhad, Tajbakhsh & Mahdavi, 2010; Cho & Kung, 2005). In this work we report an alternative, simple solvent-free procedure for the synthesis of tetrahydro-di-Schiff bases that uses sodium borohydride as a reducing agent.



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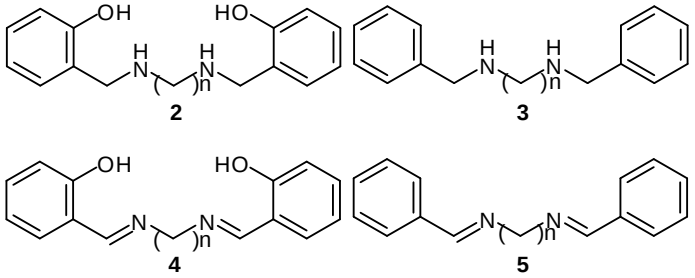


2 **3**

4 **5**

n = 2 or 3

2. Experimental

2.1 Materials and Equipment

All chemical reagents and starting materials were purchased from commercially available vendors and used without further purification. Reactions were monitored by thin-layer chromatography at 0.25 mm using E. Merck silica gel 60 plates (F254). Melting points were measured in open capillaries using an Electrothermal 9100 melting point apparatus and are uncorrected. FT-IR spectra were recorded in potassium bromide pellets using a Thermo Nicolet IS10 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ using a Bruker Avance AV-400 MHz spectrometer operated at 400.130 MHz for ^{1}H and at 100.634 MHz for ^{13}C. Elemental analyses (C, H, N) were performed with a Thermo Scientific Flash 2000.

*2.2 Procedure for the Synthesis of Diimines (**10e-p**)*

An appropriate aromatic aldehyde (**9a-d**) (0.68 mmol) was slowly added to a solution of the appropriate diamine (**6-8**) (0.34 mmol) in water (5 mL). After addition, the mixture was strongly stirred for 3 h at room temperature. The solid was then filtered and washed with abundant water and was dried outdoors if there was a precipitate, but if there was no precipitate, the excess water was removed under vacuum.

2.2.1 Characterization Data of the Compounds

*N,N'–bisbenzylideneethane-1,2-diamine (**10e**)*: White solid, mp 53.0–54.0 ℃, (52.0–53.0 ℃ lit., Simion et al., 2001), yield 100%; IR (KBr): 3080–3028 cm^{-1} (Aromatic C–H stretch), 2929 (C–H stretch, CH_2), 2846 (C–H stretch, N=C–H), 1960–1675 (Overtone and combination aromatic bands), 1641 (C=N stretch) cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): 3.97 (s, 4H, CH_2–CH_2), 7.38 (m, 6H, Ar–H), 7.68 (m, 4H, Ar–H), 8.28 (s ,2H, H–C=N).

*N,N'–bis(o–hydroxybenzylidene)ethane–1,2–diamine (**10f**)*: Yellow solid, mp 133.0–134.0 ℃, (127.0–129.0 ℃ lit. Bordbar, Faal, Ahari–Mostafavi, Graragozlou, & Fazaeli, 2013), yield 88%; IR (KBr) 3451 (O–H stretch), 3051–3009 (Aromatic C–H stretch), 2930–2900 (C–H stretch, CH_2), 2868 (C–H stretch, N=C–H), 1941–1797 (Overtone and combination aromatic bands), 1635 (C=N stretch), 1283 (C–O stretch) cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): 3.91 (s, 4H, CH_2–CH_2), 6.85 (td, 2H, J = 0.87 Hz; and 7.6 Hz, Ar–H7'), 7.22 (dd, 2H, J = 1.64 Hz; J = 7.6 Hz, Ar–H5'), 7.28 (td, 2H, J = 1.64 Hz; J = 7.6 Hz, Ar–H6'), 8.35 (s, 2H, H–C=N), 13.2 (s, 2H, OH).

*N,N'–bis(p–methoxybenzylidene)ethane–1,2–diamine (**10g**)*: White solid, mp 119.0–120.0 ℃, (110.0–111.0 ℃ lit. Ünaleroğlu, Temelli, & Hökelek, 2002), yield 95%; IR (KBr) 3047–3015 (Aromatic C–H stretch), 2971 (C–H stretch, CH_2), 2920 (C–H stretch, CH_3), 2888 (C–H stretch, N=C–H), 2842 (Symmetric C–O–C stretch, Ar–OCH_3), 2025–1900 (Overtone and combination aromatic bands), 1640 (C=N stretch), 1251 (Asymmetric C–O–C stretch, Ar–OCH_3) cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): 3.82 (s, 6H, OCH_3), 3.91 (s, 4H, CH_2–CH_2), 6.90 (m, 4H, Ar–H), 7.63 (m, 4H, Ar–H), 8.20 (s, 2H, H–C=N).

*N,N'–bis(p–dimethylaminobenzylidene)ethane–1,2–diamine (**10h**)*: White solid, mp 181.0–182.0 ℃, yield 86%; IR (KBr) 3042 (Aromatic C–H stretch), 2910 (C–H stretch, CH_2), 2882 (C–H stretch, CH_3), 2852 (C–H stretch, N=C–H), 2000–1900 (Overtone and combination aromatic bands), 1639 (C=N stretch), 1340 (C–N stretch, N(CH_3)$_2$) cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): 2.96 (s, 12H, N(CH_3)$_2$), 3.87 (s, 4H, CH_2–CH_2), 6.65 (d, 4H, J = 8.0 Hz, Ar–H5' and Ar–H7'),

7.57 (d, 4H, *J* = 8.3 Hz, Ar–H4' and Ar–H8'), 8.15 (s, 2H, H–C=N).

N,N'–bis(benzylidene)propane–1,3–diamine ***(10i)***: Light yellow oil, yield 82.4%; IR (KBr) 3060–3026 cm^{-1} (Aromatic C–H stretch), 2925 (C–H stretch, CH_2), 2838 (C–H stretch, N=C–H), 1958–1718 (Overtone and combination aromatic bands), 1644 (C=N stretch) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 2.12 (m, 2H, CH_2), 3.72 (t, 4H, *J* = 7.1 Hz, CH_2–N), 7.37–7.42 (m, 6H, H–Ar), 7.68–7.74 (m, 4H, H–Ar), 8.28 (bs, 2H, H–C=N).

N,N'–bis(o–hydroxybenzylidene)propane–1,3–diamine ***(10j)***: Lemon yellow powder, mp 55.0–57.0 ℃, (54.0–55.0 lit. Frost & Freedman, 1959) 81% yield; IR (KBr) 3424 (O–H stretch), 3049 (Aromatic C–H stretch), 2994–2945 (C–H stretch, CH_2), 2868 (C–H stretch, N=C–H), 1936–1786 (Overtone and combination aromatic bands), 1635 (C=N stretch), 1280 (C–O stretch) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): 2.11 (m, 2H, CH_2), 3.71 (t, 4H, *J* = 7.1 Hz, CH_2–N), 6.86 (t, 2H, *J* = 7.2 Hz, H–Ar), 6.95 (d, 2H, *J* = 8.2 Hz, H–Ar), 7.22 (d, 2H, *J* = 8.2 Hz, H–Ar), 7.29 (ddd, 2H, *J* = 8.2 Hz, H–Ar), 8.35 (s, 2H, H–C=N), 13.39 (bs, 2H, OH).

N,N'–bis(p–methoxybenzylidene)propane–1,3–diamine ***(10k)***: White solid, mp 81.0–82.0 ℃, (74.0–76 ℃ lit. Simion et al., 2001) yield 63.4%; IR (KBr) 3006 (Aromatic C–H stretch), 2954 (C–H stretch, CH_2), 2948 (C–H stretch, CH_3), 2836 (C–H stretch, N=C–H), 2788 (Symmetric C–O–C stretch, Ar–OCH_3), 2005–1900 (Overtone and combination aromatic bands), 1640 (C=N stretch), 1259 (Asymmetric C–O–C stretch, Ar–OCH_3) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): (m, 2H, CH_2), 3.66 (t, 4H, *J* = 7.1 Hz, CH_2–N), 3.82 (s, 6H, O–CH_3), 6.90 (d, 4H, *J* = 9.0 Hz, H–Ar), 7.64 (d, 4H, *J* = 9.0 Hz, H–Ar), 8.20 (bs, 2H, H–C=N).

N,N'–bis(p–dimethylaminobenzylidene propane–1,3–diamine ***(10l)***: Beige solid, mp 155.0–156 ℃, (144.5–145.0 ℃ lit. Billman & Dorman, 1962), yield 75.0%; IR (KBr) 3019 (Aromatic C–H stretch), 2918 (C–H stretch, CH_2), 2904 (C–H stretch, CH_3), 2821 (C–H stretch, N=C–H), 2000–1996 (Overtone and combination aromatic bands), 1639 (C=N stretch), 1363 (C–N stretch, $N(CH_3)_2$) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 2.05 (m, 2H, CH_2–3), 2.99 (s, 12H, $(CH_3)_2$–N), 3.61 (t, 4H, *J* = 6.8 Hz, CH_2–N), 6.67 (d, 4H, *J* = 8.4 Hz, H–Ar), 7.57 (d, 4H, *J* = 8.4 Hz, H–Ar), 8.12 (s, 2H, H–C=N).

N,N'–bisbenzylidene–1,3–diamino–2–propanol ***(10m)***: White solid, mp 104–105 ℃, yield 74.0%; ^1H NMR ($CDCl_3$, 400 MHz):3.76 (ddd, 2H, *J* = 1.2 Hz, *J* = 6.8 Hz, *J* = 12.3 Hz, CH_2–2 or CH_2–4), 3.86 (ddd, 2H, *J* = 1.2 Hz, *J* = 5.0 Hz and *J* = 12.3 Hz, CH_2–2 or CH_2–4), 4.22–4.28 (m, 1H, H–C3), 7.41–743 (m, 6H, Ar–H), 7.73–776 (m, 4H, Ar–H), 8.36 (bs, 2H, H–C=N). ^{13}C NMR ($CDCl_3$, 100 MHz): 63.7, 70.1, 128.75, 129.1, 131.2, 137.0, 162.2. Elem. anal. calcd. For $C_{17}H_{18}N_2O$: C 76.69%; H 6.77%; N 10.53%, O 6.02% found C 73.00%; H 6.76%; N 10.85%.

N,N'–bis(o–hydroxybenzylidene)–1,3–diamino–2–propanol ***(10n)***: Yellow solid, mp 131–132 ℃, yield 94.4%; ^1H NMR ($CDCl_3$, 400 MHz): 3.73 (dd, 2H, *J* = 6.4 Hz, *J* = 12.4 Hz, CH_2–2 or CH_2–4), 3.87 (dd, 2H, *J* = 4.4 Hz, *J* = 12.4 Hz, CH_2–2 or CH_2–4), 4.24–4.30 (m, 1H, H–C3), 6.89 (t, 2H, *J* = 7.2 Hz, *J* = 7.6 Hz Ar–H7'), 6.97 (d, 2H, *J* = 8.4 Hz, Ar–H5'), 7.28 (d, 2H, *J* = 1.2 Hz, Ar–H8'), 7.33 (t, 2H, *J* = 1.6 Hz, *J* = 7.8 Hz, Ar–H6') 8.41 (s, 2H, H–C=N), 13.11 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$, 100 MHz): 63.47, 70.91, 117.57, 119.22, 119.33 132.11, 133.13, 161.92, 168.20. Elem. anal. calcd. For $C_{17}H_{18}N_2O_3$: C 68.46%; H 6.04%; N 9.40%, O 16.11% found C 67.53%; H 5.97%; N 9.21%.

N,N'–bis(p–methoxybenzylidene)–1,3–diamino–2–propanol ***(10o)***: White solid, mp 129–130 ℃, yield 98.0%; ^1H NMR ($CDCl_3$, 400 MHz): 3.71 (ddd, 2H, *J* = 1.2 Hz, *J* = 6.4, 6.8 Hz, *J* = 12.2 Hz, CH_2–2 or CH_2–4), 3.81 (ddd, 2H, *J* = 1.2, Hz, *J* = 4.8 Hz, *J* = 12.4 Hz, CH_2–2 or CH_2–4), 3.84 (s, 6H, OCH_3–C6'), 4.17–4.23 (m, 1H, H–C3), 6.92 (d, *J* = 8.8 Hz, Ar–H), 7.69 (d, *J* = 8.8 Hz, Ar–H), 8.27 (bs, 2H, H–C=N). ^{13}C NMR ($CDCl_3$, 100 MHz): 55.41, 64.98, 71.52, 114.56, 130.00, 130.07, 162.68, 162.71. Elem. anal. calcd. For $C_{19}H_{22}N_2O_3$: C 69.94%; H 6.75%; N 8.59%, O 14.72% found C 69.68%; H 6.71%; N 8.52%.

N,N'–bis(p–dimethylaminobenzylidene)–1,3–diamino–2–propanol ***(10p)***: Pale yellow solid, mp 142–143 ℃, yield 83.4%; ^1H NMR ($CDCl_3$, 400 MHz): 3.00 (s, 12H, $N(CH_3)_2$), 3.67 (dd, 2H, *J* = 6.4 Hz, *J* = 11.6 Hz, CH_2–2 or CH_2–4), 3.77 (dd, 2H, *J* = 5.2 Hz, *J* = 11.6 Hz, CH_2–2 or CH_2–4), 4.15–4.21 (m, 1H, H–C3), 6.70 (d, 4H, *J* = 4.0 Hz, Ar–H5' or Ar–H7'), 7.61 (d, 4H, *J* = 8.4 Hz, Ar–H4' or Ar–H8'), 8.20 (s, 2H, H–C=N), 9.74 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 100 MHz): 40.11, 64.97, 71.61, 112.09, 130.10, 152.90 163.27, 190.96. Elem. anal. calcd. For $C_{21}H_{28}N_4O$: C 71.59%; H 7.96%; N 15.91%, O 4.55% found C 71.15%; H 7.92%; N 15.74%

2.3 General Procedure of the Reduction Reactions ***(11e-p)***

The diimine (0.10 mmol) and sodium borohydride (0.20 mmol) were ground together with an agate mortar, and then heated to between 307 and 361 K for 15 min. After cooling to room temperature, the residue was dissolved in ethanol 95% until it stopped bubbling, and it was then extract in chloroform. The organic layer was dried with (Na_2SO_4) and the solvent was removed under vacuum.

2.3.1 Characterization Data of the Compounds

N,N'–bis(benzyl)ethane–1,2–diamine ***(11e)***: Yellow oil, yield 82.0%; ^1H NMR ($CDCl_3$, 400 MHz): 1.75 (bs, 2H, NH)

2.74 (s, 4H, N–CH_2–), 3.87 (s, 4H, Ph–CH_2–N), 7.23–7.27 (m, 10H, Ar–H).

N,N'–bis(o–hydroxybenzyl)ethane–1,2–diamine (***11f***): Orange oil, yield 88.0%; ^{1}H NMR ($CDCl_3$, 400 MHz): 1.25 (bs, 1H), 2.85 (s, 4H, CH_2–CH_2), 3.99 (s, 4H, CH_2–Ar), 6.78 (td, 2H, *J* = 1.2 Hz; *J* = 7.2 Hz, Ar–H7'), 6.83 (dd, 2H, *J* = 1.2 Hz; *J* = 8.4 Hz, Ar–H5'), 6.98 (dd, 2H, *J* = 1.2 Hz; *J* = 7.4 Hz, Ar–H8'), 7.18 (td, 2H, *J* = 1.6 Hz; *J* = 7.6 Hz, Ar–H6').

N,N'–bis(p–methoxybenzyl)ethane–1,2–diamine (***11g***): Yellow solid, mp 119–120 ℃, yield 83.1%; ^{1}H NMR ($CDCl_3$, 400 MHz): 2.65 (s, 2H, NH), 2.83 (s, 4H, CH_2–CH_2), 3.81 (s, 4H, CH_2–Ar), 3.76 (s, 6H, OCH_3), 6.87–6.92 (m, 4H, Ar–H), 7.21–7.25 (m, 4H, Ar–H).

N,N'–bis(p–dimethylaminobenzyl)ethane–1,2–diamine (***11h***): Orange oil, yield 59.0%; ^{1}H NMR ($CDCl_3$, 400 MHz): 2.26 (bs, 2H, NH), 2.77 (s, 4H, CH_2–CH_2), 2.93 (s, 12H, $(CH_3)_2$–N), 3.68 (s, 4H, CH_2–Ar), 6.70 (d, 4H, *J* = 8.4 Hz, Ar–H5'and Ar–H7'), 7.18 (d, 4H, *J* = 8.8 Hz, Ar–H4' and Ar–H8').

N,N'–bis(benzyl)propane–1,3–diamine (***11i***): Yellow oil, yield 67.0%; ^{1}H NMR ($CDCl_3$, 400 MHz): 1.66 (bs, 2H, NH), 1.73 (q, 2H, *J* = 6.8 Hz, CH_2–3), 2.71 (t, 4H, *J* = 6.8 Hz, CH_2–N), 3.78 (s, 4H, CH_2–Ar), 7.30–7.37 (m, 10H, H–Ar).

N,N'–bis(o–hydroxybenzyl)propane–1,3–diamine (***11j***): Yellow solid, mp 110–111 ℃, yield 48.0%; ^{1}H NMR ($CDCl_3$, 400 MHz): 1.25 (bs, 2H, NH), 1.78 (q, 2H, *J* = 7.2 Hz, CH_2–3), 2.75 (t, 4H, *J* = 7.2 Hz, CH_2–N), 3.99 (s, 4H, CH_2–Ar), 6.77 (td, 2H, *J* = 1.2 Hz, *J* = 7.4 Hz, Ar– H7'), 6.82 (dd, 2H, *J* = 0.8 Hz, *J* = 8.4 Hz, Ar– H5'), 6.98 (dd, 2H, *J* = 1.2 Hz, *J* = 7.6 Hz, Ar– H8'), 7.16 (td, 2H, *J* = 0.8, *J* = 7.6 Hz, Ar– H6').

N,N'–bis(p–methoxybenzyl)propane–1,3–diamine (***11k***): Yellow oil, yield 74.0%; ^{1}H NMR ($CDCl_3$, 400 MHz): 1.69 (bs, 2H, NH), 1.72–1.75 (m, 2H, CH_2–3), 2.68 (t, 4H, *J* = 13.6 Hz, CH_2–N), 3.71 (s, 4H, CH_2–Ar), 3.79 (s, 6H, CH_3–O), 6.85 (d, 4H, *J* = 8.4 Hz, Ar–H5' and Ar–H7'), 7.21 (d, 4H, *J* = 8.4 Hz, Ar–H4' and Ar–H8').

N,N'–bis(p–dimethylaminobenzyl)propane–1,3–diamine (***11l***): Yellow oil, yield 64.0%; ^{1}H NMR ($CDCl_3$, 400 MHz): 1.73 (m, 2H, CH_2–3), 2.04 (bs, 2H, NH), 2.69 (t, 4H, *J* = 6.8 Hz, CH_2–N), 2.93 (s, 12H, $(CH_3)_2$–N), 3.68 (s, 4H, CH_2–Ar), 6.70 (d, 4H, *J* = 8.8 Hz, Ar– H5' and Ar– H7'), 7.16 (d, 4H, *J* = 8.8 Hz, Ar– H4' and Ar– H8').

N,N'–bisbenzyl–1,3–diamino–2–propanol (***11m***): Yellow oil, yield 95.0%; ^{1}H NMR ($CDCl_3$, 400 MHz): 1.91 (bs, 2H, NH), 2.61 (dd, 2H, *J* = 7.6 Hz, *J* = 12.0 Hz, CH_2–2 or CH_2–4), 2.76 (dd, 2H, *J* = 3.6 Hz, *J* = 12.0 Hz, CH_2–2 or CH_2–4), 3.75–3.82 (m, 4H, CH_2–Ar), 3.83–3.84 (m 1H, H–C(OH)), 7.29–7.34 (m, 10H, H–Ar). ^{13}C NMR ($CDCl_3$, 100 MHz): 48.81, 49.58, 62.07, 128.31, 128.64, 129.99, 131.40. Elem. anal. calcd. For $C_{17}H_{22}N_2O$: C 75.55%; H 6.66%; N 10.37%, O 5.92%, found C 78.74%; H 8.66%; N 9.80%.

N,N'–bis(o–hydroxybenzyl)–1,3–diamino–2–propanol (***11n***): Lemon yellow oil, yield 86.0%; ^{1}H NMR ($CDCl_3$, 400 MHz): 2.63–2.74 (m, 4H, CH_2–2 and CH_2–4), 3.94–3.99 (m, 4H, CH_2–Ar), 4.03 (bs, 1H, H–C(OH)), 4.43 (bs, 2H, NH), 6.78 (t, 2H, *J* = 7.6 Hz, Ar–H7'), 6.81 (d, 2H, *J* = 8.0 Hz, Ar–H5'), 6.97 (dd, 2H, *J* = 1.0 Hz, *J* = 7.4 Hz, Ar–H8'), 7.16 (td, 2H, *J* = 1.6 Hz, *J* = 8.0 Hz, Ar–H6'). ^{13}C NMR ($CDCl_3$, 100 MHz): 51.19, 51.45, 68.28, 115.64, 118.56, 121.54, 127.86, 128.23, 157.39. Elem. anal. calcd. For $C_{17}H_{22}N_2O_3$: C 67.55%; H 7.28%; N 7.28%, O 15.89% , found C 56.94%; H 6.04%; N 7.18%.

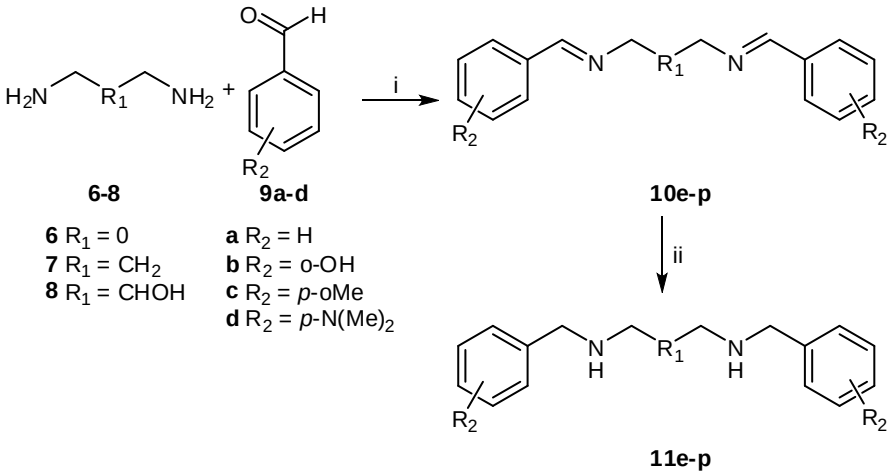
N,N'–bis(p–methoxybenzyl)–1,3–diamino–2–propanol (***11o***): Yellow oil, yield 93.0%; ^{1}H NMR ($CDCl_3$, 400 MHz): 1.25 (bs, 2H, NH), 2.58 (dd, 2H, *J* = 7.6 Hz, *J* = 12.0 Hz, CH_2–2 or CH_2–4), 2.73 (dd, 2H, *J* = 3.6 Hz, *J* = 12.0 Hz, CH_2–2 or CH_2–4), 3.68–3.77 (m, 4H, CH_2–Ar), 3.79 (s, 6H, OCH_3), 3.80–3.84 (m, 1H, H–C(OH)), 6.85 (d, 4H, *J* = 8.8 Hz, Ar–H5' and Ar–H7'), 7.22 (d, 4H, *J* = 8.4 Hz, Ar–H4' and Ar–H8'). ^{13}C NMR ($CDCl_3$, 100 MHz): 51.65, 52.03, 54.17, 67.24, 113.11, 128.71, 131.24, 158.29. Elem. anal. calcd. For $C_{19}H_{26}N_2O_3$: C 69.09%; H 7.88%; N 8.48%, O 14.54% , found C 75.25%; H 8.61%; N 9.12%.

N*,N'–bis(p–dimethylaminobenzyl)–1,3–diamino–2–propanol* (***11p***): Brown oil, yield 85.0%; ^{1}H NMR ($CDCl_3$, 400 MHz): 2.23 (bs, 2H, NH), 2.60 (dd, 2H, *J* = 6.4 Hz, *J* = 12.0 Hz, CH_2–2 or CH_2–4), 2.81 (dd, 2H, *J* = 2.4 Hz, *J* = 12.0 Hz, CH_2–2 or CH_2–4), 2.93 (s, 12H, $N(CH_3)_2$), 3.67 (d, 2H, *J* = 12.8 Hz, CH_2–Ar), 3.75 (d, 2H, *J* = 12.8 Hz, CH_2–Ar), 3.86 (bs, 1H, H–C(OH)), 6.69 (d, 4H, *J* = 8.8 Hz, Ar–H5' and Ar–H7'), 7.17 (d, 4H, *J* = 8.8 Hz, Ar–H4' and Ar–H8'). ^{13}C NMR ($CDCl_3$, 100 MHz): 39.46, 39.52, 64.33, 111.75, 111.86, 128.00, 129.38, 149.44. Elem. anal. calcd. For $C_{21}H_{32}N_4O$: C 70.68%; H 8.97%; N 15.70%, O 4.49%, found C 67.04%; H 8.30%; N 12.93%.

3. Results and Discussions

As shown in Scheme 1, we quickly and efficiently synthesized a series of diimine derivatives (**10e-p**) by condensing some aromatic aldehydes (**9a-d**) and diamines –namely ethane-1,2-diamine (**6**), propane-1,3-diamine (**7**) and 1,3-diamino-2-propanol (**8**)– using water as the reaction medium at room temperature. Compared to current procedures (Patil & Adimurthy, 2013), most of which employ various catalysts or use harsh conditions or vigorous drying of the solvents, this procedure is less hazardous, non-toxic, cheap, and benign to the environment. We found that the reactions occur smoothly, producing di-Schiff bases with yields of 63–100% (Table 1). The reaction times were short (12 h). All

di-Schiff bases (except **10i**, which was viscous) were solids isolated by simple filtration without further purification. In methods used to prepare di-Schiff bases such as **4** and **5**, the amine is generally reacted with a carbonyl source catalyzed by protic or Lewis acids and a dehydrating agent; for example, the mixture is refluxed in heptane in the presence of acetic acid, or an azeotrope of the mixture with benzene is processed in a Dean-Stark apparatus in the presence of sulfuric acid (H_2SO_4) (Love, Boston, Nguyen, & Rorer, 1999; Ryabukhin et al., 2012). Our method is advantageous because the reactions occur very efficiently in water, and neither an acid catalyst nor an aromatic solvent are needed. The structures of di-Schiff bases **10e-p** were established with spectral data. IR spectra of the corresponding condensed product (**10e-p**) displayed the characteristic absorption bands within 1613-1636 cm^{-1} due to the stretching of the C=N bond. In the ^1H NMR spectra of **10e-p**, the aromatic hydrogens of the phenylene ring were observed as multiplets at δ 6.39-7.90. The CH=N hydrogen resonated as a singlet at δ 8.40-8.72. ^{13}C NMR chemical shifts for compounds **10e-p** were observed in their expected regions.



Scheme 1. *Reagents and conditions*: (i) water at room temperature for 3 h; (ii); $NaBH_4$ ground gently at room temperature for 10 min

Table 1. Synthesis of **10e-p** and **11e-p** using green chemistry procedures

Entry	diamine	aldehyde	diimine	Yield (%)	product	Yield (%)
1	6	9a	10e	100.0	11e	82.0
2	6	9b	10f	88.0	11f	88.0
3	6	9c	10g	95.0	11g	83.1
4	6	9d	10h	86.0	11h	59.0
5	7	9a	10i	82.4	11i	67.0
6	7	9b	10j	81.0	11j	48.0
7	7	9c	10k	63.4	11k	74.0
8	7	9d	10l	75.0	11l	64.0
9	8	9a	10m	74.0	11m	95.0
10	8	9b	10n	94.4	11n	86.0
11	8	9c	10o	98.0	11o	93.0
12	8	9d	10p	83.4	11p	85.0

Reduction of the di-Schiff bases **10e-p** by sodium borohydride under catalyst-free and solvent-free conditions produced tetrahydro-di-Schiff bases **11e-p**. The direct solid-solid reductive aminations were carried out by grinding the corresponding di-Schiff base and sodium borohydride with an agate mortar and pestle at room temperature. Then, the reactions were conducted by heating at 60-90 ℃ on a hot plate and were complete within 15 minutes, producing compounds **11e-p** in 48–95% yields. The reactions produced an oily residue, which was extracted with cold chloroform. From the perspective of green chemistry, it is preferable not to use solvents containing halogens. Therefore, we tried to use solvents such as ethyl ether that do not contain halogen atoms, but our attempts were unsuccessful. Chloroform facilitates isolation of the product. Removal of the solvent produced tetrahydro-di-Schiff bases **11e-p** as viscous liquids needing no further purification in most cases. This technique has an easy procedure and a short reaction time, and it does not require significant effort to isolate the products with a high-percentage yield. The structures of products **11e-p** were established by IR and NMR experiments. The preparation of 1,3-bis((E)-benzylideneamino)propan-2-ol **11m** is representative of the general procedure employed. Various temperatures, reaction times and reaction equivalents were explored until we obtained good isolated yields of **11m.** These experiments led to the use of a 1:2 ratio of di-Schiff bases (**10e-p**) with $NaBH_4$, heated at 60–90 ℃ for 15 min.

In conclusion, we have developed a facile, efficient and green method for the synthesis of 1,2 and 1,3-diimines by the condensation of aldehydes with 1,2- and 1,3-diamines in water. Then, in a second step, the resulting Schiff bases were treated with $NaBH_4$ to produce *N,N´*-dibenzyl-diamines (**1**) or *N,N´*-(2-hydroxybenzyl)-diamines (**2**) under solvent-free conditions. This reaction proceeds in the absence of a solvent and a catalyst. Compared to the previously reported methodologies, our protocol offers considerable benefits, including that it has a simple procedure, is environmentally benign, produces high yields, does not require the use of a catalyst, and allows for the product to be synthesized on the gram scale. Further studies regarding this protocol are ongoing in our laboratory.

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References

Abdel-Magid, A. F. (2014). Reduction of C=N to CH-NH by metal hydrides. In P. Knochel & G. A. Molander (Eds): *Comprehensive Organic Synthesis* (2nd ed.) (Vol.8; pp 85–149). Amsterdam, Netherlands: Elsevier Ltd.

Alinezhad, H., & Tollabian, Z. (2010). One-pot reductive amination of carbonyl compounds using sodium borohydride-cellulose sulfuric acid. *Bulletin of the Korean Chemical Society*, *31*(7), 1927-1930. http://dx.doi.org/10.5012/bkcs.2010.31.7.1927

Alinezhad, H., Tajbakhsh, M., & Mahdavi, N. (2010). One-pot reductive amination of carbonyl compounds using sodium borohydride-Amberlyst 15**.** *Synthetic Communications*, *40*(7), 951–956. http://dx.doi.org/10.1080/00397910903026731

Billman, J. H., & Dorman, L. C. (1962). Hexahydropyrimidines I. Preparation of 2-substituted-1,3-bis(*p*-dimethylaminobenzyl)-hexahydropyrimidines. *Journal of Pharmaceutical Sciences*, *51*(11), 1071–1073. http://dx.doi.org/10.1002/jps.2600511113

Bisceglia, J. A., Díaz, J. E., Torres, R. A., & Orelli, L. R. (2011). 1,n-Diamines. Part 3: Microwave-assisted synthesis of N-acyl-N´-arylhexahydropyrimidines and hexahydro-1,3-diazepines. *Tetrahedron Letters*, *52*(41), 5238–5240. http://dx.doi.org/10.1016/j.tetlet.2011.07.131

Bordbar, M., Faal, A. Y., Ahari–Mostafavi, M., Graragozlou, M., & Fazaeli, R. K. (2013). Multi-wavelength spectrophotometric determination of acidity constants of some salicylaldimine derivatives. *Journal of Molecular Liquids*, *178*, 70–77. http://dx.doi.org/10.1016/j.molliq.2012.10.039

Cho, B. T., & Kung, S. K. (2005). Direct and indirect reductive amination of aldehydes and ketones with solid acid-activated sodium borohydride under solvent-free conditions. *Tetrahedron*, *61*(24), 5725–5734. http://dx.doi.org/10.1016/j.tet.2005.04.039

Frost, A. E., & Freedman, H. H. (1959). Addition of hydrogen cyanide to aromatic Schiff bases. *Journal of Organic Chemistry*, *24*(12), 1905-1907. http://dx.doi.org/10.1021/jo01094a021

Hasanloie S. T., & Setamdideh, D. (2014). $NaBH_4$/C: A convenient system for reductive amination of aldehydes. *Oriental Journal of Chemistry*, *30*(1), 341-344. http://dx.doi.org/10.13005/ojc/300145

Koteswara, R. V., Subba, R. S., Satheesh, K. B., Reddi, M., Naidu, K., Naga, R. C., & Ghosh, S. K. (2010). Synthesis of Schiff's bases in aqueous medium: a green alternative approach with effective mass yield and high reaction rates. *Green Chemistry Letters and Reviews*, *3*(3), 217-223. http://dx.doi.org/10.1080/17518251003716550

Love, B. E., Boston, T. S., Nguyen, B. T., & Rorer, J. R. (1999). A comparison of imine forming methodologies. *Organic Preparation and Procedures International*, *31*(4), 399–406. http://dx.doi.org/10.1080/00304949909355728

Mohammadi, N., & Setamdideh, D. (2015). $NaBH_4$/$PhCO_2H$: An efficient system for reductive amination of aldehydes. *Oriental Journal of Chemistry*, *31*(4), 2435-2437. http://dx.doi.org/10.13005/ojc/310476

Patil, R. D., & Adimurthy, S. (2013). Catalytic methods for imine synthesis. *Asian Journal of Organic Chemistry*, *2*(9), 726–744. http://dx.doi.org/10.1002/ajoc.201300012

Ryabukhin, S. V., Panov, D. M., Plaskon, A. S., Chuprina, A., Pipko, S. E., Tolmachev, A. A., & Shivanyuk, A. N. (2012). Combinatorial synthesis of chemical building blocks 1. Azomethines. *Molecular Diversity*, *16*(4), 625-637. http://dx.doi.org/10.1007/s11030-012-9407-9

Saeed, B. A., & Musad, I. A. (2009). Synthesis of symmetrical and non-symmetrical diimines from dimedone.

Molecules, *14*(6), 2278-2285. http://dx.doi.org/10.3390/molecules14062278

Setamdideh, D., & Sepehraddin, F. (2014). Convenient reductive amination of aldehydes by $NaBH_4$/Cation exchange resin. *Journal of the Mexican Chemical Society*, *58*(1), 22-26. Retrieved from http://www.scielo.org.mx/scielo.php?script=sci_arttext&pid=S1870-249X2014000100005&lng=es

Simion, A., Simion, C., Kanda, T., Nagashima, S., Mitoma, Y., Yamada, T.,…Tashiro, M. (2001). Synthesis of imines, diimines and macrocyclic diimines as possible ligands, in aqueous solution. *Journal of the Chemical Society, Perkin Transactions, 1*, 2071-2078. http://dx.doi.org/10.1039/B102749M

Tanaka, K., & Toda, F. (2000). Solvent-free organic synthesis. *Chemical Reviews*, *100*(3), 1025-1074. http://dx.doi.org/10.1021/cr940089p

Ünaleroğlu, C., Temelli, B., & Hökelek, T. (2002). A facile synthesis and characterization of the novel 2,2-dichloro-1-[3-(2,2-dichloro-acetyl)-2-(4-methoxy-phenyl)-imidazolidin-1-yl]-ethanone. *Synthetic Communications*, *32*(21), 3255–3261. http://dx.doi.org/10.1081/SCC-120014029

Wang, C. C., Tang, Y., Pan, Y. H., Yang, J., & Zhang, Y. M. (2015). A novel one-pot synthesis of vicinal diamines with benzaldehyde and aniline derivatives mediated by $BiCl_3$/Zn. *Tetrahedron Letters*, *56*(22), 2863–2866. http://dx.doi.org/10.1016/j.tetlet.2015.04.067