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Efficient and Mild Synthesis of Novel Schiff Bases Via One-Pot, Three-Component Reaction Under Solvent-Free Conditions

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A simple, efficient, and cost-effective method has been developed for the synthesis of N,N'-bis(2-hydroxybenzylidene)-1,1-diaminoalkanes through one-pot, three-component reaction of salicylaldehyde, aliphatic aldehydes, and ammonium nitrate in the presence of a base under solvent-free conditions at room temperature.

Keywords Aldehydes; ammonium nitrate; Schiff base; solvent free; three component

INTRODUCTION

Over the past few years, significant research has been directed toward the development of new technologies for environmentally benign processes (green chemistry),¹ which are both economically and technologically feasible.^{2,3} An important area of green chemistry deals with solvent minimization. In a solvent-free process, the cost of processing, handling, and disposal of the solvent is completely eliminated, resulting in improved process efficiency.¹

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry for various reasons.⁴ In times where a premium is put on speed, diversity, and efficiency in the process, MCR strategies offer significant advantages over conventional linear-type synthesis.⁵ MCR condensations involve three or more compounds reacting consecutively in a single event, to form a new product, which contains the essential parts of all the starting materials. The search and discovery for new MCRs on the one hand and the full exploitation of already known multicomponent reactions on the other hand are

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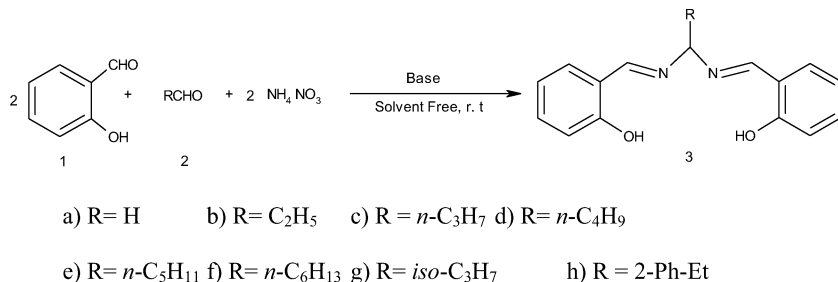
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therefore of considerable current interest.⁶ Schiff bases, as a class of compounds with an imine group, are very important compounds in organic chemistry. A great deal of effort has been made concerning the synthesis of Schiff bases.⁷ Those are once again topical in connection with a diverse range of applications in organic synthesis and bioorganic and medicinal chemistry, such as catalysts in the synthesis of chiral cyanohydrins,⁷ as liquid crystals,⁸ as catalysts in the ring opening of epoxides,⁹ in the preparation of ion-selective electrodes,^{10–15} inhibition of cytosolic/tumor-associated carbonic anhydrase isozymes,¹⁶ and in solid extraction.¹⁷ Schiff bases have been usually produced by a two-component reaction that involves one carbonyl compound with primary amines or diamines in protic solvents. In order to increase the environmental and economical concerns, it is essential for chemists to search environmentally reactions as many as possible.

Because of these economical and environmental reasons, and in conjunction with ongoing work in our laboratory on the preparation of double Schiff bases and their complexes,^{18,19} here we decided to report the synthesis of double Schiff bases by a one-pot, three-component reaction under mild and solvent-free conditions at room temperature.

RESULTS AND DISCUSSION

In this reaction, two different aldehydes were reacted with ammonium nitrate in the presence of a base to produce *N, N'*-bis(2-hydroxybenzylidene)-1,1-diaminoalkanes as shown in Scheme 1.



SCHEME 1

As shown in Scheme 1, when 2 mol eq. of salicylaldehyde and 1 mol eq. of propanal reacted with 2 eq. NH₄NO₃ in the presence of a base at room temperature under solvent-free conditions, after a short time the yellow oil product was obtained. In order to study the effect of the base, this reaction was carried out in the presence of various bases. The results of the reaction are indicated in Table I. As shown in this

TABLE I Reaction of Salicylaldehyde, Propanal, and Ammonium Nitrate at Room Temperature

Entry	Base	Time (min)	Yield (%)
1	NaHCO ₃	20	40
2	NaOOCCH ₃	15	45
3	KOH	8	90
4	NaOH	8	90
5	Pyridine	Overnight	—
6	NEt ₃	8	94
7	None	Overnight	—

table, triethylamine, KOH, and NaOH were the most effective in the reaction.

Then, by dissolving the oil product in methanol and cooling the solution, the yellow crystalline product in excellent yield was purely obtained. In order to study the generality of this process, several examples of aldehydes with salicylaldehyde and ammonium nitrate in the presence of NEt₃ have been studied. The results are summarized in Table II. As shown in Table II, in these reactions, the Schiff bases **3a–3h** were formed in excellent yield and short reaction times at room temperature.

The structures of products have been assigned from spectroscopic data. In the IR spectra, the characteristic Schiff base C=N stretching frequency is found in the region between 1600 and 1700 cm⁻¹ as a signal strong band. The OH stretching frequency is found at 3000 cm⁻¹ with particular width as a broad band. The stretching vibration of C-H in the alkyl groups appears at region between 2700 and 2800 cm⁻¹ with sharp absorptions. In the ¹H NMR spectra, the broad signal around

TABLE II Reaction of Salicylaldehyde, Ammonium Nitrate, and Different Aldehydes in the Presence of NEt₃ at Room Temperature

Entry	Substrate	Product	Mp (°C)	Time (min)	Yield ^a (%)
1	Methanal	3a	116–118	8	90
2	Propanal	3b	92–94	7	94
3	Butanal	3c	72–74	7	94
4	Pentanal	3d	82–84	5	95
5	Hexanal	3e	72–74	3	95
6	Heptanal	3f	82–84	3	95
7	Isobutanal	3g	74–76	2	98
8	3-Phenylpropanal	3h	oil	3	95

^aIsolated yield based on salicylaldehyde.

with 12.00–13.00 ppm is assigned to the protons of the hydroxyl groups. Two protons of CH=N have the same chemical shifts in 8.30–8.46 ppm and the signal around the 4.60–5.00 ppm is assigned to the protons of the NCHN. The UV spectra show maximum absorptions between 200 and 400 nm dependent on the particular compound.

In summary, we have developed an economical environmentally friendly procedure for synthesis of the Schiff bases with excellent yields and short reaction times under free solvent conditions through one-pot, three-component reaction.

EXPERIMENTAL

Materials and Apparatus

Chemicals were purchased from the Merck Chemical Company in high purity. All the materials were of commercial reagent grade. The aldehydes were purified by standard procedures.²⁰ The purity was determined by thin-layer chromatography (TLC) and gas chromatography (GC).

IR spectra were recorded as KBr pellet on a Perkin-Elmer 781 Spectrophotometer and an Impact 400 Nicolet FTIR Spectrophotometer. ¹H NMR spectra were recorded in CDCl₃ using a spectrometer at 400 MHz using TMS as an internal reference. Melting points obtained with a Yanagimoto micro melting point apparatus are uncorrected. The purity determination of the substrates and the reactions monitoring were accomplished by TLC on silica-gel polygram SILG/UV 254 plates.

Typical Procedure for Synthesis of N,N'-bis(2-Hydroxybenzylidene)-1,1-diamino-propane

To a mixture of salicylaldehyde (0.4 g, 3.27 mmol) and propanal (R=C₂H₅, 0.095 g, 1.64 mmol) was added NH₄NO₃ (0.25 g, 3.27 mmol) in the presence of the NEt₃ (1 mL) as a base by stirring in one portion. The mixture was stirred for a further 7 min. The progress of the reaction was monitored by TLC. After the completion of the reaction, a yellow oily substance was obtained. Then, by dissolving the mixture in 2 mL MeOH and cooling overnight, a yellow solid precipitated. The solid product was filtered off and washed with cold MeOH. The crude product was purified by recrystallization in ethanol and the pure Schiff base, N,N'-bis(2-hydroxybenzylidene)-1,1-diaminopropane, was obtained in 94% yield, mp = 92–94°C. The Schiff base products were identified by spectroscopic data.

***N,N'*-bis(2-Hydroxybenzylidene)-1,1-diaminomethane (3a)**

mp 116–118°C; IR (KBr)/ ν (cm^{-1}) 3150–3450 (br, OH); 2980 (C-H, alkyl), 1620 (s, C=N), 1587, 1501 (Ar); ^1H NMR/ CDCl_3/δ ppm: 4.46 (s, 2H), 6.90–7.60 (m, 8H), 8.60 (s, 2H), 12.70 (s, 2H, 2OH); ^{13}C NMR/ CDCl_3/δ ppm: 85.0, 117.6, 119.9, 118.7, 133.0, 133.9, 155.0, 161.0; MS: m/z = 255 ($\text{M}^+ + 1$, 7), 254 (M^+ , 8), 132 (14), 133 (100), 91 (17), 77 (44), 58 (60); UV (CHCl_3)/ λ_{max} (nm) 320 (w), 260 (s); Anal. Calcd for C, H, N: C, 70.87; H, 5.51; N, 11.02; Found: C, 71.01; H, 5.54; N, 11.10.

***N,N'*-bis(2-Hydroxybenzylidene)-1,1-diaminopropane (3b)**

mp 92–94°C; IR (KBr)/ ν (cm^{-1}): 3150–3450 (br, OH), 2965 (C-H, alkyl), 1625 (s, C=N), 1501, 1587 (Ar); ^1H NMR/ CDCl_3/δ ppm: 4.80 (t, 1H, NCHN), 0.90 (t, 3H, CH_3), 1.99 (m, 2H, CH_2), 6.90–7.60 (m, 8H), 8.70 (s, 2H, C=N), 13.01 (s, 2H, 2OH); ^{13}C NMR/ CDCl_3/δ ppm: 19.0, 20.2, 85.0, 116.4, 118.40, 119.6, 133.0, 133.7, 155.4, 161.3; MS: m/z = 283 ($\text{M}^+ + 1$, 6%), 282 (M^+ , 10), 162 (13), 161 (100), 91 (20), 77 (45), 58 (59); UV (CHCl_3)/ λ_{max} (nm); Anal. Calcd for C, H, N: C, 72.34; H, 6.38; N, 9.93; Found: C, 72.37; H, 6.41; N, 9.93.

***N,N'*-bis(2-Hydroxybenzylidene)-1,1-diaminobutane (3c)**

mp 72–74°C; IR (KBr)/ ν (cm^{-1}) 3100–3440 (br, OH); 2960 (C-H, alkyl), 1625 (s, C=N), 1502, 1576 (Ar); ^1H NMR/ CDCl_3/δ ppm: 0.90 (t, 3H, CH_3), 1.40 (m, 2H, CH_2), 1.90 (q, 2H, CH_2), 4.99 (t, 1H, NCHN), 6.90–7.70 (m, 8H), 8.70 (s, 2H, C=N), 13.00 (s, 2H, 2OH); ^{13}C NMR/ CDCl_3/δ ppm: 15.3, 18.0, 20.0, 84.0, 117.4, 118.8, 119.0, 133.0, 133.7, 155.2, 161.0; UV (CHCl_3)/ λ_{max} (nm) 322 (w), 260 (s); MS: m/z = 297 ($\text{M}^+ + 1$, 6), 296 (M^+ , 7), 176 (15), 175 (100), 91 (17), 77 (45), 58 (55), 56 (30), 42 (15); Anal. Calcd for C, H, N: C, 73.55; H, 7.09; N, 9.03; Found: C, 73.60; H, 7.12; N, 9.05.

***N,N'*-bis(2-Hydroxybenzylidene)-1,1-diaminopentane (3d)**

mp 82–84°C; IR (KBr)/ ν (cm^{-1}) 3250–3430 (br, OH); 2950 (C-H, alkyl), 1625 (s, C=N), 1491, 1577 (Ar); ^1H NMR/ CDCl_3/δ ppm: 0.90 (t, 3H, CH_3), 1.40 (m, 4H, 2 CH_2), 1.90 (q, 2H, CH_2), 4.99 (t, 1H, NCHN), 6.90–7.70 (m, 8H), 8.70 (s, 2H, C=N), 12.93 (s, 2H, 2OH); ^{13}C NMR/ CDCl_3/δ ppm: 15.3, 17.2, 20.0, 82.0, 117.0, 118.0, 119.0, 133.0, 133.2, 158.0, 165.0; UV (CHCl_3)/ λ_{max} (nm) 320 (w), 260 (s); MS: m/z = 311 ($\text{M}^+ + 1$, 5), 310 (M^+ , 9), 190 (12), 189 (100), 91 (20), 77 (40), 58 (55), 56 (25), 42 (14); Anal. Calcd for C, H, N: C, 73.55; H, 7.09; N, 9.03; Found: C, 73.57; H, 7.10; N, 9.03.

***N,N'*-bis(2-Hydroxybenzylidene)-1,1-diaminohexane (3e)**

mp 72–74°C; IR (KBr)/ ν (cm⁻¹) 3000–3350 (br, OH), 2970 (C-H, alkyl), 1629 (s, C=N), 1486, 1573 (Ar); ¹H NMR/CDCl₃/ δ ppm: 0.90 (t, 3H, CH₃), 1.40 (m, 6H, 3CH₂), 1.90 (q, 2H, CH₂), 4.99 (t, 1H, NCHN), 6.90–7.70 (m, 8H), 8.50 (s, 2H, C=N), 13.10 (s, 2H, 2OH); ¹³C NMR/CDCl₃/ δ ppm: 12.3, 15.1, 17.0, 19.0, 21.0, 86.0, 118.0, 119.0, 120.5, 133.0, 133.2, 158.0, 166.0; UV(CHCl₃)/ λ_{max} (nm) 322 (w), 261 (s); Anal. Calcd for C, H, N: C, 74.07; H, 7.41; N, 8.64; Found: C, 74.11; H, 7.42; N, 8.64.

***N,N'*-bis(2-Hydroxybenzylidene)-1,1-diaminoheptane (3f)**

mp 82–84°C; IR (KBr)/ ν (cm⁻¹) 3250–3500 (br, OH), 2950 (C-H, alkyl), 1631 (s, C=N), 1491, 1571 (Ar); ¹H NMR/CDCl₃/ δ ppm: 0.80 (t, 3H, CH₃), 1.30 (m, 8H, 4CH₂), 1.90 (q, 2H, CH₂), 5.00 (t, 1H, NCHN), 6.90–7.60 (m, 8H), 8.70 (s, 2H, C=N), 13.20 (s, 2H, 2OH); ¹³C NMR/CDCl₃/ δ ppm: 13.4, 16.0, 17.0, 18.0, 19.0, 22.0, 87.0, 117.0, 119.0, 120, 133.0, 134.1, 157.0, 165.0; MS: m/z = 339 (M⁺+1, 10%), 338 (M⁺, 15), 220 (20), 220 (100), 91 (29), 77 (50), 58 (57), 56 (34), 42 (20); UV (CHCl₃)/ λ_{max} (nm) 320 (w), 262 (s); Anal. Calcd for C, H, N: C, 74.56; H, 7.69; N, 8.28; Found: C, 74.58; H, 7.71; N, 8.28.

***N,N'*-bis(2-Hydroxybenzylidene)-1,1-diaminoisobutane (3g)**

mp 74–76°C; IR (KBr)/ ν (cm⁻¹) 3250–3520 (br, OH), 2965 (C-H, alkyl), 1615 (s, C=N), 1502, 1577 (Ar); ¹H NMR/CDCl₃/ δ ppm: 0.80 (d, 6H, CH₃), 2.01 (m, 1H, CH), 4.40 (t, 1H, NCHN), 6.90–7.20 (m, 8H), 8.20 (s, 2H, C=N), 12.90 (s, 2H, 2OH); ¹³C NMR/CDCl₃/ δ ppm: 18.4, 35.2, 92.0, 117.4, 119.4, 119.7, 133.0, 133.7, 161.3; UV (CHCl₃)/ λ_{max} (nm) 323 (w), 242 (w), 262 (s); MS: m/z = 297 (M⁺+1, 5), 296 (M⁺, 6), 177 (12), 176 (100), 133 (11), 132 (58), 91 (18), 77 (42), 58 (58); Anal. Calcd for C, H, N: C, 72.97; H, 6.76; N, 9.46; Found: C, 72.99; H, 6.79; N, 9.46.

***N,N'*-bis(2-Hydroxybenzylidene)-1,1-diamino-3-phenylpropane (3h)**

Oil; IR (neat)/ ν (cm⁻¹) 3000–3300 (br, OH), 2955 (C-H, alkyl), 1625 (s, C=N), 1490, 1576 (Ar); ¹H NMR/CDCl₃/ δ ppm: 0.90 (d, 6H, CH₃), 1.40 (m, 1H, CH₂), 1.90 (q, 2H, CH₂), 4.99 (t, 1H, NCHN), 6.90–7.70 (m, 13H), 8.70 (s, 2H, C=N), 13.02 (s, 2H, 2OH); ¹³C NMR/CDCl₃/ δ ppm: 32.1, 45.0, 91.0, 117.3, 119.2, 119.6, 133.0, 137.2, 158.0, 164.0; UV(CHCl₃)/ λ_{max} (nm) 323 (w), 262 (s). Anal. Calcd for C, H, N: C, 77.09; H, 6.14; N, 7.82; Found: C, 77.24; H, 6.17; N, 7.83.

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