Orbital: The Electronic Journal of Chemistry
journal homepage: www.orbital.ufms.br
ISSN 1984-6428

| Vol 7 | | No. 3 | | July-September |

Full Paper

Solvent-free, Environmentally Benign Syntheses of Some Imines and Antioxidant Activity

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Article history: Received: 05 September 2014; revised: 25 December 2014; accepted: 02 January 2015. Available online: 04 July 2015. DOI: http://dx.doi.org/10.17807/orbital.v7i3.608

Abstract: Environmentally benign, economically feasible, and solvent-free syntheses of series of imines by the condensation of a substituted hydroxynaphthyl ketone with several substituted iodoanilines under grinding approach are described. Imines were further tested for antioxidant activity; most of them show moderate activity.

Keywords: solvent-free synthesis; imines; substituted ketones; substituted anilines; grinding technique

1. INTRODUCTION

In recent years, the use of hazardous and toxic solvents in chemical laboratories, chemical industry has been considered a very serious problem for the health, safety of workers, and environmental pollution. For these purposes, the emerging area of green chemistry plays an important role into the development of synthetic strategies [1,2]. Grinding technique, which is reacting under solvent-free conditions, is one of the green synthetic routes that has gained popularity towards designing the structure of new molecules [3-6]. Grinding technique has been increasingly used in organic synthesis as compared to traditional methods [7-9], because these reactions are not only of interest from an economical point of view, but also in many cases they offer considerable advantages in terms of yield, selectivity, and simplicity of reaction procedure with high atom efficiency. Many well known reactions have been reported under solvent-free environments using the grinding technique [10-17].

Schiff bases (imines) are well known for their wide applications and are useful intermediates in organic synthesis [18]. These compounds have intrinsic biological activities including anticancer [19], antitumour [20], antitubercular [21], antibacterial [22], antioxidant [23], and anticonvulsant [24] activities. Moreover, Schiff bases also exhibit fluorescence [25], photoluminescence [26], and aggregation [27] properties. In view of these observations, we plan to synthesize some novel imines by a condensation reaction of a substituted hydroxyketone with substituted anilines in the presence of sulfuric acid under grinding technique (Scheme 1).

2. MATERIAL AND METHODS

Melting points were determined in open capillary tubes and are uncorrected. FT-IR spectra were recorded in KBr pellets on a Perkin-Elmer [8201] spectrometer. ^{1}H NMR spectra were recorded on a Gemini 300-MHz instrument in DMSO-d_6 as the solvent and TMS was used as an internal standard. The mass spectra were recorded on SHIMADZU (GCMS-QP 1000 EX) GC-EI-MS spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 CHN elemental analyser. The reactions were carried out in open glass mortar and pestle. Purification of the compound was indicated using TLC (ethyl acetate / hexane (0.25 mL: 0.25 mL, v/v) as the mobile phase).

General procedure for the synthesis of imines

A mixture of the hydroxyketone **1** (0.01 mol)

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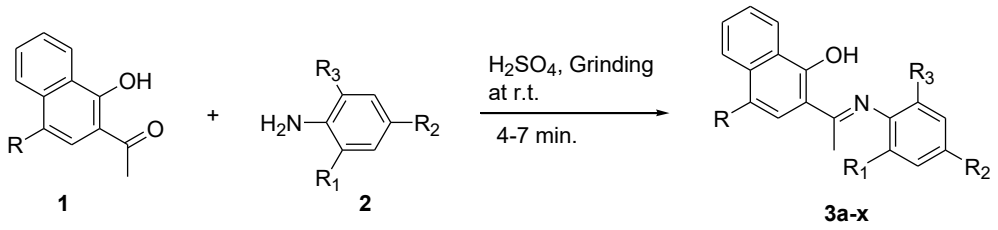
and substituted anilines **2** (0.01 mol) were ground with a pestle in an open mortar at room temperature for 2-3 minutes. To this reaction mixture sulfuric acid (0.002 mmol) was added and grinding continued for 4-7 minutes. On completion of reaction as monitored by TLC, the light greenish-coloured solid was separated out. The obtained solid was diluted with cold water and isolated by simple Buchner filtration and recrystallized from ethanol to give pure imines **3a-x** as light yellow crystals.



Scheme 1. Synthesis of imines under solvent-free conditions using grinding technique **3a-x**

2-[1-(4-Chloro-2-iodophenylimino)-ethyl]-4-iodonaphthalen-1-ol (**3a**): Yield 75%, m.p. 145-147 °C; FT-IR (KBr, ν, cm^{-1}): 1435, 1528 (C=C), 1582 (C=N), 3240 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.32 (s, 3H, CH_3), 5.28 (s, 1H, OH), 6.27-6.95 (m, 8H, ArH). (MS (EI), *m/z* (%): 547 (M^+, 42%). Anal. calcd. For $C_{18}H_{12}Cl\ I_2NO$: C, 39.48; X (I, Cl) 52.83; H, 2.19; N, 2.55%. Found: C, 39.57; X (I, Cl) 52.98; H, 2.28; N, 2.62%.

4-Bromo-2-[1-(4-chloro-2-iodophenylimino)-ethyl]-naphthalen-1-ol (**3b**): Yield 78%, m.p. 142-144 °C; FT-IR (KBr, ν, cm^{-1}): 1432, 1525 (C=C), 1580 (C=N), 3235 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.35 (s, 3H, CH_3), 5.26 (s, 1H, OH), 6.23-6.89 (m, 8H, ArH). (MS (EI), *m/z* (%): 500 (M^+, 35%). Anal. calcd. For $C_{18}H_{12}BrCl\ INO$: C, 43.20; X (I, Br, Cl) 48.40; H, 2.40; N, 2.80%. Found: C, 43.28; X (I, Br, Cl) 48.59; H, 2.52; N, 2.93%.

4-Chloro-2-[1-(4-chloro-2-iodo-phenylimino)-ethyl]-naphthalen-1-ol (**3c**): Yield 74%, m.p. 155-157 °C; FT-IR (KBr, ν, cm^{-1}): 1434, 1528 (C=C), 1582 (C=N), 3234 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.34 (s, 3H, CH_3), 5.26 (s, 1H, OH), 6.25-6.89 (m, 8H, ArH). (MS (EI), *m/z* (%): 456 (M^+, 42%). Anal. calcd. For $C_{18}H_{12}Cl_2INO$: C, 47.36; X (I, Cl) 43.20; H, 2.63; N, 3.07%. Found: C, 47.46; X (I, Cl) 43.34; H, 2.75; N, 3.18%.

4-Iodo-2-[1-(4-iodo-2-nitrophenylimino)-ethyl]-naphthalen-1-ol (**3d**): Yield 81%, m.p. 138-140 °C; FT-IR (KBr, ν, cm^{-1}): 1436, 1530 (C=C), 1583 (C=N), 3232 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.33 (s, 3H, CH_3), 5.24 (s, 1H, OH), 6.29-6.94 (m, 8H, ArH). (EI, *m/z* (%): 558 (M^+, 48 %). Anal. calcd. For $C_{18}H_{12}O_3N_2I_2$: C, 38.70; X (I) 45.51; H, 2.15; N, 4.83%. Found: C, 38.85; X (I) 45.64; H, 2.27; N, 4.96%.

4-Bromo-2-[1-(4-iodo-2-nitrophenylimino)-ethyl]-naphthalen-1-ol (**3e**): Yield 77%, m.p. 133-135 °C; FT-IR (KBr, ν, cm^{-1}): 1434, 1535 (C=C), 1580 (C=N), 3235 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.26 (s, 1H, OH), 6.28-6.95 (m, 8H, ArH). (MS (EI), *m/z* (%): 511 (M^+, 53%). Anal. calcd. For $C_{18}H_{12}O_3N_2IBr$: C, 42.27; X (I, Br) 46.50; H, 2.34; N, 2.73%. Found: C, 42.38; X (I, Br) 46.64; H, 2.47; N, 2.88%.

4-Chloro-2-[1-(4-iodo-2-nitrophenylimino)-ethyl]-naphthalen-1-ol (**3f**): Yield 83%, m.p. 147-150 °C; FT-IR (KBr, ν, cm^{-1}): 1435, 1536 (C=C), 1583 (C=N), 3236 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.35 (s, 3H, CH_3), 5.25 (s, 1H, OH), 6.27-6.94 (m, 8H, ArH). (MS (EI), *m/z* (%): 466 (M^+, 53%). Anal. calcd. For $C_{18}H_{12}Cl\ IN_2O_3$: C, 46.35; X (I, Cl) 34.76; H, 2.57; N, 3.00%. Found: C, 46.47; X (I, Cl) 34.88; H, 2.69; N, 3.12%.

2-[1-(2-Chloro-4-iodophenylimino)-ethyl]-4-iodonaphthalen-1-ol (**3g**): Yield 80%, m.p. 162-164 °C; FT-IR (KBr, ν, cm^{-1}): 1437, 1542 (C=C), 1582 (C=N), 3237 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.27 (s, 1H, OH), 6.29-6.91 (m, 8H, ArH). (MS (EI), *m/z* (%): 547 (M^+, 60%). Anal. calcd. For $C_{18}H_{12}Cl\ I_2NO$: C, 39.48; X (I, Cl) 52.83; H, 2.19; N, 2.55%. Found: C, 39.56; X (I, Cl) 52.97; H, 2.32; N, 2.64%.

4-Bromo-2-[1-(2-chloro-4-iodo-phenylimino)-ethyl]-naphthalen-1-ol (**3h**): Yield 75%, m.p. 168-171 °C; FT-IR (KBr, ν, cm^{-1}): 1438, 1542 (C=C), 1582 (C=N), 3236 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.28 (s, 1H, OH), 6.30-6.91 (m,

8H, ArH). (MS (EI), *m/z* (%): 500 (M^+, 55 %). Anal. calcd. For $C_{18}H_{12}BrCl$ INO: C, 43.20; X (I, Br, Cl) 48.40; H, 2.40; N, 2.80%. Found: C, 43.36; X (I, Br, Cl) 48.54; H, 2.52; N, 2.93%.

4-Chloro-2-[1-(2-chloro-4-iodo-phenylimino)-ethyl]-naphthalen-1-ol (**3i**): Yield 85%, m.p. 150-152 ºC; FT-IR (KBr, ν, cm^{-1}): 1438, 1540 (C=C), 1582 (C=N), 3235 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.27 (s, 1H, OH), 6.30-6.93 (m, 8H, ArH). (MS (EI), *m/z* (%): 456 (M^+, 52%). Anal. calcd. For $C_{18}H_{12}Cl_2INO$: C, 47.36; X (I, Cl) 43.20; H, 2.63; N, 3.07%. Found: C, 47.51; X (I, Cl) 43.33; H, 2.70; N, 3.18%.

*4-Iodo-2-[1-(2-iodo-4-nitrophenylimino)-ethyl]-naphthalen-1-ol (***3j**): Light Yellow Crystal, Yield 88%, m.p. 162-165 ºC; FT-IR (KBr, ν, cm^{-1}): 1434, 1535 (C=C), 1582 (C=N), 3235 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.37 (s, 3H, CH_3), 5.26 (s, 1H, OH), 6.28-6.95 (m, 8H, ArH). (MS (EI), *m/z* (%): 558 (M^+, 56%). Anal. calcd. For $C_{18}H_{12}I_2N_2O_3$: C, 38.70; X (I) 46.51; H, 2.15; N, 4.83%. Found: C, 38.82; X (I) 46.68; H, 2.26; N, 4.96%.

4-Bromo-2-[1-(2-iodo-4-nitrophenylimino)-ethyl]-naphthalen-1-ol (**3k**): Yield 78%, m.p. 139-141 ºC; FT-IR (KBr, ν, cm^{-1}): 1436, 1535 (C=C), 1582 (C=N), 3235 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.28 (s, 1H, OH), 6.28-6.94 (m, 8H, ArH). (MS (EI), *m/z* (%): 511 (M^+, 65 %). Anal. calcd. For $C_{18}H_{12}BrIN_2O_3$: C, 42.27; X (I, Br) 46.50; H, 2.34; N, 2.73%. Found: C, 42.39; X (I, Br) 46.68; H, 2.40; N, 2.82%.

*4-Chloro-2-[1-(2-iodo-4-nitrophenylimino)-ethyl]-naphthalen-1-ol (***3l**): Yield 72%, m.p. 170-172 ºC; FT-IR (KBr, ν, cm^{-1}): 1438, 1535 (C=C), 1583 (C=N), 3237 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.25 (s, 1H, OH), 6.29-6.96 (m, 8H, ArH). (MS (EI), *m/z* (%): 466 (M^+, 53%). Anal. calcd. For $C_{18}H_{12}ClIN_2O_3$: C, 46.36; X (I, Cl) 34.76; H, 2.57; N, 3.00%. Found: C, 46.45; X (I, Cl) 34.88; H, 2.64; N, 3.10%.

2-[1-(2,6-Dichloro-4-iodophenylimino)-ethyl]-4-iodonaphthalen-1-ol (**3m**): Yield 88%, m.p. 128-131 ºC; FT-IR (KBr, ν, cm^{-1}): 1442, 1540 (C=C), 1581 (C=N), 3235 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.35 (s, 3H, CH_3), 5.27 (s, 1H, OH), 6.31-6.96 (m, 7H, ArH). (MS (EI), *m/z* (%): 582 (M^+, 85 %). Anal. calcd. For $C_{18}H_{11}Cl_2I_2NO$: C, 37.11; X (I, Cl) 55.67; H, 1.89; N, 2.40%. Found: C, 37.23; X (I, Cl) 55.80; H, 1.96; N, 2.52%.

4-Bromo-2-[1-(2,6-dichloro-4-iodophenylimino)-ethyl]-naphthalen-1-ol (**3n**): Yield 84%, m.p. 140-142 ºC; FT-IR (KBr, ν, cm^{-1}): 1444, 1540 (C=C), 1582 (C=N), 3235 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.35 (s, 3H, CH_3), 5.27 (s, 1H, OH), 6.33-6.99 (m, 7H, ArH). (MS (EI), *m/z* (%): 535 (M^+, 80 %). Anal. calcd. For $C_{18}H_{11}BrCl_2INO$: C, 40.37; X (I, Br, Cl) 42.23; H, 2.05; N, 2.61%. Found: C, 40.46; X (I, Br, Cl) 42.36; H,2.12; N, 2.73%.

4-Chloro-2-[1-(2,6-dichloro-4-iodophenylimino)-ethyl]-naphthalen-1-ol (**3o**): Light Yellow Crystal, Yield 82%, m.p. 148-150 ºC; FT-IR (KBr, ν, cm^{-1}): 1440, 1543 (C=C), 1580 (C=N), 3235 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.26 (s, 1H, OH), 6.31-6.97 (m, 7H, ArH). (MS (EI), *m/z* (%): 490 (M^+, 76%). Anal. calcd. For $C_{18}H_{11}Cl_3INO$: C, 44.08; X (I, Cl) 40.20; H, 2.24; N, 2.85%. Found: C, 44.15; X (I, Cl) 40.31; H, 2.32; N, 2.95%.

2-[1-(4-Bromo-2,6-dichlorophenylimino)-ethyl]-4-iodo-naphthalen-1-ol (**3p**): Yield 86%, m.p. 144-146 ºC; FT-IR (KBr, ν, cm^{-1}): 1444, 1545 (C=C), 1584 (C=N), 3232 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.28 (s, 1H, OH), 6.33-6.99 (m, 7H, ArH). (MS (EI), *m/z* (%): 535 (M^+, 87 %). Anal. calcd. For $C_{18}H_{11}Cl_2BrINO$: C, 43.37; X (I, Br, Cl) 51.77; H, 2.05; N, 2.61%. Found: C, 43.46; X (I, Br) 51.86; H, 2.18; N, 2.80%.

4-Bromo-2-[1-(4-bromo-2,6-dichlorophenylimino)-ethyl]-naphthalen-1-ol (**3q**): Light Yellow Crystal, Yield 80%, m.p. 150-152 ºC; FT-IR (KBr, ν, cm^{-1}): 1442, 1546 (C=C), 1582 (C=N), 3234 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.35 (s, 3H, CH_3), 5.27 (s, 1H, OH), 6.31-6.98 (m, 7H, ArH). (MS (EI), *m/z* (%): 488 (M^+, 81%). Anal. calcd. For $C_{18}H_{11}Br_2Cl_2NO$: C, 44.26; X (Cl, Br) 47.13; H, 2.25; N, 2.86%. Found: C, 44.38; X (Cl, Br) 47.22; H, 2.34; N, 2.98%.

2-[1-(4-Bromo-2,6-dichlorophenylimino)-ethyl]-4-chloronaphthalen-1-ol (**3r**): Yield 89%, m.p. 182-184 ºC; FT-IR (KBr, ν, cm^{-1}): 1442, 1544 (C=C), 1584 (C=N), 3236 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.34 (s, 3H, CH_3), 5.25 (s, 1H, OH), 6.28-6.94 (m, 7H, ArH). (MS (EI), *m/z* (%): 443 (M^+, 74 %). Anal. calcd. For $C_{18}H_{11}BrCl_3NO$: C, 48.36; X (Cl, Br) 42.09; H, 2.43; N, 3.16%. Found: C, 48.45; X (Cl, Br) 42.18; H, 2.51; N, 3.23%.

2-[1-(2,6-Dichlorophenylimino)-ethyl]-4-iodonaphthalen-1-ol (**3s**): Yield 81%, m.p. 176-178 ºC; FT-IR (KBr, ν, cm^{-1}): 1442, 1544 (C=C), 1583 (C=N), 3234 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.35 (s, 3H, CH_3), 5.27 (s, 1H, OH), 6.28-6.92

(m, 8H, ArH). (MS (EI), *m/z* (%): 456 (M^+, 78%). Anal. calcd. For $C_{18}H_{12}Cl_2INO$: C, 47.36; X (I, Cl) 43.42; H, 2.63; N, 3.07%. Found: C, 47.45; X (I, Cl) 43.55; H, 2.70; N, 3.14%.

4-Bromo-2-[1-(2,6-dichlorophenylimino)-ethyl]-naphthalen-1-ol (**3t**):): Yield 87%, m.p. 168-170 °C; FT-IR (KBr, ν, cm^{-1}): 1443, 1543 (C=C), 1585 (C=N), 3235 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.27 (s, 1H, OH), 6.28-6.94 (m, 8H, ArH). (MS (EI), *m/z* (%): 409 (M^+, 92 %). Anal. calcd. For $C_{18}H_{12}BrCl_2NO$: C, 52.81; X (Br, Cl) 36.91; H, 2.93; N, 3.42%. Found: C, 52.81; X (Br, Cl) 37.03; H, 3.02; N, 3.50%.

4-Chloro-2-[1-(2,6-dichlorophenylimino)-ethyl]-naphthalen-1-ol (**3u**): Yield 77%, m.p. 186-188 °C; FT-IR (KBr, ν, cm^{-1}): 1446, 1547 (C=C), 1583 (C=N), 3233 (OH). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.27 (s, 1H, OH), 6.27-6.94 (m, 8H, ArH). (MS (EI), *m/z* (%): 364 (M^+, 96%). Anal. calcd. For $C_{18}H_{12}Cl_3NO$: C, 59.34; X (Cl) 29.25; H, 3.29; N, 3.84%. Found: C, 59.41; X (Cl) 29.30; H, 3.38; N, 3.92%.

4-[1-(4-Bromo-1-hydroxynaphthalen-2-yl)ethylideneamino]-3,5-diiodobenzoic acid (**3v**): Yield 72%, m.p. 159-161 °C; FT-IR (KBr, ν, cm^{-1}): 1254 (C-O), 1445, 1551 (C=C), 1584 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.29 (s, 1H, OH), 6.32-7.05 (m, 7H, ArH). (MS (EI), *m/z* (%): 636 (M^+, 54%). Anal. calcd. For $C_{19}H_{12}BrI_2NO_3$: C, 35.84; X (I, Br) 52.51; H, 1.88; N, 2.20%. Found: C, 35.92; X (I, Br) 52.60; H, 1.95; N, 2.27%.

4-[1-(1-Hydroxy-4-iodonaphthalen-2-yl)ethylideneamino]-3,5-diiodobenzoic acid (**3w**): Yield 78%, m.p. 152-154 °C; FT-IR (KBr, ν, cm^{-1}): 1257 (C-O), 1448, 1554 (C=C), 1584 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.28 (s, 1H, OH), 6.32-7.07 (m, 7H, ArH). (MS (EI), *m/z* (%): 683 (M^+, 59%). Anal. calcd. For $C_{19}H_{12}O_3I_3N$: C, 33.38; X (I) 55.78; H, 1.75; N, 2.04%. Found: C, 33.46; X (I) 55.86; H, 1.82; N, 2.12%.

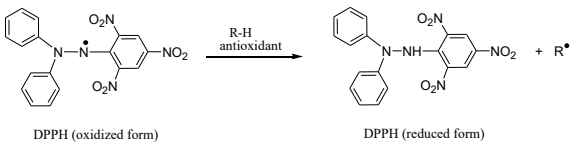
4-[1-(4-Chloro-1-hydroxynaphthalen-2-yl)-ethylideneamino]-3,5-diiodobenzoic acid (**3x**): Yield 84%, m.p. 163-166 °C; FT-IR (KBr, ν, cm^{-1}), 1256 (C-O), 1446, 1555 (C=C), 1583 (C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm: 1.36 (s, 3H, CH_3), 5.28 (s, 1H, OH), 6.33-7.06 (m, 7H, ArH). (MS (EI), *m/z* (%): 591 (M^+, 65 %). Anal. calcd. For $C_{19}H_{12}I_2NO_3$: C, 38.57; X (I, Cl) 48.98; H, 2.03; N, 2.36%. Found: C, 38.64; X (I, Cl) 49.10; H, 2.13; N, 2.44%.

Antioxidant activity

The following antioxidant methods were used to evaluate the antioxidant properties of our test compounds.

1) DPPH• Scavenging Activity

DPPH (2,2-diphenyl-1-(2,4,6-trinitrophenyl) hydrazyl) is a stable free radical that can accept an electron or hydrogen radical to become a stable diamagnetic molecule (Scheme 2). Due to its singlet electron, the methanolic solution of DPPH shows a strong absorption band at 517 nm. DPPH radical reacts with various electron-donating molecules (reducing agents or antioxidants). When electrons become paired off, bleaching of the DPPH solution is what we observe as a result. This results in the formation of the colourless 2,2'-diphenyl-1-picrylhydrazine. Reduction of the DPPH radicals can be estimated quantitatively by measuring the decrease in absorbance at 517 nm.



Scheme 2. Structural changes occurring to DPPH during oxidation.

Procedure: Equal volumes of 100 µM DPPH in methanol were added to different concentrations of test compounds (0 – 200 µM/mL) in methanol, mixed well and kept in dark for 20 min. The absorbance at 517 nm was measured using the spectrophotometer UV-1650 (Shimadzu) [28]. Plotting the percentage DPPH• scavenging against concentration gave the standard curve and the percentage scavenging was calculated from the following equation:

$$\text{scavenging\%} = \frac{\text{absorbance of blank} - \text{absorbance of test}}{\text{absorbance of blank}} x100$$

IC_{50} was obtained from a plot between concentration of test compounds and percent scavenging. Ascorbic acid was used as standard for comparison.

2) Nitric Oxide Scavenging Activity

Nitric oxide (NO) will be generated by sodium nitroprusside in the solution. In the presence of an antioxidant or nitric oxide scavenger the amount of NO generated will be less. The excess NO will be estimated by Griess reagent, which is the mixture of sulphanilic acid and naphthylethylenediamine dihydrochloride. The nitric oxide will give pink-coloured complex estimated at 540 nm.

Procedure: To a reaction mixture (6 mL) containing sodium nitroprusside (10 mM, 4 mL), phosphate buffer saline (PBS, 1.0 mL) and 1.0 mL of different concentration of test compounds/standard were incubated at 25 ^{0}C for 150 min. After incubation, 0.5 mL of the reaction mixture containing nitrate was removed and 1.0 mL of sulphanilic acid was added, mixed well, and allowed to stand for 5 min for completion of diazotisation. Then 1.0 mL of naphthylethylenediamine dihydrochloride was added, mixed, and allowed to stand for 30 min in dark at room temperature. The absorbance of these solutions was measured at 540 nm against the corresponding blank solution without sodium nitroprusside [29]. The % scavenging and IC_{50} values were determined as explained in the DPPH assay. The standard rutin (2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranosyloxy]-4*H*-chromen-4-one) were used for comparison antioxidant activity of synthesized compounds.

3. RESULTS AND DISCUSSION

The present studies describe the reactions carried out using grindstone technique, simply by mixing corresponding substituted hydroxyketones **1** and substituted anilines **2**. The mixture was ground together in mortar with pestle at room temperature for 2-3 minutes, and then a catalytic amount of sulfuric acid was added to this grinded reaction mixture. The grinding was continued for 4-7 minutes and the progress of reaction was monitored on thin layer chromatography (TLC). The completion of reaction was indicated by wetting with the formation of yellow-coloured reaction mixture. The solid obtained was easily separated by using cold water and simple Buchner filtration; final purification was achieved by crystallization from ethanol to give pure samples of Schiff bases **3a-x** (Scheme 1). The reasons to use grinding technique [30] in the synthesis of title compounds, which make the reaction procedure simple, short reaction time, increase the purity of the resulting products and enhance the quantitative yield. Another advantage of the method is that it is too consistent with green chemistry approach because it does not require heating or microwave irradiation. It occurs at room temperature and is completely free from organic solvents during both the reaction and separation of the product; except for the recrystallization of product. Therefore, the method avoids the use of organic solvents during the reaction, leading to easy isolation of product.

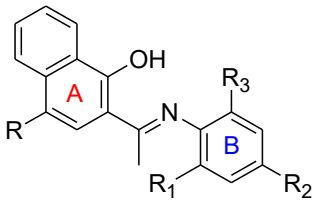
In order to optimize the capability and efficiency of the present method, we carried out the reaction above by conventional method using ethanol as reaction solvent (Table 1). We found that solid-state reaction occurs more efficiently and more selectively than does the solution-based reaction. This happens because the molecules in the crystal are arranged tightly and regularly. Thus, in grindstone technique, the reaction occurs efficiently in terms of clean reaction conditions, operationally being simple, and short reaction time giving quantitative yields of product and environmental- and eco-friendliness.

The results of antioxidant activity expressed as IC_{50} value with two different antioxidant agents are shown in Table **2**. The compound **3m** and **3n**, tested using the DPPH scavenging method, showed IC_{50} value at 70.13, 70.28 µM, when compared with that of the standard ascorbic acid at 69.08 µM, respectively. However, the compounds **3d** and **3k** did not show significant activities. Further, the antioxidant studies carried out using NO scavenging method, the only compound **3m** and **3w** showed IC_{50} values at 92.04 and 91.25 µM in comparison with standard. The compound **3f** and **3j** did not show antioxidant activity.

Table 1. Comparison of grinding technique reaction with conventional method.

Entry	Conventional Method			Grinding Technique	
	Solvent	Time (min)	Yield (%)	Time (min)	Yield (%)
3a	EtOH (10 mL)	25	60	5	75
3d	EtOH (15 mL)	28	65	4	81
3g	EtOH (10 mL)	30	68	7	80

Table 2. Antioxidant scavenging of newly synthesized imines 3a-x at different concentration.



Compound number	R	R_1	R_2	R_3	DPPH scavenging[1]			NO scavenging[1]		
					50	100	200	50	100	200
3a	I	I	Cl	H	40.0	52.52	78.07	38.0	50.10	97.89
3b	Br	I	Cl	H	43.34	54.06	85.27	39.10	47.08	105.64
3c	Cl	I	Cl	H	38.0	43.23	75.84	28.03	43.97	114.02
3d	I	NO_2	I	H	NSA	NSA	NSA	30.96	76.54	146.97
3e	Br	NO_2	I	H	58.23	42.63	170.12	75.87	65.89	165.24
3f	Cl	NO_2	I	H	48.16	63.72	155.09	NSA	NSA	NSA
3g	I	Cl	I	H	30.79	42.65	91.04	43.14	87.24	107.03
3h	Br	Cl	I	H	40.28	37.28	96.37	32.58	61.09	102.34
3i	Cl	Cl	I	H	63.04	43.21	123.14	40.67	93.67	144.78
3j	I	I	NO_2	H	52.84	50.60	183.08	NSA	NSA	NSA
3k	Br	I	NO_2	H	NSA	NSA	NSA	71.90	97.02	152.43
3l	Cl	I	NO_2	H	59.05	60.32	170.06	NSA	NSA	NSA
3m	I	Cl	I	H	20.93	18.74	70.13	39.05	59.07	92.04
3n	Br	Cl	I	H	16.48	28.90	70.28	38.81	60.45	96.28
3o	Cl	Cl	I	H	39.67	43.72	83.59	76.06	89.23	116.93
3p	I	Cl	Br	H	32.87	37.50	73.09	28.78	58.91	94.68
3q	Br	Cl	Br	H	37.39	23.06	78.53	41.02	73.93	99.14
3r	Cl	Cl	Br	H	50.09	43.02	86.28	27.03	48.23	107.47
3s	I	Cl	H	H	40.57	58.98	137.03	45.02	98.45	183.58
3t	Br	Cl	H	H	34.83	60.37	92.07	30.24	58.26	132.04
3u	Cl	Cl	H	Cl	60.23	73.49	150.73	48.34	74.71	125.97
3v	Br	I	COOH	I	47.39	43.87	112,36	24.05	42.90	93.65
3w	I	I	COOH	I	51.08	58.98	126.41	23.78	43.87	91.25
3X	Cl	I	COOH	I	56.09	66.12	137.92	45.89	65.98	102.57
Standard					67.90	68.96	69.08	89.90	90.87	91.05

4. CONCLUSION

In conclusion, we reported short a library of imines 3a-x by the condensation of substituted hydroxyketones with substituted anilines under solvent-free conditions using the grinding method. The method is efficient, convenient in terms of simple reaction procedure, short reaction time, increasing the purity of resulting products, and enhances the quantitative yield. Further preliminary *in vitro a*ntioxidant activity of newly synthesized compounds reveals that 3m, 3n and 3w shows significant activity in comparison with standard antioxidant ascorbic acid and rutin. The remaining compound shows comparative antioxidant activity. Compound 3d and 3k did not show significant activity (NSA) in comparison with ascorbic acid. Similarly compound 3f, 3j, and 3l were also did not possess antioxidant activity in comparison with rutin. Thus, the present study is useful in the field of medicinal chemistry.

5. AKNOWLEDMENTS

The authors gratefully acknowledge UGC-New Delhi for financially assistant and sanctioning major research grant (No. 38-267/2009). The authors also thankful to Director IICT, Hyderabad, for providing necessary instrumental facilities.

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