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Synthesis of β–amino carbonyl compounds using ZnO nanoparticles as a green, effective and reusable catalyst

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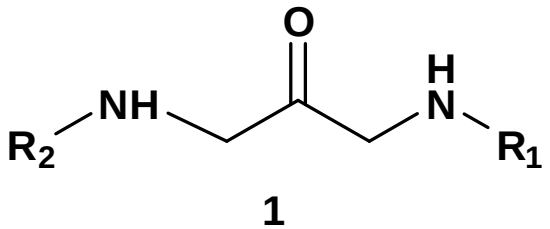
A new efficient one-pot three-component condensation of aromatic aldehydes, aromatic ketones, and aromatic amines in the presence of ZnO nanoparticles as an inexpensive and effective catalyst for the synthesis of β-amino carbonyl compounds by Mannich reaction is described. The reaction was carried out at room temperature under solvent-free conditions. Mild reaction temperature, cost-effective catalyst, simple product separation and catalyst recycling were notable achievements in the reaction. Simple experimental conditions and product isolation procedure make this protocol potentially applicable for the development of a clean and environment-friendly strategy for the synthesis of β-amino ketones. The present methodology offers several advantages such as good yields, short reaction times and a recyclable catalyst with a very easy work-up.

Keywords: Nanoparticles, ZnO, β-Amino carbonyl; β1,β2-Diamino diketone; solvent-free; Isophthalic aldehyde.

INTRODUCTION

Cysteine proteases are ubiquitous in nature and have been implicated in the etiology of a number of disease states [1]. Over the past two decades, selective and reversible inhibitors for this class of enzymes have been an area of intense research [2]. These investigations have led to a number of reversible inhibitors such as peptidyl aldehydes, α-ketoamides and α-keto heterocycles [3]. Recently, researchers from SmithKline Beecham have reported the design and synthesis of a novel class of cysteine protease inhibitors based on a 1,3-diamino ketone scaffold (Figure 1) [4].



1

Fig.1. Diamino ketone

In recent years, the use of multicomponent reactions has gained considerable attention in organic synthesis. In particular, the Mannich reaction has been widely used for the synthesis of β-amino carbonyl compounds. Owing to their importance as valuable building blocks for the preparation of 1,3-amino alcohols [5, 6], β-amino acids [7], as well as for the synthesis of various bioactive molecules such as the antibiotics nikkomycins and neopolyoxines [8, 9], several methods have been reported in the literature for the synthesis of β-amino carbonyl compounds using catalysts such as $HClO_4$-SiO_2 [10], silica supported sulfuric acid [11], bromodimethylsulfonium bromide (BDMS) [12], TMSCl [13], p-TSA [14], Sml3[15], Amberlyst-15 [16], and $AuCl_3$-PPh_3[17]. These methods have, however, certain drawbacks such as moisture sensitivity of the catalyst [7, 18], longer reaction time [4–6], and use of an expensive metal salt as catalyst [19–21]. There is still scope, therefore, for an improved method for the synthesis of β-amino carbonyl compounds which can avoid the use of expensive and sensitive catalysts. Furthermore, the use of inorganic solid supported reagents provides an attractive procedure due to their characteristic properties such as enhanced reactivity and selectivity, simple work-up procedure, and milder reaction conditions [22–25]. Among these inorganic supported reagents, iodine

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supported on dehydrated neutral alumina has found wide application because of its property to form an activated iodonium ion [24]. Therefore, activated iodonium ion produced from iodine adsorbed on neutral alumina has been used for the coupling reactions of aldehydes, enolizable ketones or 1,3-dicarbonyls with methyl carbamate or aromatic amines using microwaves as an energy source superior to conventional methods [26–28] in terms of shorter reaction time and minimized reaction by-products. Recently, a method using molecular iodine as the catalyst has been reported for the synthesis of β-amino carbonyl compounds *via* a three-component reaction involving aldehydes, ketones, and benzyl carbamates with good yields. However, this method has the disadvantage of a longer reaction time [29].

EXPERIMENTAL SECTION

Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates and visualization was effected with short-wavelength UV light (254 nm). The IR spectra were recorded on a Shimadzu model impact 400D FT-IR spectrophotometer using KBr pellets. ^{1}H NMR were recorded on a Bruker AC-300F 400 MHz spectrometer in $CDCl_3$ using TMS as an internal standard with 1H resonance frequency of 400 MHz. Zn dust (Qualigens Fine Chemicals, AR grade, 325 mesh, 99.90% purity), *o*-hydroxy benzaldehydes and 1,3-dicarbonyl compounds were commercial, procured from Hi Media Laboratories Pvt. Ltd., and were used without further purification. The melting points were determined by open capillaries and were used uncorrected.

Synthesis of 1,3-diphenyl-3-(phenylamino) propan-1-one derivatives

In a typical experiment, amine (0.20 mmol), ketone (0.20 mmol), ZnO nanoparticles catalyst (10 mol%) and aldehyde (0.20 mmol) were successively added to ethanol (2 mL) (or better solvent-free). The resultant mixture was stirred at room temperature for 4 h and then quenched with saturated $NaHCO_3$.aq (5 mL) and brine (5 mL). The mixture was extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, concentrated, distilled with solvents and crystallized in hot ethanol to give the desired product. After the required reaction time, ether was added to extract ZnO nanoparticles, the latter were separated by filtration and could be reused for the next run after a simple treatment including washing with ether (2×5 mL) and drying in air at 100 ^{o}C for 6 h.

Spectral data:

1,3-Diphenyl-3-(phenylamino)propan-1-one (4a)

IR (KBr, cm^{-1}): 3395, 3024, 2975, 1673, 1599, 1515, 1297, 1220, 1080, 1027, 1001, 860, 694, 515; ^{1}H-NMR (400 MHz, $CDCl_3$, *δ*/ppm): 7.90 (m, 2H), 7.50 (m, 10H), 6.63 (m, 3H), 5.00 (dd, *J* = 5.2 and 7.5 Hz, 1H), 4.56 (br, 1H), 3.50 (dd, *J* = 5.2 and 16.1 Hz, 1H), 3.40 (dd, *J*= 7.5 and 16.1 Hz, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$, *δ*/ppm): 198.2, 147.0, 142.8, 136.7, 133.4, 129.2, 128.7, 128.6, 128.2, 127.6, 126.3, 117.7, 113.6, 54.7, 46.2; HRMS calcd for $C_{21}H_{19}NO$ 301.1467, found 301.1471. Calcd for $C_{21}H_{19}NO$: C 83.66, H 6.37, N 4.64. Found: C 83.61, H 6.40, N 4.69%. HRMS (EI) Calcd. for $C_{21}H_{19}NO$ $[M]^{+}$, 301.1003, Found 301.1006.

3-[(4-Chlorophenyl)amino]-1,3-diphenylpropan-1-one (4b)

IR (KBr, cm^{-1}): 3393, 3034, 1672, 1595, 1515, 1377, 1292, 1224, 1080, 1005, 929, 860, 749, 690, 620, 518; ^{1}H-NMR (400 MHz, $CDCl_3$, *δ*/ppm): 7.85 (m, 2H), 7.43 (m, 8H), 7.01 (m, 2H), 6.46 (m, 2H), 4.95 (dd, *J* = 5.0 and 7.7 Hz, 1H), 3.47 (dd, *J* = 5.0 and 16.2 Hz, 1H), 3.40 (dd, *J* = 7.6 and 16.1 Hz, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$, *δ*/ppm): 198.2, 145.7, 142.1, 136.5, 133.2, 128.9, 128.7, 128.4, 128.2, 127.4, 126.2, 122.5, 114.8, 54.6, 46.2; Anal Calcd for $C_{21}H_{18}NClO$: C 75.12, N 4.16, H 5.37. Found: C 75.10, N 4.22, H 5.41%. HRMS (EI) Calcd. for $C_{21}H_{18}NClO$ $[M]^{+}$, 335.1004, Found 335.1007.

3-(N-Phenylamino)-3-(3-chlorophenyl)-1-phenylacetone (4c)

IR (KBr, cm^{-1}): 3397, 3025, 2974, 1673, 1597, 1516, 1296, 1220, 1083, 1027, 1002, 860, 694, 515. ^{1}H-NMR (400 MHz, $CDCl_3$, *δ*/ppm): 3.40 (2H, m), 4.91 (1H, m), 6.50 (2H, d, J=7.95Hz),7.36 (3H, d, J=7.95Hz), 7.47 (21H, m), 7.84 (2H, d, J=7.8Hz); ^{13}C-NMR (400 MHz, $CDCl_3$, *δ*/ppm): 211.6, 147.7, 140.6, 129.8, 129.5, 128.5, 125.9, 120.9, 1133.3, 57.9, 55.8, 41.1, 27.5. Anal Calcd for $C_{21}H_{18}ClNO$: C 75.09, N 4.15, H 5.40. Found: C 75.00, N 4.07, H 5.56%. HRMS (EI) Calcd. for $C_{21}H_{18}ClNO$ $[M]^{+}$, 335.1002, Found 335.1006.

3-(N-Phenylamino)-3-(3-bromophenyl)-1-phenylacetone (4d)

IR (KBr, cm^{-1}): 3392, 3020, 2931, 1675, 1506, 1489, 1361, 1307, 1270, 1110, 1072, 865, 752, 680, 510. ^{1}H-NMR (400 MHz, $CDCl_3$, *δ*/ppm): 3.40 (2H,m), 4.95 (1H,m), 6.52 (2H,d,J=7.95Hz),7.37 (3H, d,J=7.95Hz), 7.47 (21H,m), 7.84 (2H,d,J=7.8Hz); IR (KBr, cm^{-1}): 3397, 3025, 2974, 1674, 1596, 1515, 1296, 1220, 1080, 1027, 1004, 860, 695, 514. ^{13}C-NMR (400

MHz, $CDCl_3$, δ/ppm): 200.1, 147.5, 145.8, 145.5, 136.6, 133.1, 131.2, 129.8, 129.5, 129.2, 128.9, 128.7, 125.8, 120.6, 113.8, 113.6, 113.1, 72.5, 53.6. Anal Calcd for $C_{21}H_{18}BrNO$: C 66.31, N 3.66, H 4.76. Found: C 66.29, N 3.60, H 4.70%. HRMS (EI) Calcd. for $C_{21}H_{18}BrNO$ $[M]^+$, 379.1000, Found 379.1005.

3-(N-p-Bromophenylamino)-1,3-diphenyl-1-acetone (4e)

IR (KBr, cm^{-1}): 3398, 3023, 2935, 1675, 1509, 1485, 1366, 1307, 1275, 1119, 1073, 860, 755, 683, 518. ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 3.40 (2H,m), 4.86 (1H,m), 6.36 (2H,d,J=7.9Hz), 7.08 (2H,d, J=8.26Hz), 7.19 (3H,m), 7.34 (2H, d, J=9Hz),7.39 (2H,m), 7.49 (1H,m), 7.84 (2H, d, J=7.95Hz); ^{13}C-NMR (400 MHz, $CDCl_3$, δ/ppm): 200.1, 146.5, 145.8, 140.5, 136.6, 133.1, 132.4, 131.2, 129.8, 129.5, 129.2, 128.9, 128.7, 128.3, 126.8, 120.6, 115.2, 114.6, 114.1, 72.5, 54.3. Anal Calcd for $C_{21}H_{18}BrNO$: C 66.31, N 3.66, H 4.76. Found: C 66.29, N 3.60, H 4.70%. HRMS (EI) Calcd. for $C_{21}H_{18}BrNO$ $[M]^+$, 379.1000, Found 379.1005.

3-(N-Methyl-N-phenylamino)-1,3-diphenyl-1-acetone (4f)

IR (KBr, cm^{-1}): 3386, 3027, 2935, 1677, 1503, 1485, 1369, 1309, 1271, 1120, 1075, 862, 754, 687, 519. ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 3.42 (2H, d), 4.94 (1H, m), 6.49 (2H, d),6.57 (1H,m), 7.03 (2H, m), 4.18(3H, s), 7.25 (2H, m), 7.35 (5H, m), 7.88 (2H, d); ^{13}C-NMR (400 MHz, $CDCl_3$, δ/ppm): 200.2, 149.5, 136.6, 133.2, 129.5, 128.7, 128.5, 128.3, 127.9, 121.8, 114.4, 58.8. IR (KBr, cm^{-1}): 3397, 3025, 2976, 1670, 1598, 1515, 1296, 1220, 1080, 1025, 1001, 865, 694, 511. Anal Calcd for $C_{22}H_{21}NO$: C 83.77, N 4.41, H 6.70. Found: C 83.71, N 4.37, H 6.79%. HRMS (EI) Calcd. for $C_{22}H_{21}NO$ $[M]^+$, 315.2002, Found 315.1004.

2-[1-(N-Methyl-N-phenylamino)-1-phenyl] methylcyclohexanone (4g)

IR (KBr, cm^{-1}): 3398, 3010, 2925, 2810, 1673, 1597, 1505, 1312, 1115, 1047, 864, 695, 522. ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 1.66 (2H, m), 1.89 (4H, m), 2.45 (2H, d), 2.76 (1H, t), 4.65 (3H, s), 6.54 (2H, d, J=7.90Hz), 6.64 (1H, m),7.06 (2H, m), 7.25 (1H, m), 7.32 (2H, m), 7.38 (2H, m), 7.42 (2H, d, J=7.9Hz); ^{13}C-NMR (400 MHz, $CDCl_3$, δ/ppm): 211.6, 149.7, 142.6, 129.6, 128.5, 128.1, 125.9, 114.4, 60.3, 41.1, 27.4. Anal Calcd for $C_{20}H_{23}NO$: C 81.88, N 4.77, H 7.90. Found: C 81.80, N 4.69, H 7.69%. HRMS (EI) Calcd. for $C_{20}H_{23}NO$ $[M]^+$, 293.2004, Found 293.2007.

3-(N-*p*-Bromophenylamino)-1-phenyl] methylcyclohexanone (4h)

IR (KBr, cm^{-1}): 3398, 3010, 2925, 2812, 1675, 1599, 1505,1312, 1117, 1047, 863, 693,523. ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 1.66 (2H, m), 1.89 (4H, m), 2.40 (2H, m), 2.75 (1H, m), 4.63 (1H, d, J=7.09Hz), 6.54 (2H, d, J=7.90Hz), 6.63 (1H, m),7.05 (2H, m), 7.23 (1H, m), 7.32 (2H, m), 7.39 (2H, m), 7.41 (2H, d, J=7.9Hz); ^{13}C-NMR (400 MHz, $CDCl_3$, δ/ppm): 211.6, 147.7, 139.5, 131.4, 129.5, 128.4, 120.8, 120.4, 113.5, 57.7, 55.8, 27.5. Anal Calcd for $C_{19}H_{20}BrNO$: C 63.71, N 3.90, H 5.62. Found: C 63.65, N 3.77, H 5.69%. HRMS (EI) Calcd. for $C_{19}H_{20}BrNO$ $[M]^+$, 357.1002, Found 357.1006.

2-[1-(N-Phenylamino)-1-(3-chlorophenyl] methylcyclohexanone (4i)

IR (KBr, cm^{-1}): 3397, 3010, 2925, 2810, 1673, 1599, 1505, 1312, 1115, 1047, 863, 693,525. ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 1.65 (2H, m), 1.90 (4H, m), 2.39 (2H, m), 2.76 (1H, m), 4.64 (1H, d, J=7.09Hz), 6.54 (2H, d, J=7.90Hz), 6.64 (1H, m),7.05 (2H, m), 7.25 (1H, m), 7.33 (2H, m), 7.39 (2H, m), 7.43 (2H, d, J=7.9Hz); ^{13}C-NMR (400 MHz, $CDCl_3$, δ/ppm): 211.6, 147.7, 141.8, 134.2, 129.5, 127.8, 126.3, 126.1, 126.0, 120.7, 113.6, 57.7, 55.4, 55.3, 41.1, 27.4. Anal Calcd for $C_{19}H_{20}ClNO$: C 72.70, N 4.45, H 6.40. Found: C 72.63, N 4.38, H 6.56%. HRMS (EI) Calcd. for $C_{19}H_{20}ClNO$ $[M]^+$, 313.1001, Found 313.1008.

2-[1-(N-Phenylamino)-1-(3-bromophenyl] methylcyclohexanone (4j)

IR (KBr, cm^{-1}): 3397, 3011, 2925, 2810, 1675, 1598, 1506, 1310, 1117, 1046, 860, 695,523. ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 1.66 (2H, m), 1.90 (4H, m), 2.39 (2H, m), 2.75 (1H, m), 4.64 (1H, d, J=7.09Hz), 6.54 (2H, d, J=7.90Hz), 6.63 (1H, m),7.05 (2H, m), 7.25 (1H, m), 7.32 (2H, m), 7.39 (2H, m), 7.42 (2H, d, J=7.9Hz); ^{13}C-NMR (400 MHz, $CDCl_3$, δ/ppm): 211.6, 147.7, 142.8, 132.6, 129.6, 129.3, 127.2, 120.8, 113.6, 57.9, 55.1, 24.4. Anal Calcd for $C_{19}H_{20}BrNO$: C 63.70, N 3.90, H 5.61. Found: C 63.62, N 3.73, H 5.79%. HRMS (EI) Calcd. for $C_{19}H_{20}BrNO$ $[M]^+$, 357.1003, Found 357.1007.

2-[1-(N-Phenylamino)-1-phenyl] methylcyclohexanone (4k)

IR (KBr, cm^{-1}): 3396, 3010, 2925, 2810, 1675, 1598, 1507, 1312, 1115, 1045, 860, 694, 524. ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 1.67 (2H, m), 1.90 (4H,m), 2.41 (2H, m), 2.75 (1H, m), 4.62 (1H, d, J=7.09Hz), 6.54 (2H, d, J=7.90Hz), 6.635 (1H, m),7.05 (2H, m), 7.25 (1H, m), 7.32 (2H, m), 7.39 (2H, m), 7.43 (2H, d, J=7.9Hz); ^{13}C-NMR (400 MHz, $CDCl_3$, δ/ppm): 211.7, 147.1, 142.5, 132.1, 129.5, 129.0, 127.6, 120.1, 113.5, 57.4, 55.0, 24.7. Anal Calcd for $C_{19}H_{21}NO$: C 81.66, N 5.00, H

7.55. Found: C 81.60, N 5.23, H 7.64%. HRMS (EI) Calcd. for $C_{19}H_{21}NO$ $[M]^+$, 279.2001, Found 279.2009.

1,3-Bis[1-(phenylamino)-3-oxo-3-phenylpropyl]-benzene (4l)

IR (KBr, cm^{-1}): 3340, 3077, 2955, 1676, 1594, 1528, 1380, 1312, 1281, 1214, 1187, 1168, 1076, 1113, 1077, 1016, 812, 738, 515; ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 7.91 (m, 10H), 7.76 (m, 10H), 7.48 (s, 1H), 6.63 (m, 3H), 5.00 (m, 2H), 4.37 (m, 4H), 3.50 (m, 1H), 3.40 (m, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$, δ/ppm): 207.05, 163.84, 148.50, 141.85, 131.17, 129.88, 128.53, 126.18, 122.51, 119.58, 117.23, 115.12, 114.28, 110.47, 50.88, 40.80; Anal Calcd for $C_{36}H_{33}N_2O_2$: C 82.28, H 6.29. Found: C 82.35, H 6.19. HRMS (EI) Calcd. for $C_{36}H_{33}N_2O_2$ $[M]^+$, 524.2004, Found 524.2008.

1,3-Bis[1-(methylphenylamino)-3-oxo-3-phenylpropyl]-benzene (4m)

IR (KBr, cm^{-1}): 3337, 3010, 2922, 2812, 1675, 1592, 1508, 1485, 1366, 1308, 1274, 1119, 1072, 863, 697, 520; ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 7.96 (m, 10H), 7.53 (m, 10H), 6.67 (m, 3H), 5.05 (m, 2H), 4.38 (m, 4H), 3.51 (m, 1H), 3.46 (m, 1H), 2.04 (s, 6H); ^{13}C-NMR (400 MHz, $CDCl_3$, δ/ppm): 206.95, 165.84, 149.20, 142.05, 131.47, 129.19, 129.13, 127.01, 122.61, 119.58, 118.11, 115.42, 113.98, 111.23, 50.78, 40.76, 25.12; Anal Calcd for $C_{38}H_{36}N_2O_2$: C 82.46, H 6.69. Found: C 82.55, H 6.61. HRMS (EI) Calcd. for $C_{38}H_{36}N_2O_2$ $[M]^+$, 552.3001, Found 552.3005.

1,3-Bis[1-(4-methylphenylamino)-3-oxo-3-phenylpropyl]-benzene (4n)

IR (KBr, cm^{-1}): 3337, 3012, 2925, 2810, 1675, 1594, 1508, 1486, 1367, 1309, 1273, 1119, 1070, 864, 699, 522; ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 7.89 (m, 10H), 7.39 (m, 10H), 6.61 (m, 3H), 4.92 (m, 2H), 4.27 (m, 4H), 3.52 (m, 1H), 3.28 (m, 1H), 1.30 (S, 6H); ^{13}C-NMR (400 MHz, $CDCl_3$, δ/ppm): 206.93, 165.84, 149.24, 142.13, 131.27, 129.21, 129.83, 127.11, 122.64, 119.61, 118.21, 115.32, 113.98, 111.23, 50.77, 40.77, 25.13; Anal Calcd for $C_{38}H_{36}N_2O_2$: C 82.46, H 6.69. Found: C 82.52, H 6.63. HRMS (EI) Calcd. for $C_{38}H_{36}N_2O_2$ $[M]^+$, 552.3001, Found 552.3005.

1,3-Bis[1-(3-bromatedphenylamino)-3-oxo-3-phenylpropyl]-benzene (4o)

IR (KBr, cm^{-1}): 3338, 3020, 2936, 1677, 1508, 1485, 1369, 1305, 1274, 1119, 1073, 859, 755, 684, 517; ^{1}H-NMR (400 MHz, $CDCl_3$, δ/ppm): 8.11 (m, 4H), 8.01 (m, 4H), 7.84 (m, 10H), 7.51 (m, 4H), 7.47 (s, 2H), 4.42 (m, 4H), 3.56 (m, 1H), 3.52 (m, 1H); ^{13}C-NMR (400 MHz, $CDCl_3$, δ/ppm): 206.93, 165.85, 149.33, 142.15, 131.57, 129.61, 129.93, 127.16, 122.69, 119.51, 118.32, 115.42, 113.95, 111.41, 50.69, 40.87; Anal Calcd for $C_{36}H_{30}N_2O_2Br_2$: C 63.34, H 4.40. Found: C 63.39, H 4.39. HRMS (EI) Calcd. for $C_{36}H_{30}N_2O_2Br_2$ $[M]^+$, 680.1005, Found 680.1008.

Catalyst preparation

Zinc oxide nanoparticles used in the experiments were produced according to the procedure [30] modified as follows. Zinc powder 0.019 g (0.3 mmol) in dust form was sonicated for 2 h with 4 mL of *n*-butanol. To the above solution, 1.2 mL of triethanolamine (TEA) was added slowly. It was then sonicated for ten more minutes. Finally, the mixture was irradiated in a closed vessel mono-mode microwave reactor at 140°C and 10.9 bar for 6 min. The obtained white solid suspension was centrifuged, washed several times with distilled water and vacuum dried. After calcination at 900°C for 1 h the product could be stored for an extended period of time. It was characterized using scanning electron microscopy (SEM), and X-ray powder diffraction (XRD) techniques.

RESULTS AND DISCUSSION

In general, nanoparticles are considered to be more reactive because they offer higher surface area and more coordination sites. The surface area of the catalyst increases tremendously when the size decreases to nano levels which are responsible for the higher catalytic activity. Studies on the interaction of alcohols with Zn metal have revealed that the C–O bond of the alcohol is readily cleaved on the zinc metal surface giving hydrocarbons and oxide species on the metal surface [31]. The structure directing additive is a common approach to control morphology, as shown by the effect of ethylene diamine in hydrothermal ZnO nanorod synthesis. Di- and tri-organic amines, as well as long-chain glycols are reported to promote rod-like morphologies by increasing the base content during synthesis [32]. Thus, triethanol amine was used as size stabilizer and was found effective in directing the morphology of ZnO nanoparticles. The obtained particles were characterized by X-ray powder diffraction (XRD) (Figure 2). The XRD pattern of the newly prepared zinc oxide nanoparticles showed the presence of peaks corresponding to hexagonal wurtzite structure [33]. The size of the particles was computed from the width of the first peak using the Debye-Scherrer formula $D = K\lambda/\beta \cos\theta$, where K is a constant, λ is the wavelength of X-ray radiation (1.54056 Å), β is the corrected full width at half maximum and θ is Bragg angle. The 2θ value is 19.0104.

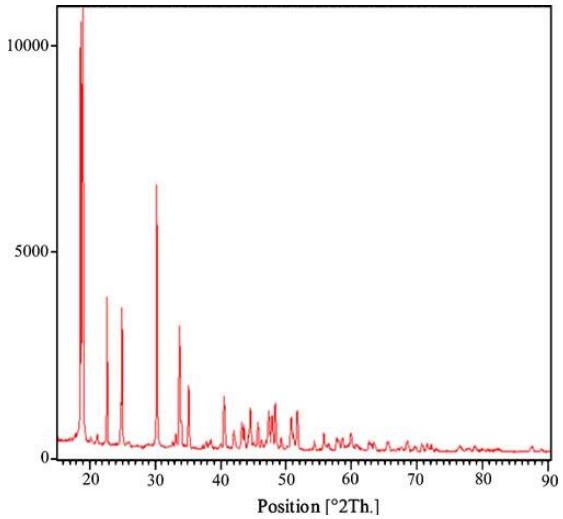


Fig. 2. XRD pattern of the ZnO nanoparticles.

Surface structure of all samples was characterized on a Nicolet Avatar 360 Fourier transform infrared (FT-IR) spectroscope. Measurements were performed with pressed pellets using KBr powder as a diluent. The FT-IR spectrum was recorded in the range between 400 and 4000 cm^{-1}. The crystallite size of the powder particles was calculated as about 30 nm. The morphology of the sample was investigated with scanning electron microscopy (SEM) (see Figure 3) which showed ZnO to be nanostructured. This may be the result of the presence of a small amount of triethanolamine, which acts as a stabilizer. These nanoparticles are generally not uniform, very similar to those described in the literature [32].

In order to evaluate the catalytic efficiency of ZnO nanoparticles, a model reaction was carried out on the synthesis of Mannich base **4a** by condensation of acetophenone, benzaldehyde and aniline (Scheme 1). The results of the synthesis of (1,3-diphenyl-3-(phenylamino)propan-1-one (**4a**) using various catalysts are shown in Table 1. As Table 1 indicates, the reaction proceeded efficiently in the presence of ZnO nanoparticles catalyst and the desired product (**4a**) was obtained in good to excellent yield, 94% (Table 1, entry 1). In the absence of catalyst, the reaction did not procees (Table 1, entry 9).

With the optimized of amount of catalyst, we found that 10 mol% of ZnO nanoparticles could effectively catalyze the reaction for synthesis of the desired product. Using 5 mol% of ZnO nanoparticles, the reaction took place for a longer time. Using more than 20 mol% ZnO nanoparticles had a weaker effect on the yield and time of the reaction. It is remarkable that the reaction carried out by changing the size of the particles from nanoparticles to bulk resulted in a drop in the catalytic activity. It is interesting to note that the ZnO nanoparticle catalyst catalyses the reaction in excellent yield within a shorter reaction time than the bulk (Table 2).

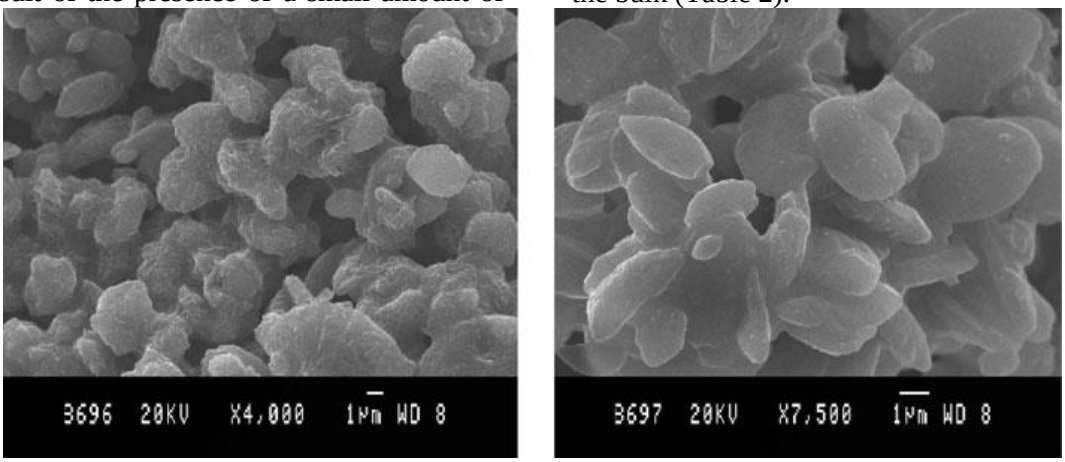
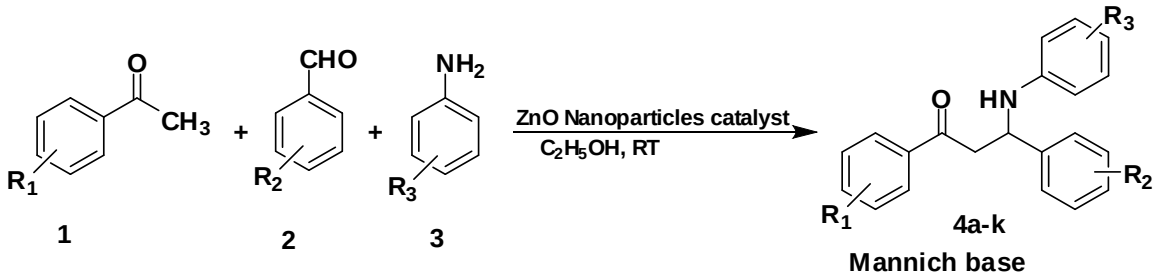


Fig. 3. Scanning electron microscopy (SEM) image of the synthesized ZnO nanoparticles.



Scheme 1. Synthesis of β-amino carbonyl compounds from amines, acetophenone and aldehydes catalyzed by ZnO nanoparticles catalyst

Table 1. Mannich reaction in the synthesis of (1,3-diphenyl-3-(phenylamino)propan-1-one (**4a**) with various catalysts

Entry	Catalyst	Time (h)	[a]Yield (%)
1	ZnO nanoparticles	1	94
2	$SnCl_2.2H_2O$	12	71
3	$Fe_2(SO_4)_3.6H_2O$	12	0
4	$Al_2(SO_4)_3.18H_2O$	14	0
5	$AlCl_3.6H_2O$	4	85
6	$CeCl_3.7H_2O$	15	57
7	$Zn(OAc)_2.2H_2O$	14	0
8	CH_3COOH	27	0
9	Free	24	0

[a]Isolated yield.

Table 2. Optimization of the ZnO nanoparticles catalysed model reaction for the synthesis of 1,3-diphenyl-3-(phenylamino)propan-1-one (4a).

Entry	Catalyst (mol %)	Time (h)	[a]Yields(%)
1	Free (No catalyst)	19	0
2	ZnO nano (5%)	4	60[b]
3	ZnO nano (10%)	1	94[b]
4	ZnO nano (20%)	2.5	74[c]
5	ZnO bulk (10%)	6.5	36.5[b]
6	ZnO nano (20%)	3.5	71[d]
7	ZnO nano (30%)	4	68.5[c]
8	ZnO nano (30%)	5	57.5[d]
9	ZnO nano (40%)	6	52[c]
10	ZnO nano (40%)	7.5	46[d]

[a]Isolated yield; [b]Reaction was carried out at room temperature; [c]Reaction was carried out at 70^{O}C; [d]Reaction was carried out at 80^{O}C

Effect of catalyst

When the experiment was conducted at room temperature, the corresponding product was generated with a good yield (Table 2, entries 2, 3, 5). The effect of temperature was studied by carrying out the reactions at different temperatures [room temperature (25 ºC), 70 and 80 ºC] and various moles (10, 20, 30 and 40 mol%). As Table **2** shows, by raising the reaction temperature from ambient temperature (25 ºC) to 70 and 80 ºC, the yield decreased. From these results, it was concluded that 25 ºC would be the best temperature for all reactions. In other words, any further increase in the amount of the catalyst and temperature would have a negative effect on the reaction yield. From these experiments we found that the optimum reaction conditions are: 10 mol% catalyst and room temperature. Different types of amines with either electron pumping or electron withdrawing groups were subjected to Mannich condensation reactions with various ketones (aromatic and alicyclic) and various aldehydes (aromatic and alicyclic) with either electron pumping or electron withdrawing substituents, in the presence of ZnO nanoparticles under solvent-free conditions at room temperature. To compare the efficiency of solvent-free *vs.* solution conditions, the reaction was examined in several solvents. Thus, a mixture of benzaldehyde, acetophenone, aniline and ZnO nanoparticles catalyst at room temperature in different solvents was used. The results are depicted in Table 3. As it is seen, lower yields and longer reaction times are observed in solution conditions. Therefore, the solvent-free method is more efficient. To investigate the versatility and capacity of the present method, the reactions of amines were examined with ketones and aldehydes at room temperature (Table 4). As Table 4 indicates, the reactions proceeded efficiently and the desired products were obtained in good to excellent yields (compound **4a**).

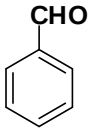
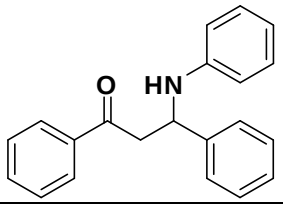
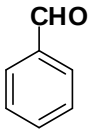
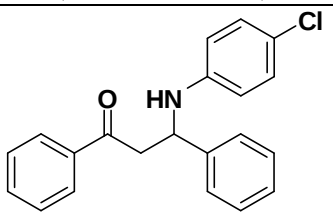
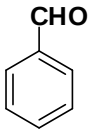
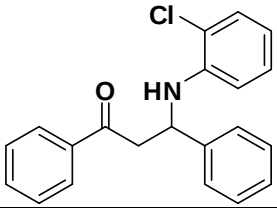
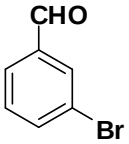
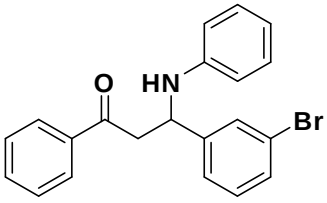
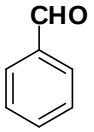
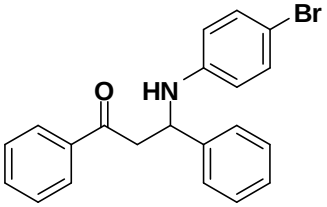
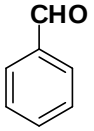
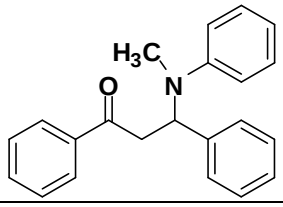
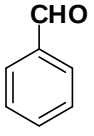
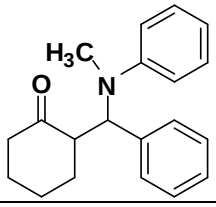
Table 3. Effect of solvents on the condensation between benzaldehyde, acetophenone and aniline in the presence of ZnO nanoparticles at room temperature, (4a).

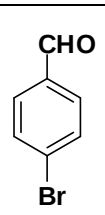
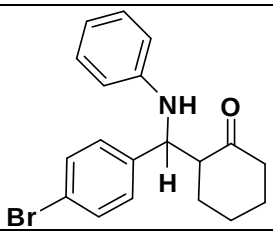
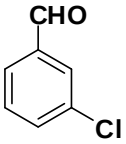
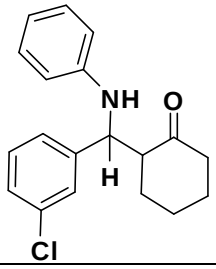
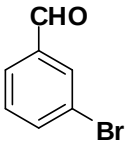
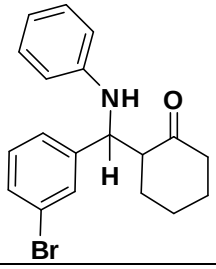
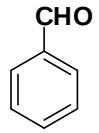
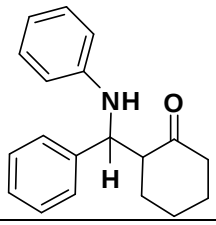
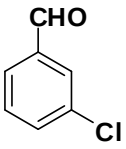
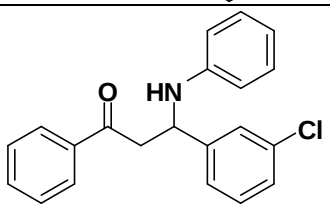
Entry	Solvents	Time (h)	[a,b]Yield (%)
1	Free	1	94
2	CH_3CN	5	84
3	CH_3OH	3	81
4	$C_6H_5CH_3$	3	29
5	C_2H_5OH	3	88
6	H_2O	9	41
7	DMF	5	27
8	Dioxane	5	32
9	THF	6	30
10	DMSO	4.5	31

[a]Reaction conditions: aniline (0.2 mmol), acetophenone (0.2 mmol) and aldehyde (2 mmol); catalyst: ZnO nanoparticles (10 mol%); reaction temperature: 25 ºC;
[b]Isolated yield of 1,3-diphenyl-3-(phenylamino)propan-1-one.

A wide variety of aromatic ketones, aromatic aldehydes and aromatic amines were tested to establish the scope of this catalytic transformation (Table 4). In all cases it was observed that the reactions proceed smoothly at room temperature. Besides ortho-substituted aromatic amine, the aromatic ketones, aromatic aldehydes and aromatic amines bearing both electron donating and electron withdrawing groups underwent this one-pot three components condensation to furnish the corresponding Mannich base in high yields. Particularly, substituents having weak electron-donating groups such as –Cl are favorable for the transformation. Meta-substituted and para-substituted aromatic amines all gave good results, but ortho-substituted aromatic amine afforded the corresponding Mannich base in a moderate yield after long reaction time because of a large steric hindrance effect (Table 4, entry 3).

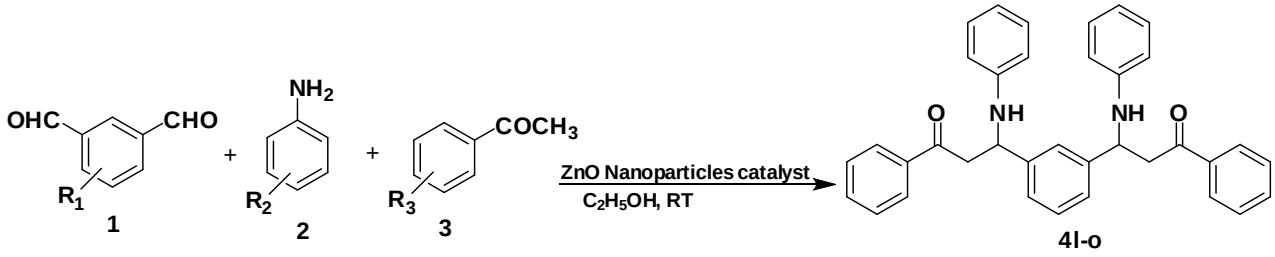
Table 4. Synthesis of β-amino carbonyl compounds from amines, ketones, and aldehydes at room temperature over ZnO nanoparticles catalyst

Entry	Aldehyde	Product	Time (h)	[a,b]Yield (%)	m.p.°C (lit)
1			1	94(94, 93,91, 90.5)[c]	168-170(119)[33]
2			1	90	169-71 (170-71) [32,33]
3			17	59	115-116
4			11	96(96, 95, 94, 93.5)[c]	165-168
5				92.5	178-180(178)[32]
6			1	97(96, 95, 94, 92.5)[c]	135-137
7			1	96	149-151

8			1	94	141-143
9			1	92	130-132
10			1	97	134-135
11			1	91	128-129(129)[33]
12			2.5	96	119-120(119)[33]

[a]Reaction conditions: amines (0.2 mmol), ketones (0.2 mmol) and aldehydes (0.2 mmol)
[b]Isolated yield. [c]Yield of catalyst recycled four times

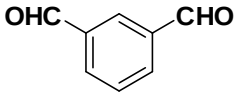
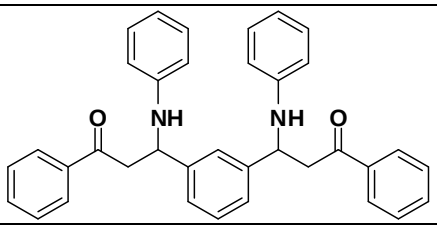
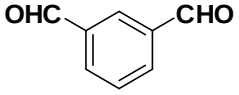
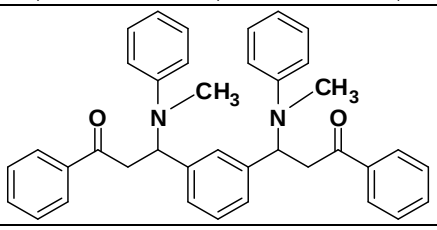
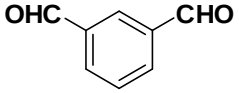
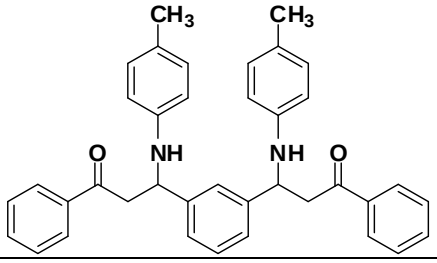
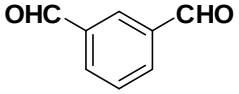
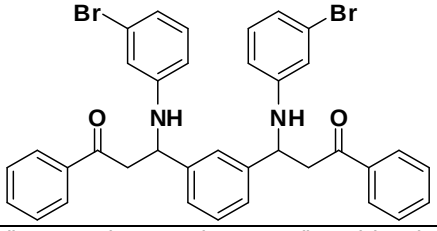
Based on such a good result, we tested isophthalic aldehyde and aniline under the same conditions and found that they also possessed good activity in the reaction. However, so far, attention has been paid mainly to the synthesis of mono-functional *β*-amino carbonyl compounds derivatives, and *β1,β2*-diamino diketone compounds were seldom investigated. Therefore, we firstly synthesized *β1,β2*-diamino diketone compounds and their derivatives with good yields (Scheme 2).



Scheme 2. Synthesis of β1,β2-diamino diketone compounds from amines, acetophenone and isophthalic aldehyde catalyzed by ZnO nanoparticles catalyst

With the best catalyst in hand, further experiments were carried out to test the different parameters affecting the reaction system. So the effect of reaction temperature, time, and solvents was tested. Additionally, aromatic aldehydes with different structures were tested, and their activities in this system were compared, too. These results showed that solvent-free conditions were the best (Table 3, entry 1). Various aldehydes, amines and ketones catalyzed by ZnO nanoparticles at ambient temperature (Table 4) were found to be efficient. The following features were excellent in these reactions: (1) A 1:1:1 mixture of benzaldehyde, aniline, and acetophenone with 10 mmol% of ZnO nanoparticles gave the Mannich adduct in 94% yield (Table 4, entry 1). All examined amines could readily react with acetophenone and aldehyde to give the corresponding *β*-amino carbonyl compounds with good yields. Using 4-methyl aniline as a substrate, the yields of β-amino carbonyl compounds were nearly the same as using aniline as a substrate, which indicated the good activity of ZnO nanoparticles for β-amino carbonyl compounds synthesis (Table 4, entry 4). An important feature was that all products listed in Table 4 could be simply separated. Monoaldehydes, as well as dialdehydes reacted well with amines and ketones, and dialdehydes behaved similarly to monoaldehydes. When isophthalic aldehyde reacted with lower steric hindrance amines, good yields were obtained. However, when it reacted with N-methylaniline, the yields of *β1,β2*-diamino diketone compounds were relatively low, which showed the importance of the electronic effect upon these reactions (Table 5, Entries 1-4).

Table 5. Synthesis of β1,β2-diamino diketone compounds from aniline, acetophenone, and aldehyde at room temperature over ZnO nanoparticles catalyst

Entry	Aldehyde	Product	Time (h)	[a]Yield (%)	m.p.^{o}C
1			4.5	87.5	164-166
2			12.5	64	172-175
3			5	92	184-186
4			5.5	95.5	198-200

[a]Reaction conditions: aniline (0.2 mmol), acetophenone (0.2 mmol) and isophthalic aldehyde (0.2 mmol); catalyst: ZnO nanoparticles (10 mol%); reaction temperature: room temperature; reaction solvent: EtOH.
[b]Isolated yield

3. 1. Regeneration of catalyst

To examine the reusability, the catalyst recovered by filtration from the reaction mixture after dilution with ethyl acetate was reused in subsequent experiments (up to four cycles) under similar reaction conditions. The product yields remained comparable in these experiments (Figure 4), which points to the recyclability and reusability of the catalyst without significant loss of activity.

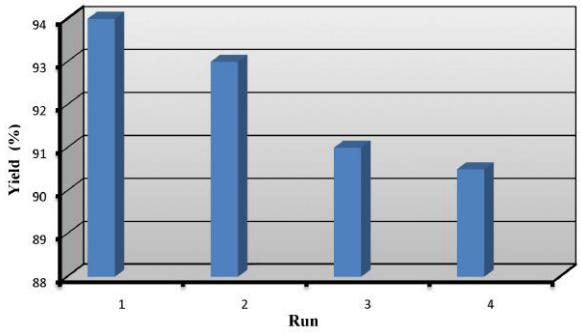


Fig. 4. Recyclability of ZnO nanoparticles catalyst for the synthesis of 1,3-diphenyl-3-(phenylamino)propan-1-one **(4a)**.

CONCLUSION

Three-component reactions of aldehydes, ketones and various amines were efficiently catalyzed by ZnO nanoparticles in organic solvents. Aromatic and aliphatic aldehydes all reacted with good yields. ZnO nanoparticles played an important role in acceleration of the reactions. So, ZnO nanoparticles behaved as a green catalyst in Mannich reactions. The ZnO nanoparticles were used to catalyze Mannich reactions under solvent-free conditions to afford the corresponding *β*-amino carbonyl compound (Mannich base) in excellent yields in a shorter time. The ZnO nanoparticles were easily separated from the reaction mixture by extraction with ether. The ZnO nanoparticles are reusable several times without any significant loss in potentiality. We have demonstrated an efficient and environmentally friendly approach for the synthesis of β-amino carbonyl compounds *via* one-pot three-component condensation of aromatic ketones, aromatic aldehydes and aromatic amines using ZnO nanoparticles as a recyclable catalyst. High yields, reduced reaction time, mild reaction condition, easy work-up procedure, inexpensive and commercially available catalyst make this approach an interesting alternative to the existing methods. The present method is a very efficient and selective protocol for Mannich condensation reactions of various aldehydes, amines and ketones in the presence of a reusable and environmentally benign catalyst. We have developed an efficient, facile and environmentally acceptable methodology for the synthesis of coumarin derivatives using ZnO nanoparticles catalyst under solvent-free conditions. The advantages of this environmentally benign and safe protocol include a simple reaction setup, very mild reaction conditions, high product yields, short reaction times, possibility for reusing the catalyst, selectivity and solvent-free conditions.

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СИНТЕЗА НА β–АМИНО-КАРБОНИЛНИ СЪЕДИНЕНИЯ ИЗПОЛЗВАЙКИ НАНОЧАСТИЦИ ОТ ZNO КАТО ЗЕЛЕН, ЕФЕКТИВЕН И МНОГОКРАТНО УПОТРЕБЯВАН КАТАЛИЗАТОР

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(Резюме)

Описана е нова едноетапна и ефективна трикомпонентна кондензация на ароматни алдехиди, ароматни кетони и ароматни амини в присъствие на наночастици от ZnO като евтин и ефективен катализатор за синтезата на β-амино-карбонилни съединения по реакцията на Mannich. Реакцията протича при стайна температура без разтворител. Умерената температура, евтиният катализатор, лесното отделяне на продуктите и рециклирането на катализатора са главните постижения при тази реакция. Простите експериментални условия и процедурата по изолирането на продуктите прави този метод приложим за разработването на чиста и екологически съвместима стратегия за синтезата на β-кетони. Настоящата методология предлага няколко предимства: добър добив, кратко реакционно време и рециклируем катализатор.