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Heteropoly acids as solid green Brønsted acids for a one-pot synthesis of β-acetamido ketones by Dakin–West reaction

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Abstract—An efficient improved procedure for the synthesis of β-acetamido ketones has been developed by a heteropoly acid (HPA) catalyzed three-component coupling protocol. The present methodology offers several advantages such as excellent yields, simple procedure, short reaction times, and mild conditions.
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In recent decades, use of eco-friendly applicable industrial and green catalysts has been of interest. Thus, green chemistry has been defined as a set of principles that reduces or eliminates the use or generation of hazardous substances throughout the entire life of chemical materials.[1] Along this line, using heteropoly acids (HPAs) which are strong, low in toxicity, highly stable toward humidity, and air-stable has found more attention.[2] They have been widely used as acid catalysts for organic synthesis and found several industrial applications.[3–9] The HPA-based solid acid catalysts, especially those comprising the strongest Keggin-type HPAs such as $H_3PW_{12}O_{40}$ (PW), $H_3PMo_{12}O_{40}$ (PMo) or $H_4SiW_{12}O_{40}$ (SiW), are more active than conventional inorganic and organic acids such as zeolites, SiO_2/Al_2O_3, and H_3PO_4/SiO_2.[9–12] HPAs have many advantages over liquid acid catalysts including being noncorrosive and environmentally benign, thus presenting fewer disposal problems.[13]

Multicomponent reactions (MCRs) are one of the most important protocols in organic synthesis and medicinal chemistry.[14–18] These processes consist of two or more synthetic steps, which are performed without isolation of any intermediates thus reducing time and saving both energy and raw material. The diversity, efficiency, and rapid access to small and highly functionalized organic molecules make this approach of central interest in the construction of combinatorial libraries and optimization in drug discovery processes.[19] Dakin–West reaction is the best known route for the synthesis of β-acetamido ketones.[20,21] These compounds are versatile intermediates, in that their skeletons exist in a number of biologically or pharmacologically important compounds.[22,23] Recently, Singh and co-workers proposed a procedure for the formation of these compounds in the presence of $Cu(OTf)_2$.[24] β-Acetamido ketones have also been synthesized using Zn(II), Bi(III), Sn(II), Sc(III) triflates, BF_3, $CuCl_2$, $BiCl_3$, $LaCl_3$, $LiClO_4$, $InCl_3$,[24] $CoCl_2$,[25], montmorillonite K-10 clay,[26] and H_2SO_4/SiO_2[27] as catalyst. Although these methods are valuable, they suffer from one or more of the following disadvantages such as high temperature, long reaction time, low yield, and tedious workup. Hence, the development of new catalysts with more efficiency is still in demand.

In continuation of our interest on the catalytic activities of heteropoly anions,[28] here, a very efficient and environmentally benign catalysis by the strong HPAs for the synthesis of β-acetamido ketones is reported (Scheme 1).

Keywords: β-Acetamido ketones; Heteropoly acid; Dakin–West reaction; Multi component reactions (MCRs).
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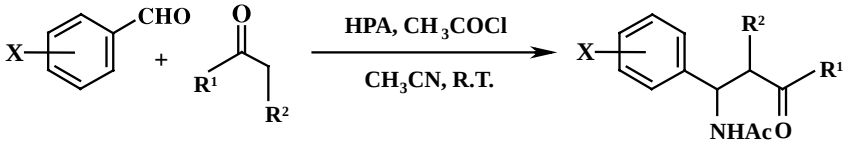
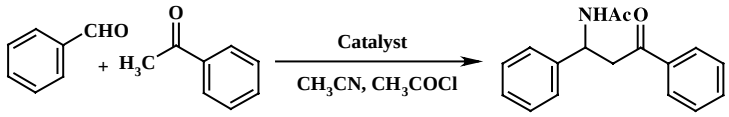


Scheme 1.

Table 1. Effect of catalysts on the three-component Dakin–West reaction to give β-acetamido ketones



Entry	Catalyst	Temperature (°C)	*T* (h)	Yield[a] (%)
1	—	80	10	0
2	PW (5 mol %)	RT	50 (min)	95
3	PMo (5 mol %)	RT	50 (min)	88
4	SiW (5 mol %)	RT	50 (min)	90
5	$Zn(OTf)_2$ (10 mol %)[24]	RT	30	60
6	$Bi(OTf)_3$ (10 mol %)[24]	RT	30	69
7	$Sn(OTf)_2$ (10 mol %)[24]	RT	30	68
8	$Sc(OTf)_3$ (10 mol %)[24]	RT	30	82
9	$Cu(OTf)_2$ (10 mol %)[24]	RT	30	64
10	$Yb(OTf)_3$ (10 mol %)[24]	RT	30	75
11	$BF_3.OEt_2$(100 mol %)[24]	RT	30	78
12	$CuCl_2$(100 mol %)[24]	RT	30	79
13	$BiCl_3$(100 mol %)[24]	RT	30	77
14	$LaCl_3$(100 mol %)[24]	RT	30	77
15	$LiClO_4$(100 mol %)[24]	RT	30	59
16	$InCl_3$(100 mol %)[24]	RT	30	19
17	SiO_2/H_2SO_4 (0.3 g)[27]	80	65 (min)	91
18	Montmorillonite K-10 (2 g)[26]	70	7	80

[a] Isolated yield.

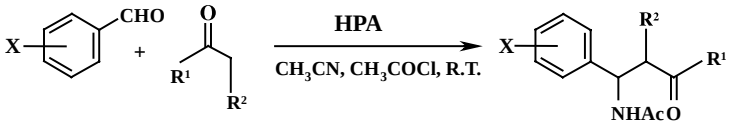
At first the three-component condensation reaction of benzaldehyde, acetophenone, and acetyl chloride was performed in the presence of catalytic amount of several HPAs (Table 1, entries 2–4). The synthesis could not be achieved in the absence of the catalyst (Table 1, entry 1). The reaction was more efficient in the presence of HPAs when compared to the literature procedures [24,26,27] (Table 1, entries 5–18).

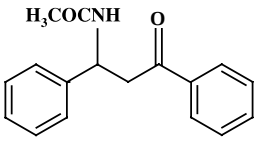
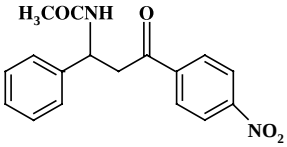
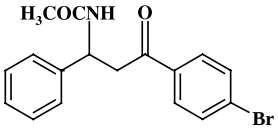
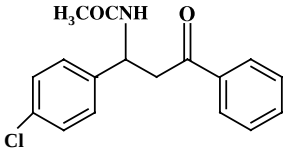
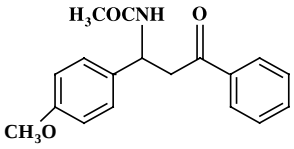
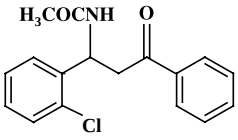
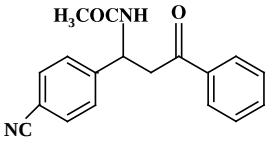
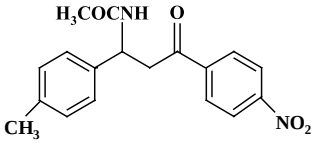
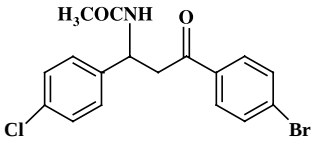
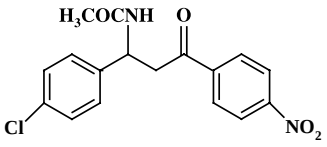
To establish the optimal conditions, a set of experiments varying the amount of the catalysts, quantities of acetyl chloride, and temperature were carried out. The best conditions to prepare the β-acetamido ketones were achieved when 5 mol %, 8 mol %, and 8 mol % of PW, PMo, and SiW were used, respectively. These conditions were applied to a series of substituted aromatic and aliphatic aldehydes and ketones.[29]

As shown in Table 2 aromatic aldehydes or acetophenones with both electron-withdrawing or -donating substitution performed afforded the β-acetamido ketones without the formation of any side products, in excellent yields and in relatively short reaction times at room temperature. It is noteworthy that, no acetylation of an aromatic hydroxyl group was observed when salicylaldehyde was used, and the corresponding β-acetamido ketones were isolated in an excellent yield (Table 2, entries 12–14). Aliphatic aldehyde and acyclic aliphatic ketone gave unsatisfactory results (Table 2, entries 17 and 19) but show good results at reflux condition (Table 2, entries 18 and 20). As expected,[30] the results show tungsten HPAs (PW and SiW) are preferred over molybdenum HPA (PMo) as acid catalysts and PW—the strongest acid in the HPA series—is particularly recommended. Based on the literature[24,26,27] the authors suggest a reaction mechanism that is shown in Scheme 2.

In summary, a new and important catalytic activity of HPAs (cheap, commercially available, noncorrosive, and environmentally benign compounds) has been studied for the synthesis of β-acetamido ketones in excellent yields under mild reaction conditions. The simple experimental procedure combined with the easy workup, the mild reaction conditions, and excellent yields of products are the strong features of the method presented herein.

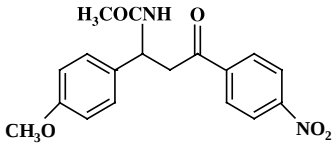
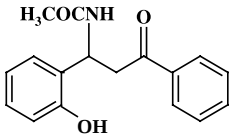
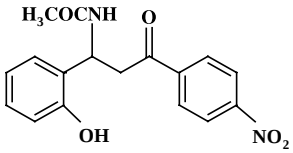
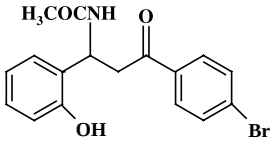
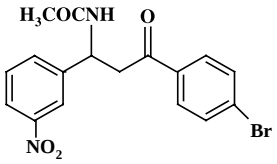
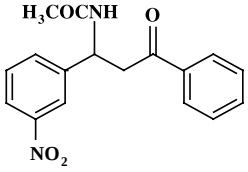
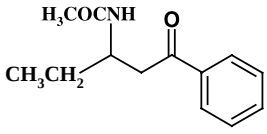
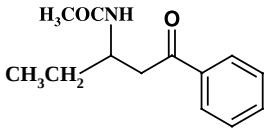
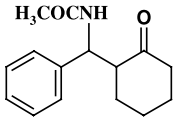
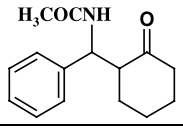
Table 2. Synthesis of β-acetamido ketones at room temperature in the presence of catalytic amounts of $H_3PW_{12}O_{40}$, $H_3PMo_{12}O_{40}$ or $H_3SiW_{12}O_{40}$



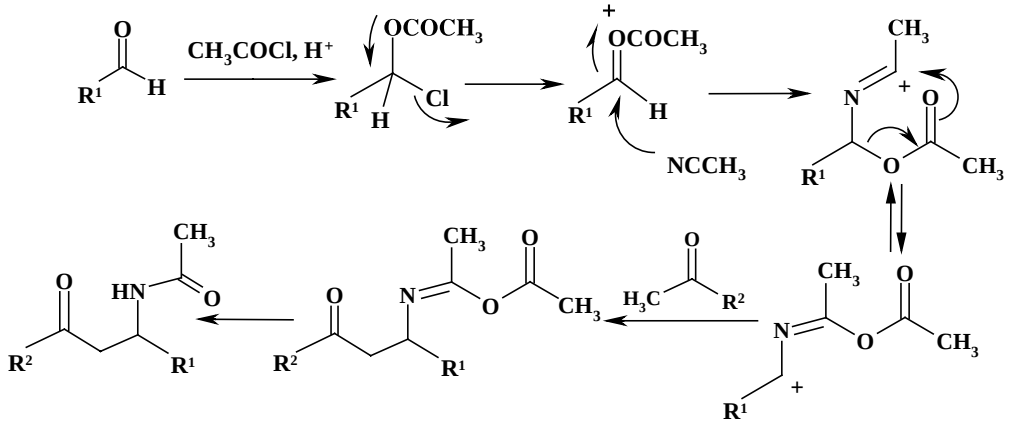
Entry	R^1	R^2	Product	Yield[a] (%)/time (min)		
				PW[b]	PMo[c]	SiW[d]
1	C_6H_5	C_6H_5		95/50	90/30	92/30
2	C_6H_5	4-$NO_2C_6H_4$		90/35	90/70	90/40
3	C_6H_5	4-BrC_6H_4		93/35	90/40	95/40
4	4-ClC_6H_4	C_6H_5		92/45	93/60	90/50
5	4-$CH_3OC_6H_4$	C_6H_5		80/40	85/40	90/40
6	2-ClC_6H_4	C_6H_5		90/50	90/50	90/50
7	4-CNC_6H_4	C_6H_5		75/60	85/60	80/40
8	4-$CH_3C_6H_4$	4-$NO_2C_6H_4$		85/50	85/40	90/60
9	4-ClC_6H_4	4-BrC_6H_4		90/80	97/40	95/40
10	4-ClC_6H_4	4-$NO_2C_6H_4$		87/60	90/60	91/60

(*continued on next page*)

Table 2 (*continued*)

Entry	R^1	R^2	Product	Yield[a] (%)/time (min)		
				PW[b]	PMo[c]	SiW[d]
11	4-$CH_3OC_6H_4$	4-$NO_2C_6H_4$		90/70	87/50	90/50
12	2-HOC_6H_4	C_6H_5		75/60	80/90	90/80
13	2-HOC_6H_4	4-$NO_2C_6H_4$		85/70	85/60	87/60
14	2-HOC_6H_4	4-BrC_6H_4		87/50	90/60	90/60
15	3-$NO_2C_6H_4$	4-BrC_6H_4		90/70	90/50	95/50
16	3-$NO_2C_6H_4$	C_6H_5		85/60	90/40	93/40
17	CH_3CH_2	C_6H_5		0/120[e]	20/120	20/120
18	CH_3CH_2	C_6H_5		35/120[f]	40/120[f]	35/120[f]
19	C_6H_5	$C_6H_{10}O$		50/80	20/80	20/80
20	C_6H_5	$C_6H_{10}O$		85/80[f]	80/80[f]	80/80[f]

[a] Isolated yield, All products were identified by comparing their NMR and IR values with those for authentic samples.[31]
[b] The mole ratio of aldehyde to ketone to $H_3PW_{12}O_{40}$ is 1:1:0.05.
[c] The mole ratio of aldehyde to ketone to $H_3PMo_{12}O_{40}$ is 1:1:0.08.
[d] The mole ratio of aldehyde to ketone to $H_3SiW_{12}O_{40}$ is 1:1:0.08.
[e] Reaction did not occur.
[f] The reaction performed at reflux condition.



Scheme 2.

Acknowledgments

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29. Typical procedure for the synthesis of β-acetamido ketones: A solution of aryl aldehyde (1 mmol), ketone (1 mmol), acetyl chloride (0.3 mL), and acetonitrile (3 mL) in the presence of appropriate amount of catalyst (Table 2) was stirred at ambient temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the solution was poured into 50 mL ice water. The solid product was filtered, washed with ice water, and recrystallized from ethyl acetate/*n*-heptane to give the pure product. All products were identified by comparing their NMR and IR values with those for authentic samples.[31]
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31. Spectroscopic data of products: β-Acetamido-β-(phenyl)propiophenone (Table 2, entry 1). Mp: 101–103 °C, ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.03 (s, 3H), 3.34 (dd, J = 6.6 and 9.7 Hz, 1H), 3.67 (dd, J = 6.6 and 9.7 Hz, 1H), 5.60 (m, 1H) 6.87 (s, 1H), 7.58 (d, J = 9.1 Hz, 5H), 7.76 (d, J = 9.1 Hz, 5H); IR (KBr, cm^{-1}) 3252, 3046, 1667, 1624, 1574, 1288, 1082, 878, 819.
β-Acetamido-β-(phenyl)-4-nitropropiophenone (Table 2, entry 2). Mp: 74–76 °C, ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.00 (s, 3H), 3.32 (d, J = 13.8 Hz, 1H), 3.52 (d, J = 13.8 Hz, 1H), 5.70 (s, 1H), 7.32 (m, 4H), 7.88 (m,

3H), 8.08 (m, 2H); IR (KBr, cm^{-1}) 3260, 3027, 2270, 1676, 1637, 1557, 1397, 1222, 969, 817, 667, 556.

β-Acetamido-β-(phenyl)-4-bromopropiophenone (Table 2, entry 3). Mp: 98–100 °C, ^1H NMR (200 MHz, $CDCl_3$) δ 2.1 (s, 3H), 3.40 (dd, J = 8.1, 10.07 Hz, 1H), 3.81 (dd, J = 8.1, 10.07 Hz, 1H), 5.6 (s, 1H), 6.8 (d, 1H), 7.2–7.5 (m, 5H), 7.6 (d, 2H), 7.8 (d, 2H); IR (KBr, cm^{-1}) 3296, 1690, 1685, 1644, 1545, 1395, 1372, 1070, 995, 816, 759, 705.

β-Acetamido-β-(4-chlorophenyl)propiophenone (Table 2, entry 4). Mp: 144–146 °C, ^1H NMR ($CDCl_3$, 200 MHz) δ 2.00 (s, 3H), 3.40 (dd, J = 6.9 and 9.9 Hz, 1H), 3.71 (dd, J = 6.9 and 9.9 Hz, 1H), 5.54 (m, 1H), 7.02 (m, 5H), 7.45 (m, 3H), 7.84 (d, J = 9.1 Hz, 2H); IR (KBr, cm^{-1}) 3270, 3082,1668, 1635, 1556, 1255, 1104, 887, 823, 687.

β-Acetamido-β-(4-methoxyphenyl)propiophenone (Table 2, entry 5). Mp: 115–117 °C, ^1H NMR ($CDCl_3$, 200 MHz) δ 2.09 (s, 3H), 2.47 (s, 3H), 3.51 (dd, J = 7.1 and 10.0 Hz, 1H), 3.84 (dd, J = 7.1 and 10.0 Hz, 1H), 5.58 (m, 1H) 7.39 (s, 1H), 7.52 (m, 5H), 7.96 (m, 4H); IR (KBr, cm^{-1}) 3263, 3051, 1672, 1630, 1581, 1290, 1081, 878, 817.

β-Acetamido-β-(2-chlorophenyl)propiophenone (Table 2, entry 6). Mp: 135–137 °C, ^1H NMR ($CDCl_3$, 200 MHz) δ 2.06 (s, 3H), 3.43 (dd, J = 7.1 and 10.0 Hz, 1H), 3.71 (dd, J = 7.1 and 10.0 Hz, 1H), 5.60 (m, 1H), 7.12 (m, 5H), 7.52 (m, 3H), 7.90 (d, J = 9.3 Hz, 2H); IR (KBr, cm^{-1}) 3250, 3062, 1660, 1640, 1563, 1261, 1109, 890, 833, 682.

β-Acetamido-β-(4-cyanophenyl)propiophenone (Table 2, entry 7). Mp: 85–88 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.92 (s, 3H), 3.34 (dd, J = 5.1, 16.07 Hz, 1H), 3.62 (dd, J = 5.9, 16.1 Hz, 1H), 5.65 (d, J = 7.03, 1H), 7.45 (m, 4H), 7.80 (m, 3H), 8.02 (s, 1H); IR (KBr, cm^{-1}) 3294, 3035, 2250, 1690, 1650, 1541, 1439, 1225, 978, 752, 677, 548.

β-Acetamido-β-(4-methylphenyl)-4-nitropropiophenone (Table 2, entry 8). Mp: 83–85 °C, ^1H NMR (200 MHz, $CDCl_3$) δ 1.99 (s, 3H), 2.33 (s, 3H), 3.44 (d, J = 14.5 Hz, 1H), 3.73 (d, J = 14.5 Hz, 1H), 6.01 (s, 1H), 7.54 (m, 4H), 7.97 (m, 3H), 8.10 (m, 2H); IR (KBr, cm^{-1}) 3256, 3034, 2276, 1668, 1629, 1601, 1386, 1231, 974, 823, 674, 561.

β-Acetamido-β-(4-chlorophenyl)-4-bromopropiophenone (Table 2, entry 9). Mp: 140–142 °C, ^1H NMR (200 MHz, $CDCl_3$) δ 2.08 (s, 3H), 3.34 (dd, J = 7.1 and 10.1 Hz, 1H), 3.75 (dd, J = 7.1 and 10.1 Hz, 1H), 5.70 (m, 1H) 7.36 (s, 1H), 7.65 (d, J = 9.1 Hz, 4H), 7.96 (d, J = 9.1 Hz, 4H); IR (KBr, cm^{-1}) 3263, 3053, 1680, 1632, 1585, 1293, 1085, 887, 827.

β-Acetamido-β-(4-chlorophenyl)-4-nitropropiophenone (Table 2, entry 10). Mp: 116–118 °C, ^1H NMR (200 MHz, $CDCl_3$) δ 2.10 (s, 3H), 3.50 (dd, J = 6.8 and 9.9 Hz, 1H), 3.90 (dd, J = 6.8 and 9.9 Hz, 1H), 5.69 (s, 1H) 7.10 (s, 1H), 7.30–7.82 (m, 6H), 8.12 (m, 3H); IR (KBr, cm^{-1}): 3264, 1690, 1644, 1585, 1542, 1510, 1353, 1077, 1000, 820, 670, 573.

β-Acetamido-β-(4-methoxyphenyl)-4-nitropropiophenone (Table 2, entry 11). Mp: 87–89 °C, ^1H NMR (200 MHz, $CDCl_3$) δ 2.05 (s, 3H), 3.12 (s, 3H), 3.52 (d, J = 15.2 Hz, 1H), 3.77 (d, J = 15.2 Hz, 1H), 5.97 (s, 1H), 7.32 (m, 4H), 7.69 (m, 3H), 8.02 (m, 2H); IR (KBr, cm^{-1}) 3243, 3023, 2265, 1667, 1634, 1589, 1379, 1227, 969, 819, 676, 568.

β-Acetamido-β-(2-hydroxyphenyl)propiophenone (Table 2, entry 12). Mp: 130–132 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 2.00 (s, 3H), 3.49 (d, J = 7.2 Hz, 1H), 3.68 (d, J = 7.1 Hz, 1H), 6.87 (s, 1H), 7.50–7.72 (m, 5H), 7.95 (d, J = 5.9 Hz, 2H), 8.23 (d, J = 5.2 Hz, 2H); IR (KBr, cm^{-1}) 3286, 2845, 1679, 1638, 1595, 1501, 1446, 1341, 1289, 851, 747, 681, 588.

β-Acetamido-β-(2-hydroxyphenyl)-4-nitropropiophenone (Table 2, entry 13). Mp: 102–104 °C, ^1H NMR (200 MHz, $CDCl_3$) δ 2.01 (s, 3H), 3.38 (d, J = 7.1 Hz, 1H), 3.65 (d, J = 7.1 Hz, 1H), 5.98 (s, 1H), 6.79 (s, 1H), 7.44–7.69 (m, 4H), 7.95–8.25 (m, 5H);IR (KBr, cm^{-1}) 3275, 3025, 2843, 1665, 1634, 1595, 1536, 1511, 1341, 1275, 847, 739, 677, 580.

β-Acetamido-β-(2-hydroxyphenyl)-4-bromopropiophenone (Table 2, entry 14). Mp: 126–128 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 2.12 (s, 3H), 3.33 (d, J = 7.3 Hz, 1H), 3.68 (d, J = 7.3 Hz, 1H), 5.38 (s, 1H), 6.68 (s, 1H), 7.34–7.80 (m, 5H), 8.02–8.26 (m, 4H); IR (KBr, cm^{-1}) 3250, 3026, 2855, 1658, 1629, 1577, 1515, 1459, 1350, 1278, 860, 745, 679, 593.

β-Acetamido-β-(3-nitrophenyl)-4-bromopropiophenone (Table 2, entry 15):Mp: 115–118 °C, ^1H NMR ($CDCl_3$, 200 MHz) δ 2.13 (s, 3H), 3.50 (dd, J = 6.5 and 9.6 Hz, 1H), 3.85 (dd, J = 6.5 and 9.6 Hz, 1H), 5.70 (m, 1H) 7.24 (s, 1H), 7.54–7.87 (m, 4H), 7.96 (m, 4H); IR (KBr, cm^{-1}) 3264, 3035, 1690, 1637, 1585, 1510, 1353, 1285, 1077, 998, 824, 658, 576.

β-Acetamido-β-(3-nitrophenyl)propiophenone (Table 2, entry 16). Mp: 110–112 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.87 (s, 3H), 3.11 (d, J = 15.9 Hz, 1H), 3.52 (d, J = 12.1 Hz, 1H), 5.50 (s, 1H), 7.30 (m, 5H), 7.80 (d, J = 6.2 Hz, 2H), 8.00 (d, J = 6.2 Hz, 2H); IR (KBr, cm^{-1}) 3290, 3024, 2245, 1680, 1649, 1542, 1440, 1215, 987, 750, 680, 545.

β-Acetamidopentaniophenone (Table 2, entries 17 and 18). Mp: 98–100 °C, ^1H NMR ($CDCl_3$, 200 MHz)δ 1.11 (t, J = 10.1, 3H), 1.55 (m, 2H), 2.00 (s, 3H), 3.21 (dd, J = 5.9 and 9.5 Hz, 1H), 3.60 (dd, J = 5.9 and 9.5 Hz, 1H), 5.51 (m, 1H) 7.29 (s, 1H), 7.62–7.70 (m, 5H); IR (KBr, cm^{-1}) 3246, 3030, 2868, 1659, 1631, 1275, 1077, 884, 827. *N*-{1-phenyl-1-[2-oxocyclohexyl]}acetamide (Table 2, entry 19 or 20). Mp: 133–135 °C, ^1H NMR ($CDCl_3$, 200 MHz) δ 1.80 (s, 3H), 2.22–2.24 (m, 8H), 5.49 (s, 1H), 7.12 (s, 1H), 7.60–7.74 (m, 3H), 8.25–8.32 (m, 2H); IR (KBr, cm^{-1}) 3384, 2932, 1650, 1602, 1524, 1227, 858, 758, 694.