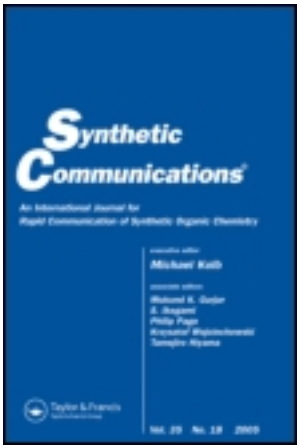

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Silica-Supported Perchloric Acid ($HClO_4$-SiO_2): An Efficient Catalyst for the Preparation of β-Amido Carbonyl Compounds Using Multicomponent Reactions

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Silica-Supported Perchloric Acid ($HClO_4$-SiO_2): An Efficient Catalyst for the Preparation of β-Amido Carbonyl Compounds Using Multicomponent Reactions

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Abstract: A new, one-pot, efficient, **three**-component condensation of benzaldehyde derivatives, enolizable ketones, acetyl chloride, and acetonitrile or benzonitrile in the presence of silica-supported perchloric acid as an effective catalyst for the synthesis of β-amido carbonyl compounds is described. The present methodology offers several advantages, such as good yields, short reaction times, and simple workup procedure.

Keywords: β-Amido carbonyl compounds, diastereoselectivity, heterogeneous catalyst, multicomponent reaction, silica-supported perchloric acid

INTRODUCTION

Multicomponent reactions (MCRs) are emerging as an efficient and powerful tool in modern synthetic organic chemistry, allowing the facile reaction of several new bonds in a one-pot transformation from three or more reactants.[1] Multicomponent, one-pot syntheses are highly important because of their wide range of applications in pharmaceutical chemistry for production of structural scaffolds and combinatorial libraries for preparation of drug-like molecules with several levels of structural

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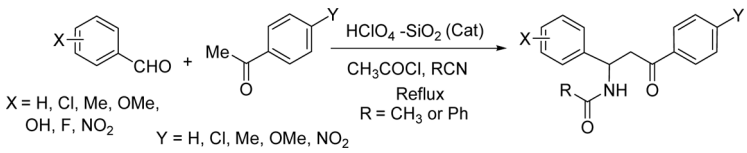
diversity.[1] β-Acetamido ketones and esters are valuable building blocks for a number of biologically and pharmaceutically bioactive important compounds.[2,3] They could easily be converted to 1,3-amino alcohols, which are precursors for the synthesis of several antibiotics such as nikkomycins or neopolyoxins.[4]

The common procedure for the synthesis of this class of compounds is the Dakin–West reaction,[5] which involves the condensation of α-amino acids with acetic anhydride in the presence of a suitable base.[5] These reactions produce α-acetamido ketones through an intermediate azalactone.[5]

Iqbal et al. reported a multicomponent reaction for the synthesis of β-acetamido ketones through the condensation of acetophenone, an aryl aldehyde, and acetyl chloride in acetonitrile in the presence of cobalt (II) chloride[6,7] or montmorillonite K-10 clay[8] as catalyst. Other catalysts such as silica sulfuric acid,[9] $BiCl_3$ generated from BiOCl,[10] $ZrOCl_2 \cdot 8H_2O$,[11] heteropoly acid,[12] $H_3PW_{12}O_{40}$,[13] sulfuric acid absorbed on silica gel,[14] $Sc(OTf)_3$,[15] $K_5CoW_{12}O_{40} \cdot 3H_2O$,[16] $CeCl_3 \cdot 7H_2O$,[17] ZnO,[18] iodine,[19] Amberlyst-15,[20] sulfated zirconia,[21] iron(III) chloride,[22] *p*-TSA,[23] $Mg(HSO_4)_2$,[24] $Fe(HSO_4)_3$[25] and ZnO nanoparticles[26] have been used for the transformation. However, some of these catalysts suffer from the drawbacks of prolonged reaction times, toxic reagents, and low yields. The recovery and reusability of the catalyst is also a problem. Therefore, introducing clean processes and utilizing ecofriendly heterogeneous and green catalysts received attention. The demand for an environmentally benign procedure with heterogeneous catalyst[27] prompt us to develop a safe alternative method for the synthesis of β-amido carbonyl compounds, and we chose silica-supported perchloric acid as catalyst for this purpose (Scheme 1).

Silica-supported perchloric acid as a solid acid catalyst was prepared from the reaction of silica gel with perchloric acid.[28,29] This catalyst is safe, easy to handle, and environmentally benign with fewer disposal problems.



Scheme 1. One-pot preparation of β-acetamido or β-benzamido ketones by using $HClO_4$-SiO_2 as catalyst.

RESULTS AND DISCUSSION

First, we optimized the amount of silica-supported perchloric acid as catalyst in the reaction of benzaldehyde, acetophenone, acetyl chloride, and acetonitrile (Table 1). The amount of silica-supported perchloric acid was 5 mol%.

Thus, we continued preparation of β-amido ketones in an optimum model experiment: aldehydes (1 equiv), enolizable ketone (1 equiv), acetyl chloride (0.5 mL), acetonitrile [reactant as well as solvent (2 mL)], or benzonitrile (2 mL) in the presence of silica-supported perchloric acid (5 mol%) (Scheme 1, Table 2).

As shown in Table 2, aromatic aldehydes and acetophenone derivatives with both electron-withdrawing and electron-donating substituents afforded the corresponding β-amido ketones without the formation of any side products, in high to excellent yields at reflux conditions (Table 2, entries 1–26). Phenolic –OH groups under the present reaction conditions were converted to acetate (–OAc) groups (Table 2, entries 17, 18, and 21).

Under the optimized reaction conditions, by using benzonitrile in place of acetonitrile, aldehydes were transformed to their corresponding β-benzamido ketones in high yield (Table 2, entries 2, 5, 7, and 9).

We also studied the multicomponent reaction of aromatic aldehydes, other enolizable ketones (methyl acetoacetate, ethyl acetoacetate, and propiophenone), and acetonitrile in the presence of acetyl chloride and $HClO_4$-SiO_2 (5 mol%) as catalyst under reflux conditions (Scheme 2).

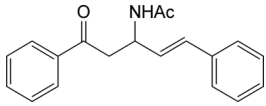
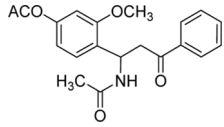
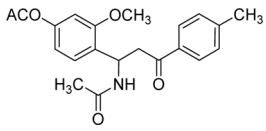
In all cases, mixtures of *syn* and *anti* diastereomers were obtained, while the diastereoselectivity depended upon the nature of the reactants (Scheme 2, Table 3). The amount of these *syn* and *anti* products was

Table 1. Optimization the amount of silica-supported perchloric acid as catalyst for preparation of N-(3-oxo-1,3-diphenylpropyl) acetamide under reflux conditions

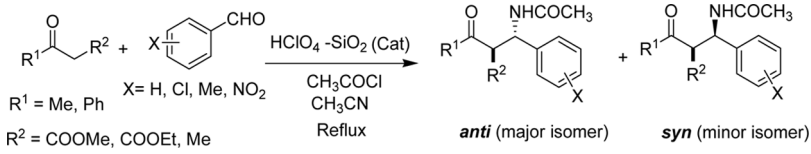
Entry	$HClO_4$-SiO_2 (mol%)	Time (h)	Yield (%)[a]
1	10	2	91
2	5	2.5	89
3	2.5	4.5	72
4	1	7	60
5	0.6	8.5	45
6	—	12	—

[a]Isolated products.

Table 2. Preparation of β-amido ketones from aldehydes and enolizable ketones in the presence of aceyl chloride, nitrile, and $HClO\text{-}SiO_2$ under reflux conditions

Entry	β-Amido ketone(s)	Time (h)	Yield (%)[a]	Mp (°C) (lit.mp)[ref]
1	X = H, Y = H, R = Me	2.5	89	102–104 (103–105)[12]
2	X = H, Y = H, R = Ph	2.0	90	153–155 (153–154)[22]
3	X = H, Y = OMe, R = Me	2.0	89	129–131 (130)[10]
4	X = 4-Cl, Y = H, R = Me	2.5	94	149–151 (149–150)[11]
5	X = 4-Cl, Y = H, R = Ph	2.5	89	179–181 (180–182)[22]
6	X = 4-NO_2, Y = H, R = Me	3.0	82	141–144 (153)[22]
7	X = 4-NO_2, Y = H, R = Ph	4.0	78	143–145 (142–144)[22]
8	X = 3-NO_2, Y = H, R = Me	3.5	82	135–137 (139–140)[11]
9	X = 3-NO_2, Y = H, R = Ph	3.5	79	192–194 (194–195)[11]
10		2.0	91	120–121 (120–121)[22]
11	X = 4-Cl, Y = Cl, R = Me	2.5	91	141–143 (143–145)[13]
12	X = 4-F, Y = Cl, R = Me	2.0	87	108–110 (108–110)[14]
13	X = H, Y = Me, R = Me	1.5	90	119–121 (121–123)[14]
14	X = 4-OMe, Y = H, R = Me	1.5	90	109–111 (110–112)[11]
15	X = 2,3-Dimethoxy, Y = H, R = Me	1.5	93	117–119 (–)
16	X = 2,3-Dimethoxy, Y = Me, R = Me	1.5	90	108–111 (108–111)[24]
17		1.2	92	129–132 (129–132)[24]
18		1.0	89	89–93 (–)
19	X = 2,5-Dimethoxy, Y = H, R = Me	2.0	90	153–156 (–)
20	X = 4-Me, Y = H, R = Me	2.0	89	10–112 (112)[11]
21	X = 4-OAc, Y = H, R = Me	1.0	85	120–122 (–)
22	X=3-NO_2, Y=Me, R=Me	3.5	87	94–97 (94–97)[24]
23	X = 4-Me, Y = Me, R = Me	2.0	91	103–105 (103–105)[24]
24	X = H, Y = NO_2, R = Me	2.0	93	74–76 (74–76)[12]
25	X = 4-Me, Y = NO_2, R = Me	2.0	90	80–83 (83–85)[12]
26	X = 4-Cl, Y = NO_2, R = Me	2.0	94	116–118 (116–119)[13]

[a]Yields refer to the pure isolated products. All known products have been reported previously in the literature and were characterized by comparison of IR and NMR spectra with authentic samples.[6–26]



Scheme 2. Diastereoselective preparation of β-acetamido ketones/esters by using $HClO\text{-}SiO_2$ as catalyst.

determined by ^1H NMR spectra; the coupling constant between H-2 and H-3 is 6–9 Hz for an *anti* isomer and 2–5 Hz for a *syn* isomer.[6–8,23]

As shown in Table 3, the *anti* diastereomer was the major product. Methyl acetoacetate and ethyl acetoacetate afforded the corresponding β-acetamido ketoesters in good yields with high diastereoselectivity.

CONCLUSION

In summary, we have demonstrated a new and important catalytic activity of silica-supported perchloric acid as an inexpensive, commercially

Table 3. Diastereoselective preparation of β-acetamido ketones/esters from the reaction of enolizable ketones/esters with aryl aldehydes, acetyl chloride, and acetonitrile (reactant as well as solvent) using $HClO\text{-}SiO_2$ as catalyst under reflux conditions

				Products[b]	
Entry	β-acetamido ketones/esters	Time (h)	Yield (%)[a]	*Anti* (%)	*Syn* (%)
1	$R^1 = Me$, $R^2 = CO_2$ Me, X = H	2.5	89	68	32
2	$R^1 = Me$, $R^2 = CO_2$ Me, X = 4-Cl	2.5	93	70	30
3	$R^1 = Me$, $R^2 = CO_2$ Me, X = 2,4-Dichloro	2.5	90	77	23
4	$R^1 = Me$, $R^2 = CO_2$ Me, X = 4-Me	2.5	92	73	27
5	$R^1 = Me$, $R^2 = CO_2$ Me, X = 2-NO_2	2.5	86	82	18
6	$R^1 = Me$, $R^2 = CO_2$ Et, X = H	3.0	91	76	24
7	$R^1 = Me$, $R^2 = CO_2$ Et, X = 4-Cl	3.0	92	72	28
8	$R^1 = Ph$, $R^2 = Me$, X = H	3.5	85	57	43
9	$R^1 = Ph$, $R^2 = Me$, X = Cl	3.5	91	65	35
10	$R^1 = Ph$, $R^2 = Me$, X = 2,4-Dichloro	3.5	88	60	40

[a]Yields are reported after aqueous workup.

[b]Ratio obtained from ^1H NMR of the crude reaction mixture. All *syn* and *anti* diastereomers have been reported previously in the literature, thus we compared ^1H NMR spectra with authentic samples.[6–8,23]

available, and noncorrosive catalyst for the synthesis of β-amido ketones/esters in high to excellent yields. The simple experimental procedure combined with the easy workup are the strong features of the presented method.

EXPERIMENTAL

All reagents were purchased from Merck and Aldrich and used without further purification. All yields refer to isolated products after purification. Silica-supported perchloric acid was prepared according to the reported procedure.[29] Products were characterized by comparison with authentic samples and by spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR spectra). The NMR spectra were recorded on a Bruker Avance DEX 500- and 300-MHz instrument. The spectra were measured in $CDCl_3$ (and DMSO-d_6) relative to TMS (0.00 ppm). Elemental analyses for C, H, and N were performed using a Heraeus CHN–O–Rapid analyzer. IR spectra were recorded on a Jasco Fourier transform infrared spectroscopy (FT-IR) 460 Plus spectrophotometer. Mass spectra were recorded on a Agilent Technologies 5973 network mass selective detector (MSD) operating at an ionization potential of 70 eV. Melting points were determined in open capillaries with a Buchi 510. Thin-layer chromatography (TLC) was performed on silica-gel PolyGram SIL G/UV 254 plates.

Typical Experimental Procedure for the One-Pot Preparation of N-(3-Oxo-1,3-diphenylpropyl) Acetamide (Table 2, Entry 1)

A solution of the benzaldehyde (1 mmol), acetophenone (1 mmol), acetyl chloride (0.5 mL), and acetonitrile in the presence of silica-supported perchloric acid (0.1 g, 5 mol%) was heated at 80 °C under reflux conditions. The reaction mixture was stirred for the appropriate time (Table 2). The progress of the reaction was followed by TLC. After completion of the reaction, the reaction mixture was filtered, and the heterogeneous catalyst was separated. Then, the residue solution was poured into 50 mL of ice water. The solid was separated and dissolved in dichloromethane (5 mL). Silica gel (2 g) was added to the solution. Evaporation of the solvent afforded a presorbed material, which was purified by column chromatography [petroleum ether (60–80 °C)/ethyl acetate (8/2)]. Solvent was evaporated under reduced pressure to give the desired pure *N*-(1,3-diphenyl-3-oxo-propyl) acetamide in 89% yield. White crystals (Table 2, entry 1): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.03$ (s, 3H), 3.45 (dd, $J = 6.0$ and 16.9 Hz, 1H), 3.77 (dd, $J = 5.2$ and 16.9 Hz, 1H), 5.58 (dd, $J = 5.6$ and

13.1 Hz, 1H), 6.90 (d, $J = 6.3$ Hz, 1H), 7.24–7.60 (m, 8H), 7.91 (d, $J = 7.5$ Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.5$, 43.3, 50.0, 126.6, 127.5, 128.2, 128.7, 128.8, 133.6, 136.7, 141.6, 169.6, 199.3 ppm; IR (KBr, cm^{-1}): 3286, 3091, 1693, 1650, 1556, 1273, 1066, 753, 691.

The desired pure products were characterized by comparison of their physical data with those of known β-amido carbonyl compound.[6–25]

The Spectral Data of Some Representative β-Amido Ketones/Esters

N-[1-(2,3-Dimethoxyphenyl)-3-oxo-3-phenylpropyl] Acetamide (Table 2, Entry 15)

^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.99$ (s, 3H), 3.40 (dd, $J = 6.0$ and 15.7 Hz, 1H), 3.55 (dd, $J = 6.6$ and 15.7 Hz, 1H), 3.85 (s, 3H), 3.97 (s, 3H), 5.73 (dd, $J = 6.4$ and 14.3 Hz, 1H), 6.85 (m, 3H), 6.98 (t, $J = 8.0$ Hz, 1H), 7.43 (t, $J = 7.7$ Hz, 2H), 7.54 (t, $J = 7.4$ Hz, 1H), 7.95 (d, $J = 7.6$ Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 23.4$, 43.7, 47.1, 55.7, 60.7, 111.7, 119.5, 124.1, 128.3, 128.6, 133.4, 134.5, 136.5, 146.2, 152.6, 169.2, 198.8 ppm; IR (KBr, cm^{-1}): 3257, 3069, 2937, 1685, 1639, 1560, 1480, 1449, 1372, 1282, 1220, 1084, 1052, 1003, 756, 690; mass [m/z (%)]: 327.2 (M^+, 10.30), 284.3 (100), 237.2 (14.91), 208.2 (21.80), 180.2 (20.96), 166.2 (73.63), 105.2 (59.40), 77.2 (31.39), 51.2 (5.36), 43.2 (1.63). Found: C, 69.55; H, 6.40; N, 4.35. $C_{19}H_{21}NO_4$ requires C, 69.71; H, 6.47; N, 4.28%.

N-[1-(2,3-Dimethoxyphenyl)-3-oxo-3-(4-methylphenyl)propyl] Acetamide (Table 2, Entry 16)

^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.99$ (s, 3H), 2.38 (s, 3H), 3.42 (dd, $J = 6.4$ and 15.6 Hz, 1H), 3.51 (dd, $J = 6.2$ and 15.6 Hz, 1H), 3.72 (s, 3H), 3.84 (s, 3H), 5.68 (dd, $J = 6.4$ and 14.8 Hz, 1H), 6.72 (dd, $J = 2.8$ and 8.8 Hz, 1H), 6.78 (d, $J = 8.8$ Hz, 1H), 6.87–6.86 (m, 2H), 7.22 (d, $J = 7.9$ Hz, 2H), 7.82 (d, $J = 8.0$ Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.6$, 23.4, 42.9, 47.9, 55.7, 55.8, 111.7, 112.7, 114.9, 128.3, 129.3, 129.7, 134.3, 144.0, 150.7, 153.6, 169.1, 198.2 ppm; IR (KBr, cm^{-1}): 3301, 3081, 2941, 1686, 1651, 1610, 1552, 1503, 1466, 1372, 1284, 1225, 1047, 807, 714; Mass [m/z (%)]: 341.2 (M^+, 19), 299.2 (21), 298.2 (100), 251.2 (23), 208.1 (20), 180.2 (30), 166.1 (70), 151.1 (15), 136.1 (13), 119.1 (65), 105.1 (14), 91.2 (27), 77.2 (12), 43.2 (20). Found: C, 70.32; H, 6.71; N, 4.07. $C_{20}H_{23}NO_4$ requires C, 70.36; H, 6.79; N, 4.10%.

N-[1-(4-Acethoxy-2-methoxyphenyl)-3-oxo-3-(4-methylphenyl)propyl] Acetamide (Table 2, Entry 18)

^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.98$ (s, 3H), 2.27 (s, 3H), 2.39 (s, 3H), 3.38 (dd, $J = 5.7$ and 16.6 Hz, 1H), 3.65 (dd, $J = 5.0$ and 16.7 Hz, 1H), 3.77 (s, 3H), 5.51 (d, $J = 6.2$ Hz, 1H), 6.82 (d, $J = 7.7$ Hz, 1H), 6.87 (d, $J = 8.1$ Hz, 1H), 6.93 (d, $J = 8.1$ Hz, 1H), 6.96 (s, 1H), 7.23 (d, $J = 7.5$ Hz, 2H), 7.79 (d, $J = 7.4$ Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 20.6$, 21.6, 23.3, 43.0, 49.9,55.9, 111.5, 118.4, 122.7, 128.2, 129.3, 134.1, 140.1, 144.4, 151.0, 169.0, 169.5, 191.0, 198.0 ppm; IR (KBr, cm^{-1}): 3261, 3252, 3076, 2946, 1768, 1679, 1649, 1608, 1547, 1512, 1466, 1422, 1372, 1265, 1200, 1126, 1035, 1013, 845, 789, 674, 603; mass [m/z (%)]: 369.3 (M^+, 6.84), 326.2 (24.66), 268.2 (8.89), 208.1 (11.55), 206.1 (12.59), 194.1 (13.90), 173.1 (22.11), 171.1 (62.91), 153.2 (21.96), 152.2 (100), 151.2 (71.54), 119.2 (41.58), 109.2 (9.12), 91.2 (19.81), 77.2 (7.10), 65.2 (9.95), 51.2 (8.80), 43.2 (35.97). Found: C, 68.19; H, 6.12; N, 3.73. $C_{21}H_{23}NO_5$ requires C, 68.28; H, 6.28; N, 3.79%.

N-[1-(2,5-Dimethoxyphenyl)-3-oxo-3-phenylpropyl] Acetamide (Table 2, Entry 19)

^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.00$ (s, 3H), 3.46 (dd, $J = 6.6$ and 15.8 Hz, 1H), 3.56 (dd, $J = 6.1$ and 15.7 Hz, 1H), 3.73 (s, 3H), 3.85 (s, 3H), 5.69 (dd, $J = 2.3$ and 6.5 Hz, 1H), 6.73 (dd, $J = 3.0$ and 8.9 Hz, 1H), 6.79 (d, $J = 8.9$ Hz, 1H), 6.83 (d, $J = 8.4$ Hz, 1H), 6.87 (d, $J = 3.0$ Hz, 1H), 7.43 (t, $J = 7.6$ Hz, 2H), 7.55 (t, $J = 7.3$ Hz, 1H), 7.92 (d, $J = 7.4$ Hz, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 23.5$, 43.0, 48.0, 55.7, 55.8, 111.7, 112.8, 115.0, 128.2, 128.6, 129.5, 133.2, 136.8, 150.8, 153.6, 169.0, 198.6 ppm; IR (KBr, cm^{-1}): 3296, 3086, 1689, 1649, 1558, 1505, 1774, 1296, 1226, 1047, 807, 754; mass [m/z (%)]: 327.2 (M^+, 17), 285.2 (19), 284.2 (100), 237.1 (16), 208.1 (17), 180.2 (27), 166.1 (62), 151.1 (13), 136.1 (12), 105.1 (45), 77.2 (23), 43.2 (14). Found: C, 69.56; H, 6.39; N, 4.34. $C_{19}H_{21}NO_4$ requires C, 69.71; H, 6.47; N, 4.28%.

N-[1-(4-Acethoxyphenyl)-3-oxo-3-phenylpropyl] Acetamide (Table 2, Entry 21)

^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.01$ (s, 3H), 2.28 (s, 3H), 3.44 (dd, $J = 6.1$ and 17.0 Hz, 1H), 3.73 (dd, $J = 5.2$ and 17.0 Hz, 1H), 5.56 (dd, $J = 5.8$ and 13.6 Hz, 1H), 6.73 (d, $J = 8.0$ Hz, 1H), 7.03 (d, $J = 8.5$ Hz, 2H), 7.35 (d, $J = 8.5$ Hz, 2H), 7.46 (t, $J = 7.7$ Hz, 2H), 7.58 (t, $J = 7.4$ Hz,

1H), 7.91 (d, $J = 7.7$ Hz, 2H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 20.8$, 22.6, 44.5, 48.4, 121.5, 127.7, 128.0, 128.7, 133.2, 136.5, 140.5, 149.2, 168.3, 169.2, 197.0 ppm; IR (KBr, cm^{-1}): 3262, 3085, 2928, 1762, 1699, 1652, 1651, 1509, 1448, 1411, 1365, 1294, 1216, 1200, 911, 759, 691; Mass [m/z (%)]: 352.2 (M^+, 8), 326.2 (2), 282.2 (100), 240.2 (41), 242.2 (19), 178.2 (20), 167.1 (26), 149.1 (62), 136.2 (37), 122.2 (55), 105.2 (86), 77.2 (40), 57.2 (16), 43.2 (41). Found: C, 70.08; H, 5.78; N, 4.24. $C_{19}H_{19}NO_4$ requires C, 70.14; H, 5.89; N, 4.31%.

N-[1-(3-Nitrophenyl)-3-oxo-3-(4-methylphenyl)propyl] Acetamide (Table 2, Entry 22)

^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.97$ (s, 3H), 2.36 (s, 3H), 3.43 (dd, $J = 5.5$ and 17.4 Hz, 1H), 3.61 (dd, $J = 8.3$ and 17.4 Hz, 1H), 5.45 (dd, $J = 7.6$ and 13.4 Hz, 1H), 7.31 (d, $J = 7.9$ Hz, 2H), 7.62 (t, $J = 7.9$ Hz, 1H), 7.86–7.75 (m, 3H), 8.08 (d, $J = 8.0$ Hz, 1H), 8.22 (s, 1H), 8.49 (d, $J = 7.5$ Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 20.7$, 22.6, 44.0, 48.5, 121.3, 121.8, 128.1, 129.1, 129.7, 133.7, 133.9, 143.7, 145.6, 147.8, 168.6, 196.1 ppm; IR (KBr, cm^{-1}): 3301, 3069, 1680, 1645, 1606, 1531, 1352, 1202, 1180, 810, 741, 696; mass [m/z (%)]: 326.3 (M^+, 0.8), 283.2 (20), 267.2 (12), 189.2 (24), 190.2 (17), 165.2 (38), 151.2 (33), 134.2 (13), 119.2 (100), 105.2 (12), 91.2 (43), 77.2 (6), 65.2 (14), 43.2 (26). Found: C, 66.23; H, 5.56; N, 8.51. $C_{18}H_{18}N_2O_4$ requires C, 66.25; H, 5.56; N, 8.58%.

(R)-Methyl 2-((S)-Acetamido(phenyl)methyl)-3-oxobutanoate (Table 3, Entry 1)

Mixture of diastereomers; data for the major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.97$ (s, 3H), 2.11 (s, 3H), 3.71 (s, 3H), 4.07 (d, $J = 5.5$ Hz, 1H), 5.72 (dd, $J = 5.5$ and 9.0 Hz, 1H), 6.91 (d, $J = 8.1$ Hz, 1H), 7.22–7.30 (m, 5H).

(R)-Ethyl 2-((S)-Acetamido(4-chlorophenyl)methyl)-3-oxobutanoate (Table 3, Entry 7)

Mixture of diastereomers; data for the major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.25$ (t, $J = 6.9$, 3H), 2.03 (s, 3H), 2.16 (s, 3H), 4.01 (d, $J = 5.7$ Hz, 1H), 4.12 (q, $J = 7.1$, 2H), 5.70 (dd, $J = 5.7$ and 8.9 Hz, 1H), 6.95 (d, $J = 8.9$ Hz, 1H), 7.20–7.35 (m, 4H).

N-((1S,2R)-1-(4-Chlorophenyl)-2-methyl-3-oxo-3-phenylpropyl) acetamide (Table 3, Entry 9)

Mixture of diastereomers; data for the major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.34$ (d, $J = 7.1$ Hz, 3H), 2.08 (s, 3H), 4.00–4.07 (m, 1H), 5.33 (dd, $J = 4.2$ and 8.6 Hz, 1H), 7.19 (s, 4H), 7.38–7.43 (m, 2H), 7.53 (t, $J = 7.1$ Hz, 1H), 7.65 (brd, $J = 8.5$ Hz, 1H), 7.76 (d, $J = 7.9$ Hz, 2H).

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