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Efficient Synthesis of β-Acetamido Ketones by Silver(I) Triflate-Catalyzed Multicomponent Reactions

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An efficient one-pot synthesis of β-acetamido ketones was accomplished by AgOTf-catalyzed multicomponent reactions of substituted acetophenones with aromatic aldehydes and acid chloride in acetonitrile in high yields. The methods offer several significant advantages of easy handling, mild reaction conditions, and use of effective and non-toxic catalyst.

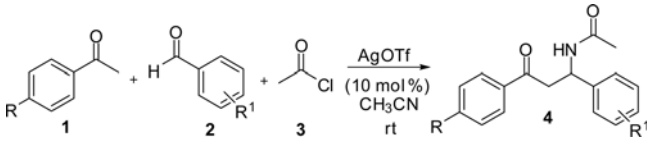
Key Words : Silver triflate, Multicomponent reaction, β-Acetamido ketone

Introduction

Multicomponent reactions (MCRs) have emerged as an efficient and powerful tool for the construction of complex molecules in organic synthesis.[1] In particular, MCRs are very useful to generate diverse combinatorial libraries for drug discovery.[2]

The synthesis of β-acetamido ketones using MCR protocol has gained considerable attention in the synthesis of a variety of molecules as valuable building blocks for the preparation of 1,3-amino acids,[3] 1,3-amino alcohols,[4] as well as a structural unit of natural peptide antibiotics nikkomycins or neopolyoxines.[5] Several methods for the synthesis of acetamido ketones have been reported through Michael addition to α,β-unsaturated ketones,[6] acylation of β-aminoketones,[7] photoisomerization of phthalimides,[8] and Darkin-West reaction.[9] Among these, the known effective method for the synthesis of acetamido ketones is Dankin-West reaction, which involves the condensation of α-amino acids with acetic anhydride in the presence of base *via* an azalacetone intermediate.[10] Recently, another new procedure for the formation of β-acetamido ketones through the MCRs of acetophenone, arylaldehyde, and acetyl chloride in acetonitrile has been developed.[11-21] This reaction has been extensively studied with the use of a variety of catalysts and reagents such as $CoCl_2$,[11] $FeCl_3$,[12] $CeCl_3{\cdot}7H_2O$,[13] $Sc(OTf)_3$,[14] $ZrOCl_2{\cdot}8H_2O$,[15] $NaHSO_4{\cdot}H_2O$,[16] $Fe(HSO_4)_3$,[17] silica supported sulfuric acid,[18] $H_3PW_{12}O_{40}$,[19] Montmorillonite K-10 clay,[20] and Amberlyst-15.[21]

Although numerous methods for the synthesis of β-acetamido ketones have been reported,[11-21] there is still demand for simpler, less toxic, more effective, and milder catalysts. Our interest in developing a mild and efficient synthetic method that provides a variety of β-acetamido ketones has led us to looking into more convenient and safely usable catalysts. Among these, we think silver (I) triflate is a viable alternative, and may be a promising catalyst for the synthesis of β-acetamido ketones due to its easy availability, sustainability, non-toxicity, and environmentally friendly properties.[22] We report herein an silver (I) triflate-catalyzed one-pot multicomponent reaction of acetophenones, arylaldehydes, and acetyl chloride in acetonitrile for the synthesis of biologically interesting β-acetamido ketones (Scheme 1).

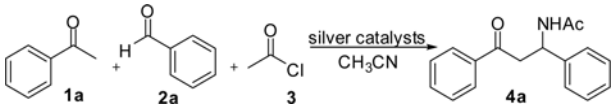


Scheme 1

Results and Discussion

The reaction of acetophenone (**1a**, 1.0 mmol) with benzaldehyde (**2a**, 1.1 mmol) and acetyl chloride (**3**, 2.0 mmol) in acetonitrile (5 mL) was first examined in the presence of several silver catalysts (Table 1). With AgO and Ag_2O for 12 h at room temperature, the desired product **4a** was produced in 82 and 85% yield, respectively. With Ag_2CO_3 for 6 h, compound **4a** was also isolated in 86% yield, whereas that with $AgNO_3$ (20 mol %) or AgOAc (10 mol %) for 12 h was produced in only 35% and 40% yield, respectively. Importantly, the best yield (91%) was obtained in the presence of 10

Table 1. Reaction of acetophenone (**1a**), benzaldehyde (**2a**), and acetyl chloride (**3**) in acetonitrile under several silver catalysts

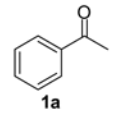
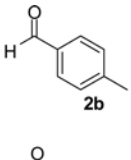
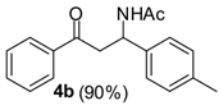
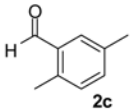
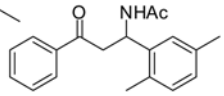
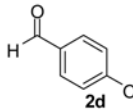
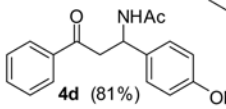
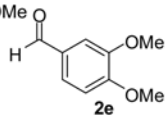
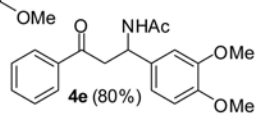
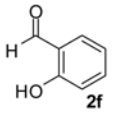
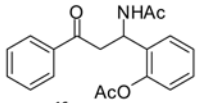
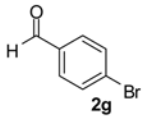
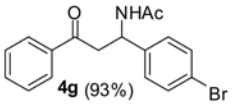
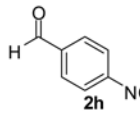
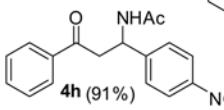
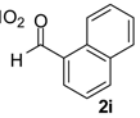
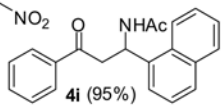
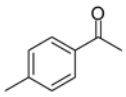
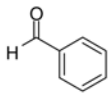
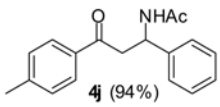
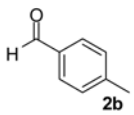
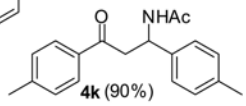
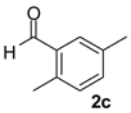
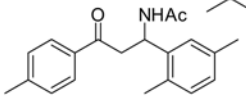
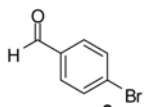
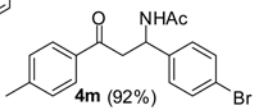
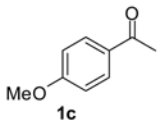
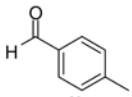
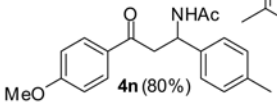
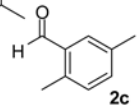
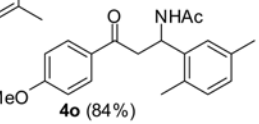
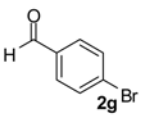
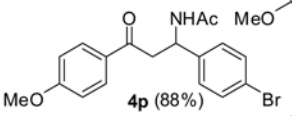
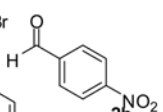
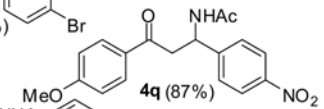
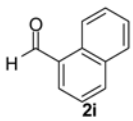
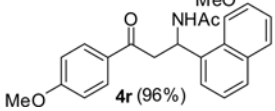


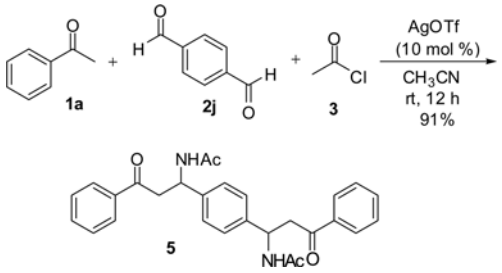
Entry	Catalyst	Condition	Yield
1	AgO (20 mol %)	rt, 12 h	82
2	Ag_2O (20 mol %)	rt, 12 h	85
3	Ag_2CO_3 (20 mol %)	rt, 6 h	86
4	$AgNO_3$ (20 mol %)	rt, 12 h	35
5	AgOAc (10 mol %)	rt, 12 h	40
6	AgOTf (10 mol %)	rt, 6 h	91
7	AgOTf (5 mol %)	rt, 6 h	85

mol % of AgOTf. The use of 5 mol % of AgOTf gave product **4a** in 85% yield. The product **4a** was determined by analysis of spectral data and compared directly with the reported data. Recently, it has been suggested that metal triflates may be catalytically active through the formation of TfOH, although the pathway of TfOH from metal triflates was not addressed.[23] In order to check a catalytic activity of TsOH, the use of 5 mol % of TfOH at room temperature for 12 h provided the desired product **4a** in 45% yield. We found that AgOTf is more efficient than TfOH for the formation of **4a**.

In order to establish the generality of this methodology, additional reactions of several substituted acetophenones with arylaldehydes and acetyl chloride in acetonitrile were carried out in the presence of 10 mol % of AgOTf. The results are summarized in Table 2. Reactions of acetophenone (**1a**) with arylaldehydes **2b-2e** bearing electron-donating groups at ortho, meta or para position on the benzene ring at room temperature for 1-6 h produced **4b-4e** in 80-90% yield (entries 1-4). Interestingly, with 2-hydroxybezaldehyde (**2f**), β-acetamido ketone **4f** with an acetyloxy group on the aromatic benzene ring was observed in 65%

Table 2. Additional AgOTf-catalyzed one-pot multicomponent reactions for the synthesis of a variety of β-acetamido ketones

Entry	Acetophenones	Arylaldehydes	Time (h)	Products (%)
1	 **1a**	 **2b**	6	 **4b** (90%)
2		 **2c**	6	 **4c** (88%)
3		 **2d**	2	 **4d** (81%)
4		 **2e**	1	 **4e** (80%)
5		 **2f**	6	 **4f** (65%)
6		 **2g**	6	 **4g** (93%)
7		 **2h**	6	 **4h** (91%)
8		 **2i**	12	 **4i** (95%)
9	 **1b**	 **2a**	6	 **4j** (94%)
10		 **2b**	6	 **4k** (90%)
11		 **2c**	6	 **4l**(95%)
12		 **2g**	6	 **4m** (92%)
13	 **1c**	 **2b**	6	 **4n** (80%)
14		 **2c**	6	 **4o** (84%)
15		 **2g** Br	6	 **4p** (88%)
16		 **2h** NO_2	6	 **4q** (87%)
17		 **2i**	12	 **4r** (96%)

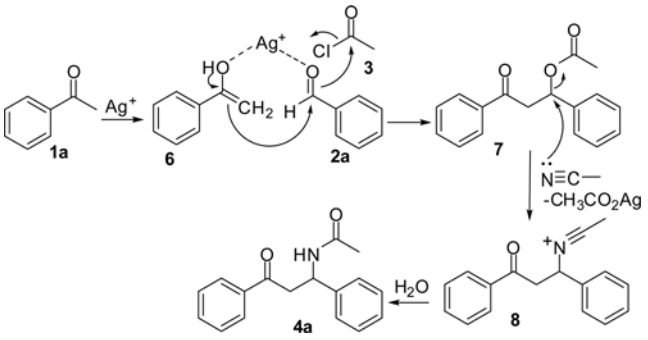


Scheme 2

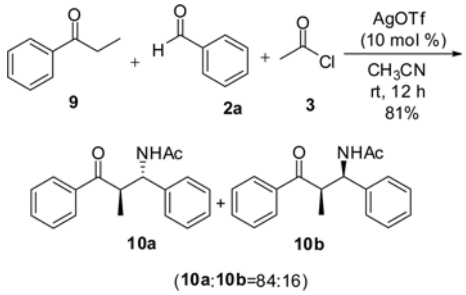
yield (entry 5). The structure of **4f** was identified by ^{1}H NMR analysis and by comparison with the reported data.[15] ^{1}H NMR spectrum of **4f** showed a characteristic methyl peak of an acetyloxy group on the benzene ring at δ 2.34 as a singlet. With arylaldehydes **2g-2h** with electron-withdrawing groups on the benzene ring, the products **4g-4h** were produced in 93 and 91% yield, respectively (entries 6-7). With 1-naphthaldehyde, product **4i** was also produced in 95% yield (entry 8). In this case, the reaction time was longer (12 h). Treatment of 4-methylacetophenone (**1b**) with benzaldehyde or arylaldehydes bearing electron-donating groups or electron-withdrawing groups on the benzene ring in acetonitrile for 6 h provided the desired products **4j-4m** in 90-95% yield (entries 9-12). Similarly, reactions of 4-methoxyacetophenone (**1c**) with arylaldehydes bearing electron-donating groups or electron-withdrawing groups on the benzene ring in acetonitrile for 6 h gave β-acetamido ketones **4n-4q** in 80-88% yield (entries 13-16). Reaction of **1c** with 1-naphthaldehyde and acetyl chloride in acetonitrile afforded product **4r** in 96% yield (entry 17). These reactions provided a rapid route to the synthesis of a variety of β-acetamido ketones in good yield.

To expand the utility of this methodology, another multicomponent reaction of acetophenone (**1a**) with terephthaldehyde (**2j**) and acetyl chloride (**3**) in acetonitrile under 10 mol % of AgOTf at room temperature was carried out (Scheme 2). In this reaction, the desired symmetric product **5** was produced in 91% yield. The product **5** was determined by analysis of spectral data and compared directly with the reported data.[24]

The formation of **4a** can be also explained by the plausible mechanism as shown in Scheme 3. For understanding the



Scheme 3. A plausible mechanism for the formation of **4a** in the presence of AgOTf.



Scheme 4

mechanism and the role of acid chloride in the reaction, we examined further reactions without acid chloride. Importantly, without any acid chloride, no products were isolated at room temperature or at reflux for 12 h. No products under such a reaction condition imply the pivotal role of acetyl chloride in this multicomponent reaction. Thus, acetophenone (**1a**) in the presence of AgOTf through Lewis acid-catalyzed enol formation first gives to an enol **6**. Subsequent attack by **6** to benzaldehyde (**2a**) and acid chloride (**3**) may generate a β-acyloxy ketone **7**. The nucleophilic attack by nitrogen on an acetonitrile to **7** may provide a stable cation intermediate **8**, which on further reaction with water during the work-up may lead to the formation of final product **4a**.

Finally, to investigate diastereoselectivity of this methodology, we have tried other multicomponent reaction. Reaction of propiophenone (**9**) with benzaldehyde (**2a**) and acetyl chloride (**3**) in acetonitrile in the presence of 10 mol % of AgOTf at room temperature for 12 h, two diastereoisomers **10a** and **10b** were produced in 81% yield with a ratio of 84:16 (Scheme 4). In this case, the *anti*-diastereoisomer **10a** was isolated as a major component. This result did not show any increase of diastereoselectivity by comparing with reported work.[20]

In summary, we have developed an efficient and general synthesis of a variety of β-acetamido ketones by AgOTf-catalyzed one-pot multicomponent reaction of substituted acetophenones with aromatic aldehydes and acid chloride in acetonitrile. The advantages of these methodologies are easy handling, mild reaction conditions, and use of an effective and non-toxic catalyst. These AgOTf-catalyzed reactions provided the desired β-acetamido ketones in high yield.

Experimental Section

All the experiments were carried out under nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian VNS (300 and 75 MHz, respectively) spectrometer in $CDCl_3$ using δ = 7.24 and 77.0 ppm as the solvent chemical shift. The IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer. The HRMS were carried out at the Korea Basic Science Institute.

General Procedure for the Synthesis of Acetamido

Keones 4a-4r. To a solution of **1a**, **1b** or **1c** (1.0 mmol) with arylaldehyde (1.1 mmol) and acetyl chloride (0.15 mL, 2.0 mmol) in acetonitrile (5 mL) was added AgOTf (25 mg, 10 mol %) and the reaction mixture was stirred at room temperature for 1-12 h. After completion of reaction as indicated by TLC, water (20 mL) was added. The mixture was extracted with ethyl acetate (15 mL × 3) and extract was washed with saturated sodium bicarbonate (25 mL). The combined organic layers were dried over anhydrous magnesium sulfate to give residue which was purified by column chromatography on silica gel using hexane/EtOAc (1:2) to give product.

***N*-(3-Oxo-1,3-diphenylpropyl)acetamide (4a):**[12] A white solid. Yield (243 mg, 91%). mp 103-105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (1H, d, *J* = 7.8 Hz), 7.47 (1H, m), 7.35 (2H, dd, *J* = 8.4, 7.2 Hz), 7.28-7.11 (5H, m), 6.73 (1H, d, *J* = 7.5 Hz, NH), 5.51-5.44 (1H, m), 3.65 (1H, dd, *J* = 16.8, 5.1 Hz), 3.34 (1H, dd, *J* = 16.8, 6.0 Hz), 1.91 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 169.7, 141.3, 136.2, 132.9, 128.2, 128.2, 128.1, 128.1, 127.7, 127.7, 126.9, 126.3, 126.3, 49.4, 43.7, 22.5; IR (KBr) 3285, 3083, 1649, 1549, 1202, 989, 750, 696 cm^{-1}.

***N*-(3-Oxo-3-phenyl-1-*p*-tolylpropyl)acetamide (4b):**[12] Off-white solid. Yield (253 mg, 90%). mp 170 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (1H, d, *J* = 7.8 Hz), 7.54 (1H, dd, *J* = 7.3, 7.2 Hz), 7.42 (2H, dd, *J* = 8.4, 6.9 Hz), 7.21 (2H, dd, *J* = 9.3, 8.1 Hz), 7.09 (2H, d, *J* = 7.5 Hz), 6.59 (1H, d, *J* = 7.5 Hz, NH), 5.47-5.53 (1H, m), 3.72 (1H, dd, *J* = 17.1, 4.8 Hz), 3.40 (1H, dd, *J* = 16.8, 6.3 Hz), 2.27 (3H, s), 1.99 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 169.6, 138.1, 137.1, 136.7, 133.5, 129.4, 129.4, 128.7, 128.7, 128.2, 128.2, 126.5, 126.5, 49.8, 43.5, 23.4, 21.1; IR (KBr) 3288, 3078, 1651, 1545, 1207, 990, 751 cm^{-1}.

***N*-{1-(2,5-Dimethylphenyl)-3-oxo-3-phenylpropyl}acetamide (4c):** Off-white solid. Yield (260 mg, 88%). mp 103-105 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 6.9 Hz), 7.55-7.50 (1H, m), 7.44-7.38 (2H, m), 7.05-7.00 (2H, m), 6.39 (1H, d, *J* = 7.8 Hz), 6.26 (1H, d, *J* = 6.0 Hz, NH), 5.70-5.63 (1H, m), 3.62 (1H, dd, *J* = 16.5, 5.7 Hz), 3.42 (1H, dd, *J* = 16.2, 7.2 Hz), 2.34 (3H, s), 2.24 (3H, s), 1.95 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.9, 169.7, 139.2, 136.6, 135.4, 133.1, 132.4, 130.5, 128.5, 128.0, 126.2, 46.4, 43.5, 22.8, 21.0, 18.8; IR (KBr) 3290, 3068, 2925, 1683, 1646, 1549, 1372, 1298, 1209, 995, 758, 694, 618 cm^{-1}; HRMS (EI) *m/z* (M^+) calcd for $C_{19}H_{21}NO_2$: 295.1572. Found 295.1570.

***N*-{1-(4-Methoxyphenyl)-3-oxo-3-phenylpropyl}acetamide (4d):**[12] Off-white solid. Yield (240 mg, 81%). mp 110-111 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (2H, d, *J* = 7.5 Hz), 7.49 (1H, dd, *J* = 7.5, 7.2 Hz), 7.37 (2H, dd, *J* = 7.5, 7.2 Hz), 7.18 (2H, d, *J* = 8.7 Hz), 6.75 (2H, d, *J* = 8.4 Hz), 6.62 (1H, d, *J* = 7.7 Hz, NH), 5.47- 5.41 (1H, m), 3.68-3.63 (4H, ds, *J* = 5.1 Hz), 3.33 (1H, dd, *J* = 16.8, 6.3 Hz), 1.93 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.8, 169.8, 158.9, 136.7, 133.6, 133.1, 128.8, 128.8, 128.2, 128.2, 127.9, 127.9, 114.1, 114.1, 55.3, 49.7, 43.4, 23.4; IR (KBr) 3301, 3076, 1647, 1538, 1234, 1032, 745 cm^{-1}.

***N*-{1-(3,4-Dimethoxyphenyl)-3-oxo-3-phenylpropyl}-acetamide (4e):**[12] Off-white solid. Yield (261 mg, 80%). mp 118-119 °C ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (2H, d, *J* = 7.5 Hz), 7.54 (1H, dd, *J* = 7.5, 7.2 Hz), 7.42 (2H, t, *J* = 7.5 Hz), 6.83 (2H, s), 6.76-6.73 (1H, m), 6.62 (1H, d, *J* = 7.8 Hz, NH), 5.35-5.51 (1H, m), 3.80 (6H, s), 3.71 (1H, dd, *J* = 17.1, 5.1 Hz), 3.38 (1H, dd, *J* = 16.8, 6.6 Hz), 1.99 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4, 169.7, 148.9, 148.2, 136.6, 133.8, 133.4, 128.6, 128.6, 128.1, 128.1, 118.6, 111.1, 110.4, 55.8, 55.8, 49.8, 43.6, 23.1; IR (KBr) 3247, 3076, 1681, 1637, 1519, 1253, 1026, 751 cm^{-1}.

***N*-{1-(1-Acyloxyphenyl)-3-oxo-3-phenylpropyl}acetamide (4f):** Yellow solid. Yield (211 mg, 65%). mp 56-58 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (2H, d, *J* = 8.1 Hz), 7.59-7.54 (1H, m), 7.47-7.38 (3H, m), 7.31-7.26 (1H, m), 7.19 (1H, t, *J* = 7.5 Hz), 7.07 (1H, d, *J* = 7.8 Hz), 6.46 (1H, d, *J* = 7.5 Hz, NH), 5.75-5.68 (1H, m), 3.64 (1H, dd, *J* = 16.2, 5.4 Hz), 3.44 (1H, dd, *J* = 16.5, 6.9 Hz), 2.34 (3H, s), 1.96 (3H, s), ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 169.9, 169.4, 148.3, 136.6, 133.5, 132.9, 128.8, 128.8, 128.7, 128.2, 128.2, 127.5, 126.3, 123.0, 44.8, 42.7, 23.2, 21.0; IR (KBr) 3281, 3065, 2933, 1762, 1656, 1545, 1448, 1369, 1202, 1003, 755, 692 cm^{-1}; HRMS (EI) *m/z* (M^+) calcd for $C_{19}H_{19}NO_4$: 325.1314. Found: 325.1314.

***N*-{1-(4-Bromophenyl)-3-oxo-3-phenylpropyl}acetamide (4g):**[12] White solid. Yield (321 mg, 93%). mp 148-150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (1H, d, *J* = 8.4 Hz), 7.58-7.52 (1H, m), 7.45-7.37 (4H, m), 7.18 (2H, d, *J* = 7.5 Hz), 6.82 (1H, d, *J* = 7.8 Hz, NH), 5.51-5.45 (m, 1H), 3.70 (1H, dd, *J* = 17.1, 5.1 Hz), 3.38 (1H, dd, *J* = 17.4, 6.0 Hz), 1.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4, 169.7, 140.3, 136.5, 133.8, 131.8, 131.8, 128.9, 128.9, 128.4, 128.4, 128.2, 128.2, 121.3, 49.4, 43.1, 23.5; IR (KBr) 3287, 3077, 1650, 1546, 1362, 1291, 1001, 752 cm^{-1}.

***N*-{1-(4-Nitrophenyl)-3-oxo-3-phenylpropyl}acetamide (4h):**[12] Off-white solid. Yield (284 mg, 91%). mp 153 °C ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (1H, d, *J* = 8.7 Hz), 7.85 (2H, d, *J* = 8.4 Hz), 7.59-7.53 (1H, m), 7.50-7.40 (4H, m), 7.01 (1H, s, NH), 5.66-5.60 (1H, m), 3.77 (1H, dd, *J* = 17.4, 4.8 Hz), 3.46 (1H, dd, *J* = 17.4, 5.4 Hz), 2.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.3, 170.2, 149.2, 146.8, 136.1, 133.8, 128.7, 128.7, 128.0, 128.0, 127.5, 127.5, 123.6, 123.6, 49.1, 43.2, 22.9; IR (KBr) 3303, 3068, 1651, 1525, 1353, 1210, 991, 845, 693 cm^{-1}.

***N*-{1-(Naphthalen-1-yl)-3-oxo-3-phenylpropyl}acetamide (4i):** Off-white solid. Yield (301 mg, 95%). mp 170-172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (1H, d, *J* = 8.4 Hz), 7.84 (3H, dd, *J* = 8.1, 6.9 Hz), 7.73 (1H, d, *J* = 8.1 Hz), 7.56-7.46 (4H, m), 7.40-7.33 (3H, m), 6.58 (1H, d, *J* = 7.5 Hz, NH), 6.38-6.32 (1H, m), 3.82 (1H, dd, *J* = 16.8, 5.1 Hz), 3.62 (1H, dd, *J* = 16.5, 6.3 Hz), 1.98 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$ and DMSO-d_6) δ 197.1, 169.0, 136.8, 136.3, 133.4, 132.8, 130.4, 128.3, 128.2, 128.2, 127.7, 127.7, 127.6, 126.0, 125.3, 124.8, 122.9, 122.8, 45.3, 43.0, 22.5; IR (KBr) 3290, 3061, 1681, 1651, 1547, 1366, 1276, 995, 779, 690 cm^{-1}; HRMS (EI) *m/z* (M^+) calcd for $C_{21}H_{19}NO_2$: 317.1416. Found: 317.1414.

***N*-{3-Oxo-1-phenyl-3-*p*-tolylpropyl}acetamide (4j):** Off-white solid. Yield (264 mg, 94%). mp 115-116 °C; ^{1}H

NMR (300 MHz, $CDCl_3$) δ 7.72 (2H, d, *J* = 8.1 Hz), 7.14-7.26 (7H, m), 6.78 (1H, d, *J* = 7.2 Hz, NH), 5.51-5.45 (1H, m), 3.63 (1H, dd, *J* = 16.8, 5.9 Hz), 3.32 (dd, *J* = 16.8, 6.0 Hz), 2.32 (3H, s), 1.93 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.6, 170.2, 144.2, 141.0, 133.9, 129.2, 129.2, 128.5, 128.5, 128.2, 128.2, 127.2, 126.5, 126.5, 49.9, 43.5, 23.2, 21.6; IR (KBr) 3274, 3081, 2928, 1681, 1646, 1557, 1407, 1370, 1297, 1181, 994, 810, 703 cm^{-1}; HRMS (EI) *m/z* (M^+) calcd for $C_{18}H_{19}NO_2$: 281.1416. Found: 281.1416.

***N*-{3-Oxo-1,3-di-*p*-tolylpropyl}acetamide (4k):** Off-white solid. Yield (265 mg, 90%). mp 109-110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (2H, d, *J* = 8.4 Hz), 7.24-7.17 (4H, m), 7.08 (2H, d, *J* = 7.8 Hz), 6.63 (1H, d, *J* = 7.2 Hz, NH), 5.51-5.48 (1H, m), 3.68 (1H, dd, *J* = 16.2, 4.5 Hz), 3.37 (1H, dd, *J* = 16.5, 6.0 Hz), 2.38 (3H, s), 2.27 (3H, s), 1.99 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.8, 169.6, 144.1, 138.3, 136.8, 134.2, 129.3, 129.3, 129.2, 129.2, 128.2, 128.2, 126.5, 126.5, 49.7, 43.5, 23.1, 21.6, 20.9; IR (KBr) 3259, 3068, 2925, 1655, 1544, 1421, 1366, 1292, 1190, 995, 814, 724 cm^{-1}; HRMS (EI) *m/z* (M^+) calcd for $C_{19}H_{21}NO_2$: 295.1572. Found: 295.1573.

***N*-{1-(2,5-Dimethylphenyl)-3-oxo-3-*p*-tolylpropyl}acetamide (4l):** White solid. Yield (293 mg, 95%). mp 136-138 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (2H, d, *J* = 8.4 Hz), 7.21 (2H, d, *J* = 7.8 Hz), 7.06-7.00 (2H, m), 6.93 (1H, d, *J* = 7.8 Hz), 6.28 (1H, d, *J* = 6.3 Hz, NH), 5.68-5.62 (1H, m), 3.53 (1H, dd, *J* = 16.2, 5.7 Hz), 3.38 (1H, dd, *J* = 16.2, 6.9 Hz), 3.37 (3H, s), 2.35 (3H, s), 2.24 (3H, s), 1.95 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 169.3, 144.1, 139.2, 135.6, 134.3, 132.7, 130.7, 129.3, 129.3, 128.3, 128.3, 128.2, 126.2, 46.8, 43.2, 23.2, 21.6, 21.1, 18.9; IR (KBr) 3296, 3040, 2922, 1652, 1544, 1437, 1361, 1288, 1217, 994, 805, 750 cm^{-1}; HRMS (EI) *m/z* (M^+) calcd for $C_{20}H_{23}NO_2$: 309.1729. Found: 309.1728.

***N*-{1-(4-Bromophenyl)-3-oxo-3-*p*-tolylpropyl}acetamide (4m):** White solid. Yield (360 mg, 92%). mp 145-146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (2H, d, *J* = 8.1 Hz), 7.39 (2H, d, *J* = 8.7 Hz), 7.16-7.24 (4H, m), 6.82 (1H, d, *J* = 7.5 Hz, NH), 5.45-5.51 (1H, m), 3.67 (1H, dd, *J* = 17.1, 4.8 Hz), 3.35 (1H, dd, *J* = 17.4, 5.7 Hz), 2.38 (3H, s), 2.00 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.0, 169.8, 144.7, 140.4, 134.1, 131.7, 131.7, 129.5, 129.5, 128.4, 128.4, 128.3, 128.3, 121.2, 49.4, 42.9, 23.4, 21.8; IR (KBr) 3272, 3073, 2924, 1645, 1546, 1420, 1371, 1298, 1215, 1089, 999, 817, 745 cm^{-1}; HRMS (EI) *m/z* (M^+) calcd for $C_{18}H_{18}BrNO_2$: 359.0521. Found: 359.0521.

***N*-{3-(4-Methoxyphenyl)-3-oxo-1-*p*-tolylpropyl}acetamide (4n):** Yellow solid. Yield (289 mg, 80%). mp 58-60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (2H, d, *J* = 8.7 Hz), 7.20 (2H, d, *J* = 7.8 Hz), 7.09 (2H, d, *J* = 8.4 Hz), 6.90 (2H, d, *J* = 8.7 Hz), 6.84 (1H, d, *J* = 7.8 Hz, NH), 5.53-5.47 (1H, m), 3.84 (3H, s), 3.66 (1H, dd, *J* = 16.5, 5.4 Hz), 3.33 (1H, dd, *J* = 16.5, 6.3 Hz), 2.28 (3H, s), 1.98 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.7, 169.8, 163.6, 138.4, 136.7, 130.4, 130.4, 129.7, 129.1, 129.1, 126.4, 126.4, 113.7, 113.7, 55.3, 49.8, 43.3, 23.0, 20.9; IR (KBr) 3276, 3063, 2931, 2842, 1671, 1647, 1600, 1550, 1367, 1259, 1173, 1027, 824, 600, 548 cm^{-1}; HRMS (EI) *m/z* (M^+) calcd for $C_{19}H_{21}NO_3$: 311.1521. Found: 311.1519.

***N*-{1-(2,5-Dimethylphenyl)-3-(4-methoxyphenyl)-3-oxopropyl}acetamide (4o):** Off-white solid. Yield (273 mg, 84%). mp 122-123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (2H, d, *J* = 9 Hz), 7.08 (1H, s), 7.00 (1H, d, *J* = 7.8 Hz), 6.92-6.84 (3H, m), 6.64 (1H, d, *J* = 7.2 Hz, NH), 5.69-5.62 (1H, m), 3.81 (3H, s), 3.53 (1H, dd, *J* = 15.9, 6.0 Hz), 3.32 (1H, dd, *J* = 15.9, 6.9 Hz), 2.34 (3H, s), 2.23 (3H, s), 1.90 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.3, 169.5, 163.4, 139.4, 135.3, 132.3, 130.4, 130.3, 130.3, 129.6, 127.9, 126.2, 113.6, 113.6, 55.2, 46.6, 43.1, 22.8, 20.9, 18.7; IR (KBr) 3334, 3010, 2931, 2841, 1662, 1601, 1516, 1264, 1174, 1026, 989, 833, 592 cm^{-1}; HRMS (EI) *m/z* (M^+) calcd for $C_{20}H_{23}NO_3$: 325.1678. Found: 325.1675.

***N*-{1-(4-Bromophenyl)-3-(4-methoxyphenyl)-3-oxopropyl}acetamide (4p):** White solid. Yield (330 mg, 88%). mp 155-157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (2H, d, *J* = 8.7 Hz), 7.42 (2H, d, *J* = 8.4 Hz), 7.21 (2H, d, *J* = 8.4 Hz), 6.92 (2H, d, *J* = 9.0 Hz), 6.86 (1H, s, br, NH), 5.53-5.46 (1H, m), 3.87 (3H, s), 3.67 (1H, dd, *J* = 17.1, 5.1 Hz), 3.34 (1H, dd, *J* = 16.8, 5.8 Hz), 2.03 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.8, 169.7, 164.0, 140.5, 131.7, 131.7, 130.5, 130.5, 129.6, 128.4, 128.4, 121.2, 114.0, 114.0, 55.6, 49.5, 42.7, 23.4; IR (KBr) 3276, 3076, 2839, 1670, 1640, 1603, 1549, 1368, 1261, 1174, 1031, 832, 751, 605 cm^{-1}; HRMS (EI) *m/z* (M^+) calcd for $C_{18}H_{18}BrNO_3$: 375.0470. Found: 375.0467.

***N*-{3-(4-Methoxyphenyl)-1-(4-nitrophenyl)-3-oxopropyl}acetamide (4q):** Yellow solid. Yield (295 mg, 87%). mp 60-62 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (2H, d, *J* = 9.0 Hz), 7.83 (2H, d, *J* = 9.0 Hz), 7.47 (2H, d, *J* = 9.0 Hz), 7.07 (1H, d, *J* = 7.8 Hz, NH), 6.88 (2H, d, *J* = 9.0 Hz), 5.62-5.56 (1H, m), 3.83 (3H, s), 3.70 (1H, dd, *J* = 17.4, 5.1 Hz), 3.38 (1H, dd, *J* = 17.4, 5.4 Hz), 2.03 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9, 170.0, 164.1, 149.3, 146.8, 130.4, 130.4, 129.2, 127.5, 127.5, 123.7, 123.7, 113.9, 113.9, 55.5, 49.4, 42.6, 23.1; IR (KBr) 3283, 3071, 2936, 1671, 1600, 1519, 1348, 1259, 1173, 1025, 836, 700 cm^{-1}; HRMS (EI) *m/z* (M^+) calcd for $C_{18}H_{18}N_2O_5$: 342.1216. Found: 342.1212.

***N*-{3-(4-Methoxyphenyl)-1-(naphthalen-1-yl)-3-oxopropyl}acetamide (4r):** Off-white solid. Yield (333 mg, 96%). mp 175-176 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (1H, d, *J* = 8.7 Hz), 7.83 (3H, d, *J* = 8.7 Hz), 7.72 (1H, d, *J* = 8.1 Hz), 7.56-7.45 (3H, m), 7.36 (1H, dd, *J* = 8.1, 7.2 Hz), 6.84 (2H, d, *J* = 9.0 Hz), 6.67 (1H, d, *J* = 7.5 Hz, NH), 6.36-6.29 (1H, m), 3.76 (1H, dd, *J* = 16.2, 5.1 Hz), 3.81 (3H, s), 3.54 (1H, dd, *J* = 16.2, 6.6 Hz), 1.99 (3H, s); ^{13}C NMR (300 MHz, $CDCl_3$) δ 197.2, 169.4, 163.9, 136.4, 134.1, 130.9, 130.6, 130.6, 129.9, 129.1, 128.5, 126.8, 125.9, 125.3, 123.7, 123.2, 113.9, 113.9, 55.6, 46.6, 42.3, 23.5; IR (KBr) 3294, 3064, 2838, 1674, 1638, 1603, 1541, 1418, 1306, 1258, 1174, 1024, 780, 608 cm^{-1}; HRMS (EI) *m/z* (M^+) calcd for $C_{22}H_{21}NO_3$: 347.1521. Found: 347.1519.

***N,N'*-{1,1'-(1,4-Phenylene)bis(3-oxo-3-phenylpropane-1,1-diyl}diacetamide (5):**[24] To a solution of **1a** (120 mg, 1.0 mmol), terephthaldehyde (**2j**, 67 mg, 0.5 mmol) and acetyl

chloride (0.3 mL, 4.0 mmol) in acetonitrile (5 mL) was added AgOTf (25 mg, 10 mol %) and the reaction mixture was stirred at room temperature for 12 h. After completion of reaction as indicated by TLC, water (20 mL) was added. The mixture was extracted with ethyl acetate (20 mL × 3) and the extract was washed with saturated sodium bicarbonate (25 mL). The combined organic layers were dried over anhydrous magnesium sulfate to give residue which was recrystalized from ethanol to give pure product **5** (207 mg, 91%) as an off-white solid. mp 190-191°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.26 (2H, d, J = 8.1 Hz), 7.95 (4H, d, J = 7.5 Hz), 7.63 (2H, dd, J = 7.5, 7.2 Hz), 7.51 (4H, d, J = 7.8, 7.2 Hz), 7.29 (2H, s, NH), 5.38-5.31 (2H, m), 3.56-3.33 (4H, m), 1.77 (6H, s); ^{13}C NMR (75 MHz, DMSO-d_6) δ 197.0, 168.2, 141.5, 136.5, 133.1, 128.6, 127.9, 126.5, 48.6, 44.4, 22.5; IR (KBr) 3256, 3067, 1682, 1647, 1547, 1370, 1270, 996 cm^{-1}.

***N*-(2-Methyl-3-oxo-1,3-diphenylpropyl)acetamide (10).**[20] To a solution of propiophenone (134 mg, 1.0 mmol) with benzaldehyde (117 mg, 1.1 mmol) and acetyl chloride (0.15 mL, 2.0 mmol) in acetonitrile (5 mL) was added AgOTf (25 mg, 10 mol %) and the reaction mixture was stirred at room temperature for 12 h. After completion of reaction as indicated by TLC, water (20 mL) was added. The mixture was extracted with ethyl acetate (15 mL × 3) and extract was washed with saturated sodium bicarbonate (25 mL). The combined organic layers were dried over anhydrous magnesium sulfate to give residue which was purified by column chromatography on silica gel using hexane/EtOAc (1:1) to give **10a** and **10b**.

***anti*-Isomer (10a):** White solid (191 mg, 68%); mp 102-104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84-7.81 (2H, m), 7.52-7.47 (1H, m), 7.41-7.36 (2H, m), 7.27-7.19 (4H, m), 7.17-7.12 (1H, m), 6.17 (1H, d, J = 8.4 Hz, NH), 5.42 (1H, dd, J = 8.4, 7.5 Hz), 4.05-3.59 (1H, m), 1.91 (3H, s), 1.16 (3H, d, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9, 169.7, 140.4, 136.2, 133.0, 128.6, 128.6, 128.4, 128.4, 128.0, 128.0, 127.3, 126.8, 126.8, 54.9, 45.5, 23.1, 13.8; IR (KBr) 3297, 3059, 2978, 1674, 1643, 1540, 1291, 968, 703 cm^{-1}.

***syn*-Isomer (10b):** White solid (37 mg, 13%); mp 170-172 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74-7.70 (2H, m), 7.52-7.46 (2H, m), 7.38-7.33 (2H, m), 7.29-7.16 (3H, m), 7.13-7.08 (1H, m), 5.35 (1H, dd, J = 8.7, 3.9 Hz), 4.11-4.03 (1H, m), 2.08 (3H, s), 1.34 (3H, d, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.9, 169.9, 140.8, 136.3, 133.4, 128.5, 128.5, 128.3, 128.3, 128.1, 128.1, 127.1, 126.2, 126.2, 55.6, 44.3, 23.3, 16.5; IR (KBr) 3298, 3065, 2977, 1682, 1645, 1547, 1303, 969, 707 cm^{-1}.

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