Article

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Pyrazinium Di(hydrogen sulfate) as a Novel, Highly Efficient and Homogeneous Catalyst for the Condensation of Enolizable Ketones with Aldehydes, Acetonitrile and Acetyl Chloride

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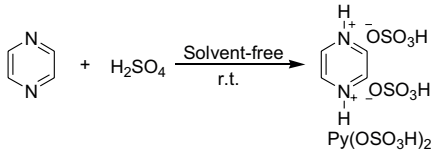
A highly efficient protocol for the synthesis of β-acetamido ketone or ester derivatives in the presence of pyrazinium di(hydrogen sulfate) {$Py(OSO_3H)_2$} as a novel, green and homogeneous solid acid catalyst at room temperature is described. One-pot multi-component condensation of enolizable ketones or alkyl acetoacetates with aldehydes, acetonitrile and acetyl chloride affords the title compounds in high to excellent yields and in relatively short reaction times. In this work, the efficiency of our recently reported solid acid catalyst, saccharin sulfonic acid (Sa-SO_3H), in the synthesis of β-acetamido ketones/esters is also studied. Moreover, in this research, some new β-acetamido ketones and esters (i.e. one complex structure) are prepared.

Keywords: Pyrazinium di(hydrogen sulfate) {$Py(OSO_3H)_2$}; Saccharin sulfonic acid (Sa-SO_3H); Enolizable ketone; β-Acetamido ketone; β-Acetamido ester; Solid acid.

INTRODUCTION

In recent decades, application of eco-friendly applicable industrial and green catalysts has received considerable interest. Thus, green chemistry has been defined as a set of principles which reduces or eliminates the use or generation of hazardous substances and catalysts throughout the entire life of chemical materials. Along this line, the use solid acid catalysts such as hydrogen sulfate salts,[1] saccharin sulfonic acid,[2] silica sulfuric acid,[3] and boron sulfonic acid,[4] which are green, inexpensive and non-toxic, has received increased attention for various types of organic transformations due to their operational simplicity, efficacy, and selectivity coupled with their green natures. For example, they have been used as efficient catalyst for synthesis of dihydropyrimidones,[5] triarylmethanes,[6] bis-*N*-acylsulfonamides,[7] gem-dihydroperoxides,[8] spiro bipyrimidine,[9] quinolines,[10] homoallylic amines,[11] xanthenes,[12] 1,1-diacetates,[13] *N*-Boc Protection of Amines,[14] Michael additions,[15] acetylation,[16] trimethylsilylation of alcohols,[17] and synthesis of 2-thiazolamines.[18] Considering the high importance of solid acid catalysts in organic synthesis, we have synthesized pyrazinium di(hydrogen sulfate) {$Py(OSO_3H)_2$} as a new solid acid catalyst, by the reaction of pyrazine (1 eq.) with sulfuric acid (2 eq.) at room temperature during an easy and clean procedure (Scheme I). On the basis of the structure of $Py(OSO_3H)_2$, we anticipate that it can act as an efficient catalyst in reactions which need the use of acidic catalysts to speed up. Herein, we have found that the synthesis of β-acetamido ketones and esters from enolizable ketones/alkyl acetoacetates, aldehydes, acetonitrile and acetyl chloride can be efficiently performed in the presence of $Py(OSO_3H)_2$.

Scheme I The synthesis of pyrazinium di(hydrogen sulfate) {$Py(OSO_3H)_2$}



Multi-component reactions (MCRs) involve three or more compounds reacting in a single event to form a product, which contains the essential parts of all the starting materials. MCRs are welcome too in terms of economic and practical considerations.[19] They contribute to the requirements of an environmentally friendly process by reducing

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the number of synthetic steps, energy consumption and waste production.[20] Therefore, in the last decade research in academia and industry has increasingly emphasized the use of MCRs as well as domino reaction sequences for a broad range of products.[19,20]

β-Acetamido ketone and ester derivatives are versatile and valuable building blocks for a number of biologically and pharmaceutically compounds.[21-27] They can be converted into 3-amino alcohols, which may be applied for the synthesis of various important antibiotics.[28] Generally, this type of compounds is prepared by Dakin-West reaction.[29-34] This reaction includes the one-pot multi-component condensation of enolizable ketones with aldehydes, acetonitrile and acetyl chloride.[29-34] Some catalysts including BiOCl,[35] $CeCl_3 \cdot 7H_2O$,[36] $ZrOCl_2 \cdot 8H_2O$,[37] I_2,[38] TMSCl,[39] selectfluor,[40] sulfamic acid,[41] $CoCl_2$,[42] $H_3PW_{12}O_{40}$ [43] have been employed for this transformation. Although some catalysts for the synthesis of β-acetamido carbonyl compounds are known, newer catalysts continue to attract attention for their difference with the others, novelty and effectiveness. Furthermore, most of the reported methods for the synthesis of these compounds have one or more of the following drawbacks: (i) low yields, (ii) long reaction times, (iii) the use of large amount of catalyst, (iv) the use of toxic or expensive catalysts, (v) tedious work-up procedure, (vi) harsh reaction conditions, and (vii) performance the reaction under certain special conditions.

Along the line of our studies in design and application of new solid acid catalysts in chemical transformations,[44-50] and also synthesis of organic compounds by multi-component reactions,[51-56] we describe here a simple new procedure for the synthesis of β-acetamido ketones/esters *via* the one-pot multi-component condensation reaction between enolizable ketones or alkyl acetoacetates, aldehydes, acetonitrile and acetyl chloride in the presence of our new catalyst pyrazinium di(hydrogen sulfate) {$Py(OSO_3H)_2$}, or saccharin sulfonic acid (Sa-SO_3H) at room temperature (Scheme II). It should be mentioned that $Py(OSO_3H)_2$ melts at 80-81 °C; thus, it can be used as solid acid in reactions which carry out at room temperature or at less than its melting point; however, the pyrazinium salt can act as ionic liquid in reactions which perform at higher than 80 °C.[57]

RESULTS AND DISCUSSION

To obtain the optimized reaction conditions for the synthesis of β-acetamido carbonyl compounds, the reaction of 4-bromoacetophenone (1 mmol) with benzaldehyde (1 mmol), acetonitrile (3 mL) and acetyl chloride (0.3 mL) was selected as a model reaction to provide compound **1k**, and its behavior was studied in the presence of different molar ratios of $Py(OSO_3H)_2$ as well as Sa-SO_3H at room temperature. The results are summarized in Table 1. As Table 1 indicates, higher yields of the product and shorter reaction times were obtained when the reaction was carried our using 10 mol% of $Py(OSO_3H)_2$ or 15 mol% of Sa-SO_3H.

To recognize efficiency and importance of the catalysts in the synthesis of β-acetamido carbonyl compounds, the model reaction was also examined using H_2SO_4 (starting material of $Py(OSO_3H)_2$) as well as $ClSO_3H$ (starting material of Sa-SO_3H), separately (Table 1, entries 9 and 10). As it can be seen in Table 1, H_2SO_4 and $ClSO_3H$ afforded the product in 39 and 27% yields within 3.5 h, respectively. In these conditions, a large amounts of the starting materials were remained, an also some by-products were obtained. This observation confirmed that to increase

Scheme II The synthesis of β-acetamido ketones/esters from enolizable ketones/alkyl acetoacetates, aldehydes, acetonitrile and acetyl chloride using $Py(OSO_3H)_2$ or Sa-SO_3H

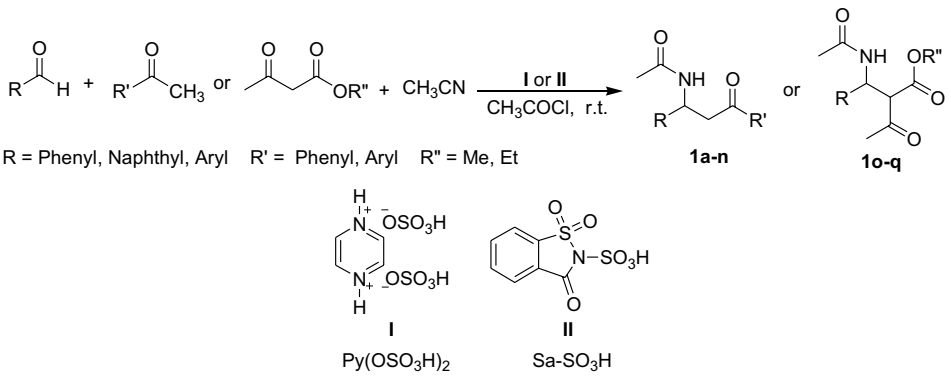


Table 1. Effect of different amounts of the catalysts on the reaction of 4-bromoacetophenone with benzaldehyde, acetonitrile and acetyl chloride at room temperature

Entry	Catalyst	Catalyst Amount (Mol%)	Time (h)	Yield[a] (%)
1	-	-	12	No reaction
2	$Py(HSO_4)_2$	5	2.5	65
3	$Py(HSO_4)_2$	10	0.5	93
4	$Py(HSO_4)_2$	15	0.5	88
5	Sa-SO_3H	5	3	60
6	Sa-SO_3H	10	2	79
7	Sa-SO_3H	15	0.75	87
8	Sa-SO_3H	20	1.25	82
9	H_2SO_4	10	3.5	39
10	$ClSO_3H$	15	3.5	27

[a] Isolated yields.

efficiency of H_2SO_4 and $ClSO_3H$ in the synthesis of β-acetamido ketones/esters, it is necessary to combine them to organic compounds (here, pyrazine and saccharin).

Under the optimal reaction conditions, various enolizable ketones (including acetophenones bearing electron-releasing substituents, electron-withdrawing substituents and halogens on their aromatic ring, as well as alkyl acetoacetates) were condensed with different aromatic aldehydes (containing electron-releasing substituents, electron-withdrawing substituents and halogens on their aromatic ring), acetonitrile and acetyl chloride in the presence of $Py(OSO_3H)_2$ and Sa-SO_3H to afford the corresponding β-acetamido ketones and esters in high to excellent yields within relatively short reaction times; the reactions were carried out efficiently within 0.75-2.75 h, and the products were produced in 85-96% yields. The results are displayed in Table 2. Moreover, the method was worked well when 2-naphthaldehyde was used instead of benzaldehydes (Table 2, compounds **1c**, **1f**, **1j**, **1n**, **1p, 1q**).

Interestingly, the reaction of 4-bromoacetophenone (3.2 equiv.) with a tris-aldehyde (1 equiv.), acetonitrile (6 mL) and acetyl chloride (0.9 mL) in the presence of $Py(OSO_3H)_2$ (**I**, 10 mol%) at room temperature afforded complex compound **2a** in 81% yield within 2.25 h (Scheme III). Sac-SO_3H (**II**) also gave compound **2a** in 79% after 2.5 h. This is the first report of the synthesis of this class of β-acetamido ketones.

In summary, we have introduced a new efficient solid acid catalyst, pyrazinium di(hydrogen sulfate), for organic synthesis. In this work, we have used our new catalyst (as well as saccharin sulfonic acid) for the preparation of β-acetamido ketones/esters from enolizable ketones or alkyl acetoacetates, aldehydes, acetonitrile and acetyl chloride. The promising points for the presented methodology are efficiency, generality, high yields, relatively short reaction times, cleaner reaction profile and simplicity.

EXPERIMENTAL

All chemicals were purchased from Merck or Fluka Chemical Companies. Sulphuric acid 98% was used for the preparation of pyrazinium di(hydrogen sulfate). Sac-SO_3H was prepared according to the reported procedure.[2] All known compounds were identified by comparison of their melting points and spectral data with those reported in the literature. Progress of the reactions was monitored by TLC using silica gel SIL G/UV 254 plates. The ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) were run on a Bruker Avance DPX-250, FT-NMR spectrometer (δ in ppm).

Scheme III The synthesis of complex compound **2a**

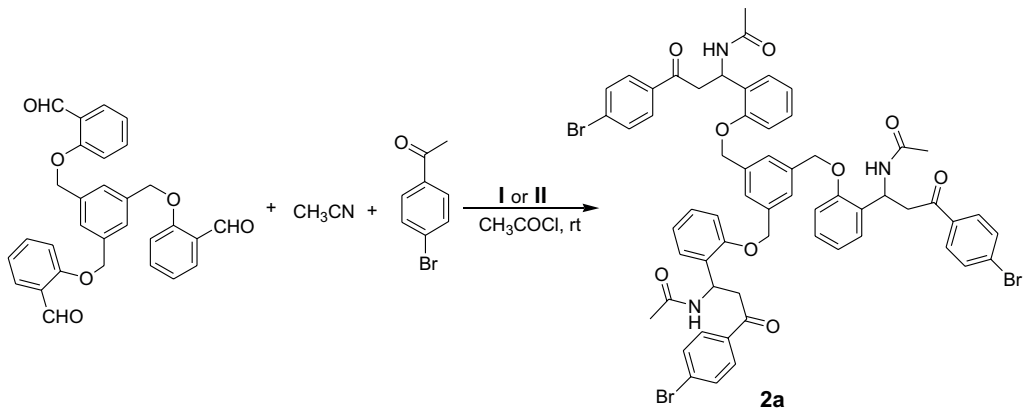
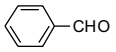
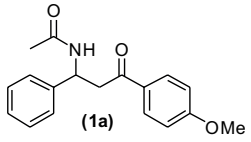
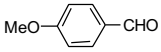
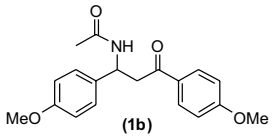
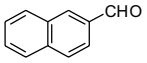
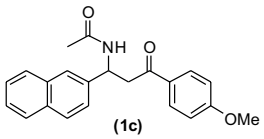
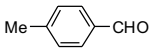
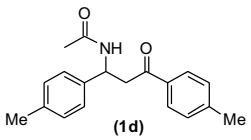
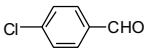
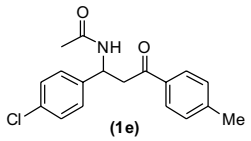
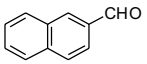
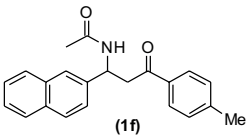
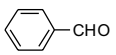
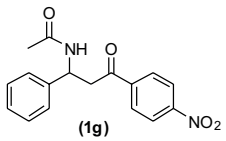
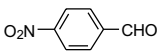
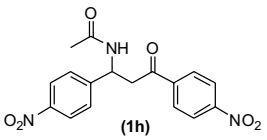
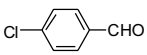
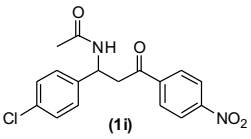
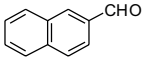
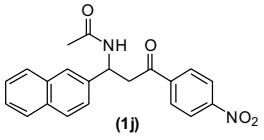
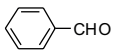
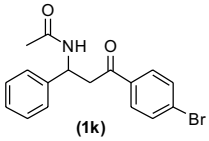
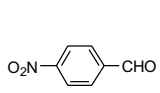
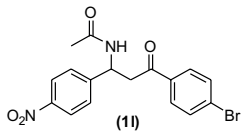
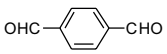
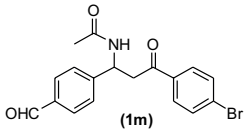
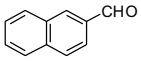
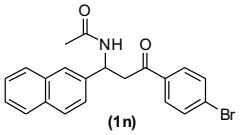
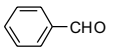
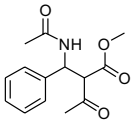
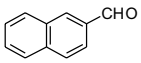
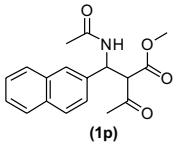
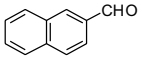
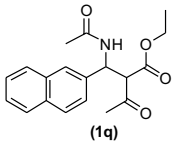


Table 2. The preparation of β-acetamido ketones/esters using $Py(OSO_3H)_2$ (**I**) or $Sa\text{-}SO_3H$ (**II**)

Aldehyde	Product	Time (h)	Yield[a] (%)	M.p. °C (lit.)
		I/II	**I/II**	
	 **(1a)**	0.75/0.75	96/94	127-129 (130-132)[33]
	 **(1b)**	1/0.75	95/93	124-127[b]
	 **(1c)**	1.25 /1	92/89	108-110[b]
	 **(1d)**	0.75/0.75	94/93	118-119 (-)[58]
	 **(1e)**	0.75/1	91/92	130-132 (-)[58]
	 **(1f)**	1/1.5	91/93	111-112 (112-114)[26]
	 **(1g)**	1.5/2	92/94	75-77 (74-76)[33]
	 **(1h)**	2/2.5	88/85	185-188 (187-188)[25]
	 **(1i)**	2/2.5	91/90	114-116 (116-118)[26]
	 **(1j)**	2/2.25	89/85	165-166[b]
	 **(1k)**	0.5/0.75	93/87	100-101 (98-100)[26]

	 (1l)	2/2.25	91/91	162-163 (-)[28]
	 (1m)	1.25/1.5	88/90	104-105[b]
	 (1n)	1.5/2	90/87	138-140[b]
	 (1o)	1/1.5	90/86	140-142 (140-141)[25]
	 (1p)	1.5/2.5	89/86	138-139[b]
	 (1q)	2.25/2.75	88/91	149-152[b]

[a] Isolated yield. [b]This compound is new.

Microanalysis was performed on a Perkin-Elmer 240-B microanalyzer. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

General procedure for the preparation of pyrazinium di(hydrogen sulfate)

A 25 mL flask charged with sulphuric acid 98% (2.50 g, containing 25 mmol of the acid) was put into an ice-bath, and pyrazine (1.00 g, 12.5 mmol) was added to it in portions over a period of 5 min. The resulting mixture was stirred for 20 min, and then $CHCl_3$ (30 mL) was added to it, and stirred for 3 min. The resulting solid was filtered, washed with $CHCl_3$, and dried to give $Py(OSO_3H)_2$ (3.42 g, 99%) as a pale yellow solid.

Spectral data of $Py(OSO_3H)_2$

M.p. 80-81 °C. ^{1}H-NMR (DMSO-d_6): δ 8.22 (s, 4H), 10.70 (s, 4H). ^{13}C NMR (DMSO-d_6): δ 141.6. MS (EI, 70 eV): *m/z* = 297.

General procedure for the synthesis of β-acetamido carbonyl compounds

To a mixture of enolizable ketone or alkyl acetoacetate (1 mmol), aldehyde (1 mmol), acetonitrile (3 mL) and acetyl chloride (0.3 mL) in a 10 mL round-bottomed flask, was added $Py(OSO_3H)_2$ (0.0276 g, 0.1 mmol) or Sac-SO_3H (0.039 g, 0.15 mmol), and the resulting mixture was stirred at room temperature. After completion of the reaction, as monitored with TLC, crushed ice (10 mL) was added to the reaction mixture and stirred thoroughly. On solidification, the crude product was filtered, dried, and purified by short column chromatography on silica gel eluted with EtOAc/*n*-hexane (1/4).

Physical properties and spectral data

Note: Compounds **1b**, **1c**, **1j**, **1m**, **1n**, **1p**, **1q** and **2a** are new.

***N*-(3-(4-Methoxyphenyl)-3-oxo-1-phenylpropyl)acetamide 1a**

IR (KBr): 1678, 3268 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 2.00 (s, 3H), 3.38 (dd, *J* = 5.9, 16.5 Hz, 1H), 3.66 (dd, *J* = 5.4, 16.6 Hz, 1H), 3.85 (s, 3H), 5.54 (q, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 2H), 7.21-7.35 (m, 6H), 7.88 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 23.3, 42.8, 50.1, 55.5, 113.8,

126.5, 127.3, 128.6, 129.7, 130.5, 141.1, 163.8, 169.6, 196.9. MS (EI, 70 eV): *m/z* = 297. Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.55; H, 6.58; N, 4.59.

***N*-(1,3-Bis(4-methoxyphenyl)-3-oxopropyl)acetamide 1b**

IR (KBr): 1678, 3273 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.02 (s, 3H), 3.67 (s, 1H), 3.76 (s, 3H), 3.86 (s, 3H), 5.49 (s, 1H), 6.88 (q, *J* = 7.8 Hz, 5H), 7.26 (d, *J* = 8.3 Hz, 2H), 7.90 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 23.4, 42.8, 49.7, 55.2, 55.5, 113.8, 113.9, 127.7, 129.6, 130.5, 133.1, 158.7, 163.7, 169.6, 197.2; MS (EI, 70 eV): *m/z* = 327. Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.58; H, 6.58; N, 4.36.

***N*-(3-(4-Methoxyphenyl)-1-(naphthalen-3-yl)-3-oxopropyl)acetamide 1c**

IR (KBr): 1671, 3276 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.03 (s, 3H), 3.43 (d, *J* = 6.6 Hz, 1H), 3.79 (s, 4H), 5.72 (s, 1H), 6.90 (q, *J* = 6.8 Hz, 2H), 7.42-7.53 (m, 4H), 7.75-8.10 (m, 5H), 8.23 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 22.6, 43.1, 50.6, 55.5, 113.8, 124.8, 125.4, 126.0, 127.6, 127.9, 128.5, 129.5, 130.5, 132.6, 133.2, 138.4, 163.7, 170.9, 196.4. MS (EI, 70 eV): *m/z* = 347. Anal. Calcd. for $C_{22}H_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.27; H, 6.19; N, 3.95.

***N*-(3-Oxo-1,3-dip-tolylpropyl)acetamide 1d**

IR (KBr): 1680, 3257 cm^{-1}, ^1H-NMR ($CDCl_3$): δ 1.93 (s, 3H), 2.27 (s, 3H), 2.37 (s, 3H), 3.36 (q, *J* = 6.2 Hz, 1H), 3.64 (q, *J* = 5.8 Hz, 1H), 5.55 (q, *J* = 7.1 Hz, 1H), 7.09 (d, *J* = 7.7 Hz, 2H), 7.22 (m, 2H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.80 (d, *J* = 7.7 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 21.1, 21.7, 23.1, 43.6, 49.8, 126.5, 128.3, 129.2, 129.3, 134.1, 136.9, 138.4, 144.2, 169.8, 197.8. MS (EI, 70 eV): *m/z* = 295. Anal. Calcd. For $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74; Found: C, 77.05; H, 7.30; N, 4.85.

***N*-(1-(4-Chlorophenyl)-3-oxo-3-p-tolylpropyl)acetamide 1e**

IR (KBr): 1689, 3302 cm^{-1}, ^1H NMR ($CDCl_3$): δ 2.02 (s, 3H), 2.40 (s, 3H), 3.35 (dd, *J* = 3.8, 17.1 Hz, 1H), 3.68 (dd, *J* = 5.3, 17.1 Hz, 1H), 5.5 (q, *J* = 5.5 Hz, 1H), 7.26 (m, 5H), 7.37 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ 21.7, 23.1, 42.8, 49.3, 127.9, 128.2, 128.7, 129.4, 133.1, 133.8, 139.6, 144.7, 170.1, 197.8. MS (EI, 70 eV): *m/z* = 312. Anal. Calcd. For $C_{18}H_{18}ClNO_2$: C, 68.46; H, 5.75; N, 4.44; Found: C, 68.65; H, 5.90; N, 4.35.

***N*-(1-(Naphthalen-3-yl)-3-oxo-3-p-tolylpropyl)acetamide 1f**

IR (KBr): 1676, 3280 cm^{-1}, ^1H-NMR ($CDCl_3$): δ 1.96 (s, 3H), 2.39 (s, 3H), 3.46 (q, *J* = 8.7 Hz, 1H), 3.78 (q, *J* = 5.1 Hz, 1H), 5.73 (d, *J* = 6.8 Hz, 1H), 7.16-7.28 (m, 2H), 7.43-7.49 (m, 4H), 7.72-7.78 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 21.7, 23.4, 43.1, 50.1, 124.7, 125.2, 125.9, 126.2, 127.9, 128.2, 128.4, 129.4, 129.6, 132.6, 133.2, 134.1, 138.4, 144.5, 169.7, 198.1. MS (EI, 70 eV): *m/z* = 331. Anal. Calcd. For $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23; Found: C, 79.55; H, 6.50; N, 4.35.

***N*-(3-(4-Nitrophenyl)-3-oxo-1-phenylpropyl)acetamide 1g**

IR (KBr): 1689, 3302 cm^{-1}, ^1H NMR ($CDCl_3$): δ 1.95 (s, 3H), 3.43 (dd, *J* = 3.5, 16.6 Hz, 1H), 3.78 (dd, *J* = 3.5, 14.1 Hz, 1H), 5.53 (q, *J* = 3.9 Hz, 1H), 6.95 (d, *J* = 6.3 Hz, 1H), 7.31 (s, 5H), 8.03 (d, *J* = 6.0 Hz, 2H), 8.23 (d, *J* = 5.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 23.1, 44.3, 50.1, 123.8, 126.5, 127.8, 129.2, 140.9, 150.3, 169.9, 196.6. MS (EI, 70 eV): *m/z* = 312. Anal. Calcd. For $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97; Found: C, 65.57; H, 5.06; N, 8.84.

***N*-(1,3-Bis(4-nitrophenyl)-3-oxopropyl)acetamide 1h**

IR (KBr): 1694, 3277 cm^{-1}, ^1H NMR ($CDCl_3$): δ 2.10 (s, 3H), 3.61 (dd, *J* = 3.5, 14.1 Hz, 1H), 3.88 (dd, *J* = 3.8, 13.3 Hz, 1H), 5.69 (s, 1H), 6.73 (s, 1H), 7.27 (s, 1H), 7.54 (s, 1H), 8.09-8.32 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 29.7, 49.1, 59.5, 124.1, 124.1, 124.4, 129.2, 140.3, 147.3, 147.7, 150.7, 169.8, 196.3. MS (EI, 70 eV): *m/z* = 357. Anal. Calcd. For $C_{17}H_{15}N_3O_6$: C, 57.14; H, 4.23; N, 11.76; Found: C, 57.36; H, 4.11; N, 11.64.

***N*-(1-(4-Chlorophenyl)-3-(4-nitrophenyl)-3-oxopropyl)-acetamide 1i**

IR (KBr): 1695, 3280 cm^{-1}, ^1H-NMR ($CDCl_3$): δ 1.99 (s, 3H), 3.46 (q, *J* = 6.9 Hz, 1H), 3.84 (s, 1H), 5.52 (s, 1H), 7.11-7.27 (m, 3H), 7.73-7.78 (m, 1H), 8.05-8.31 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 21.1, 22.7, 44.2, 44.4, 49.5, 50.1, 123.9, 126.5, 128.2, 128.9, 129.2, 129.5, 133.5, 137.1, 137.7, 140.8, 150.3, 170.7, 196.1, MS (EI, 70 eV): *m/z* = 347. Anal. Calcd. For $C_{17}H_{15}ClN_2O_4$: C, 58.88; H, 4.36; N, 8.08; Found: C, 59.02; H, 4.27; N, 8.18.

***N*-(1-(Naphthalen-3-yl)-3-(4-nitrophenyl)-3-oxopropyl)-acetamide 1j**

IR (KBr): 1665, 3280 cm^{-1}, ^1H NMR ($CDCl_3$): δ 2.08 (s, 3H), 2.85-3.05 (m, 2H), 5.50 (s, 1H), 7.47-8.5 (m, 12H); ^{13}C NMR ($CDCl_3$): δ 29.7, 49.8, 59.5, 124.7, 125.5, 126.4, 126.6, 126.8, 127.1, 127.5, 127.7, 128.1, 129.1, 129.4,

129.5, 130.5, 173.9, 194.1; MS (EI, 70 eV): *m/z* = 362. Anal. Calcd. For $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73, Found: C, 69.49; H, 5.12; N, 7.69.

N-(3-(4-Bromophenyl)-3-oxo-1-phenylpropyl)acetamide 1k

IR (KBr): 1685, 3275 cm^{-1}, ^{1}H-NMR ($CDCl_3$): δ 2.04 (s, 3H), 3.37 (q, *J* = 5.4 Hz, 1H), 3.66 (q, *J* = 5.4 Hz, 1H), 5.54 (q, *J* = 6.6 Hz, 1H), 6.99-7.75 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 23.2, 29.6, 43.5, 50.0, 126.5, 127.5, 128.6, 129.6, 131.9, 135.3, 140.8, 169.7, 197.2. MS (EI, 70 eV): *m/z* = 345. Anal. Calcd. For $C_{17}H_{16}BrNO_2$: C, 58.97; H, 4.66; N, 4.05; Found: C, 58.81; H, 4.58; N, 4.14.

N-(3-(4-Bromophenyl)-1-(4-nitrophenyl)-3-oxopropyl)-acetamide 1l

IR (KBr): 1687, 3261 cm^{-1}, ^{1}H-NMR ($CDCl_3$): δ 2.05 (s, 3H), 3.47 (q, *J* = 5.6 Hz, 1H), 3.79 (q, *J* = 5.19 Hz, 1H), 5.65 (q, *J* = 5.5 Hz, 1H), 7.02 (d, *J* = 7.86 Hz, 1H), 7.58 (d, *J* = 8.7 Hz, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 2H), 8.15 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 23.3, 42.7, 49.1, 113.8, 123.8, 127.4, 129.3, 129.5, 132.2, 134.8, 147.1, 148.4, 169.8, 196.8. MS (EI, 70 eV): *m/z* = 390. Anal. Calcd. For $C_{17}H_{15}BrN_2O_4$: C, 52.19; H, 3.86; N, 7.16; Found: C, 52.35; H, 4.05; N, 7.05.

Compound 1m

IR (KBr): 1689, 1736, 3286 cm^{-1}, ^{1}H NMR ($CDCl_3$): δ 2.07 (s, 3H), 3.46 (d, *J* = 6.8 Hz, 1H), 3.81 (d, *J* = 7.8 Hz, 1H), 5.63 (s, 1H), 7.09 (s, 1H), 7.2-7.6 (m, 3H), 7.7-8.2 (m, 4H), 9.96 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 23.3, 42.8, 49.5, 127.1, 129.2, 129.6, 130.1, 132.1, 134.9, 135.5, 147.6, 170.01, 191.8, 197.1. MS (EI, 70 eV): *m/z* = 373. Anal. Calcd. For $C_{18}H_{16}BrNO_3$: C, 57.77; H, 4.31; N, 3.74. Found: C, 57.93; H, 4.42; N, 3.19.

N-(3-(4-Bromophenyl)-1-(naphthalen-3-yl)-3-oxopropyl)acetamide 1n

IR (KBr): 1682, 3276 cm^{-1}, ^{1}H NMR ($CDCl_3$): δ 1.98 (s, 3H), 3.41 (dd, *J* = 6.4, 12.7 Hz, 1H), 3.76 (dd, *J* = 6.6, 13.2 Hz, 1H), 5.70 (s, 1H), 7.27-7.59 (m, 6H), 7.69-7.92 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 23.2, 43.5, 50.1, 124.7, 125.3, 126.1, 126.3, 127.6, 128.6, 129.6, 131.9, 132.7, 133.1, 135.1, 138.2, 170.1, 197.1. MS (EI, 70 eV): *m/z* = 395. Anal. Calcd. for $C_{21}H_{18}BrNO_2$: C, 63.65; H, 4.58; N, 3.53, Found: C, 63.48; H, 4.67; N, 3.44.

Methyl 2-(acetamido(phenyl)methyl)-3-oxobutanoate 1o

IR (KBr): 1647, 1720, 1746, 3332 cm^{-1}, ^{1}H-NMR ($CDCl_3$): δ 1.95 (s, 3H), 2.16 (s, 3H), 3.64 (s, 3H), 4.10 (s, 1H), 5.748 (s, 1H), 7.29 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 23.2, 30.6, 52.3, 52.8, 62.8, 126.6, 127.8, 128.7, 139.1, 167.6, 169.8, 203.6. MS (EI, 70 eV): *m/z* = 263. Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32; Found: C, 64.01; H, 6.43; N, 5.19.

Methyl 2-(acetamido(naphthalen-3-yl)methyl)-3-oxobutanoate 1p

IR (KBr): 1636, 1747, 3347 cm^{-1}, ^{1}H-NMR ($CDCl_3$): δ 2.01 (s, 3H), 2.19 (s, 3H), 3.65 (s, 3H), 4.26 (s, 1H), 5.96 (s, 1H), 7.46 (m, 3H), 7.77 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 23.3, 30.6, 52.6, 52.8, 62.7, 124.5, 125.7, 126.2, 127.6, 128.1, 128.6, 132.8, 133.1, 136.5, 167.6, 169.8, 203.5. MS (EI, 70 eV): *m/z* = 313. Anal. Calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47, Found: C, 69.81; H, 6.23; N, 4.56.

Ethyl 2-(acetamido(naphthalen-3-yl)methyl)-3-oxobutanoate 1q

IR (KBr): 1647, 1720, 1746, 3332 cm^{-1}, ^{1}H-NMR ($CDCl_3$): δ 1.11 (t, *J* = 5.0 Hz, 3H), 2.02 (s, 3H), 2.18 (s, 3H), 4.1 (q, *J* = 6.1 Hz, 2H), 4.17 (q, *J* = 6.3 Hz, 1H), 5.95 (s, 1H), 7.27 (m, 4H), 7.76 (t, *J* = 7.5 Hz, 4H). ^{13}C NMR ($CDCl_3$): δ 23.2, 30.6, 52.3, 52.8, 62.8, 126.6, 127.8, 128.7, 139.1, 167.6, 169.8, 203.6. MS (EI, 70 eV): *m/z* = 327. Anal. Calcd. For $C_{19}H_{21}NO_4$ C, 69.71; H, 6.47; N, 4.28. Found: C, 69.52; H, 6.34; N, 4.39.

Compound 2a

IR (KBr): 1674, 3433 cm^{-1}, ^{1}H NMR ($CDCl_3$): δ 1.86 (s, 9H), 3.36-3.49 (m, 6H), 5.16 (s, 6H), 5.83 (s, 3H), 6.91-7.02 (m, 6H), 7.15-7.38 (m, 11H), 7.51-7.64 (m, 9H), 7.67-7.83 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 23.0, 43.1, 46.8, 69.8, 112.3, 121.3, 126.2, 127.9, 128.4, 128.8, 129.7, 129.9, 131.8, 135.2, 138.1, 155.4, 168.2, 197.4; MS (EI, 70 eV): *m/z* = 1197 (M^+). Anal. Calcd. For $C_{60}H_{54}Br_3N_3O_9$: C, 60.01; H, 4.53; N, 3.50, Found: C, 59.88; H, 4.65; N, 3.42.

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