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Hydrogen peroxide-promoted metal free oxidative amidation of 2-oxoaldehydes: a facile access to unsymmetrical oxamides

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ABSTRACT

A novel and green H_2O_2-promoted oxidative amidation of 2-oxoaldehydes with amines to synthesize unsymmetrical oxamides has been developed. The reactions proceeded smoothly at room temperature under metal-free conditions and generated the corresponding products in good yields. This methodology has a broad substrate scope and opens up an interesting and attractive avenue for the synthesis of unsymmetrical oxamide derivatives.

1. Introduction

Amides, as an important structural backbone of various natural products, pharmaceuticals and polymers, have attracted considerable interest because of their important biologically active properties.[1] A recent survey on drug discovery shown that more than 50% of known drugs contain an amide functional group.[2] As an important and unique member of amides, oxamides also represents a key framework of many bioactive compounds.[3] They have been developed as acetylcholine esterase inhibitors,[4] C5a inhibitors,[5] nitric oxide synthase inhibitors,[6] *anti*-HIV agents,[7] antiepileptic drugs[8] and HIV integrase inhibitors[9] (Fig. 1).

A number of synthetic methods for oxamides have been established in the past decades.[10] However, only a few examples of the synthetic methods for unsymmetrical oxamides have been reported. Traditionally, unsymmetrical oxamides are synthesized from the condensation of corresponding carboxylic acids with amines, which needs either activating agents or conversion into more reactive derivatives (Scheme 1a).[11] In recent years, several innovative approaches have been developed, which include the direct amidation of isocyanates,[12] α-keto benzotriazole[13] or trichloropyruvamides[14] with amines (Scheme 1b–d). Nevertheless, these methods have several drawbacks, such as harsh conditions, expensive reagents, poor atom-efficiency and limited substrate scope. Therefore, a more mild, convenient and efficient method for the synthesis of unsymmetrical oxamides is still in high demand.

As far as we know, there has been no report on the synthesis of unsymmetrical oxamides via oxidative amidation yet. Our work is focused on the green oxidative amidation of 2-oxoaldehydes utilizing clean and inexpensive oxidants. Hydrogen peroxide is a very attractive candidate because of its wide application in laboratory and industrial synthesis. In this study, we report a new method for synthesizing unsymmetrical oxamides from 2-oxoaldehydes and amines by using hydrogen peroxide as a reactant (Scheme 1).

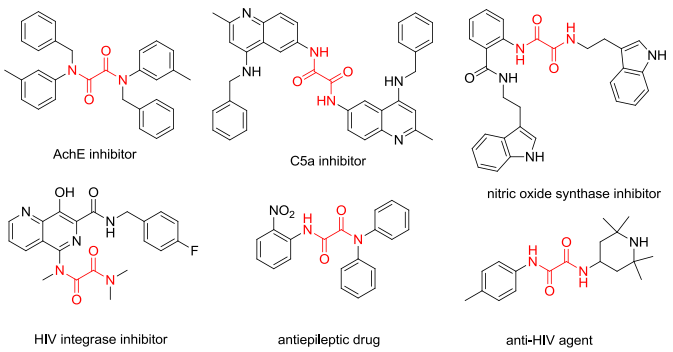

Fig. 1. Biologically active molecules containing an oxamide moiety.

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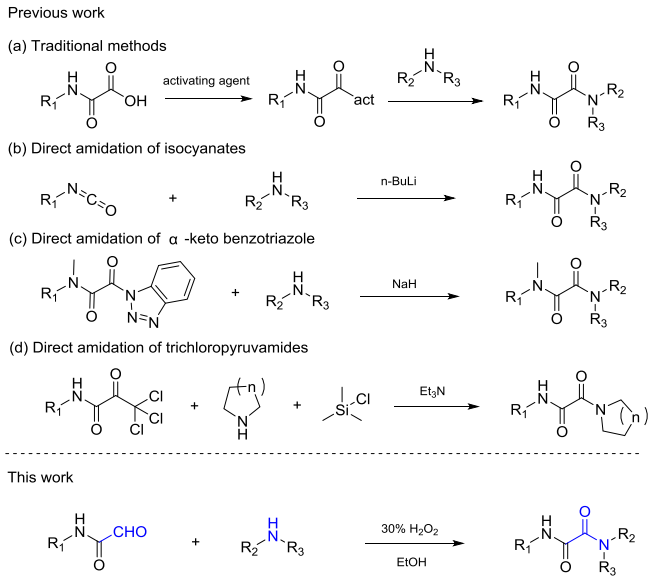
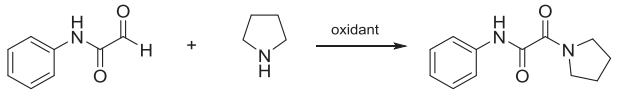


Scheme 1. Typical pathways for the synthesis of unsymmetrical oxamides.

2. Results and discussion

At the beginning of our investigation, the optimization of reaction conditions was focused on a variety of reaction parameters by using a model reaction of 2-oxo-*N*-phenylacetamide (**1a**) with pyrrolidine (**2a**). As shown in Table 1, all the peroxides could promote this reaction to give the corresponding products with moderate to high yields (Table 1, entries 1–3), while IBX, DMP, DIB, SeO_2, CrO_3 and OsO_4 had only 13–33% yields of **3aa** (Table 1, entries 4–9). Among various solvents examined, EtOH turned out to be the best choice, while others such as CH_2Cl_2, $CH_3COOC_2H_5$, CH_3CN, THF, DMSO, dioxane and PEG-400 were less effective (Table 1, entries 10–16). The yield decreased to 11% when EtOH was replaced with water (Table 1, entry 17). And addition of cosolvent such as Tween 80 or Bu4NI did not improve the yield (Table 1, entries 18–19). Further investigation indicates that temperature is important for this transformation. An excellent yield has been obtained when the reaction carries out at 25 °C (Table 1, entry 1). However, when the temperature increases to 40 °C, the yield of the desired product drops to 56% (Table 1, entry 20). And no product formation was observed when the reaction was conducted at 0 °C (Table 1, entry 21). For the optimization of the amount of H_2O_2 used in the model reaction, less than 3 equiv of H_2O_2 led to the incompletion of the reaction (Table 1, entries 22–23). Meanwhile, up to 4 equiv of H_2O_2 did not increase the yield if **3aa** significantly (Table 1, entry 24). With respect to the molar proportion of the reactants, a 3:1 M ratio of aldehyde and amine was found to be adequate, as neither bigger nor smaller proportion shows better yields (Table 1, entries 25–27). Finally, as observed in this study, the optimized reaction conditions tends to be: 2-oxoaldehyde (3.0 mmol), amine (1.0 mmol) and 30% H_2O_2 (3.0 mmol) in EtOH under standard atmosphere at 25 °C.

Table 1
Optimization studies for the synthesis of unsymmetrical oxamides[a]



1a 2a 3aa

Entry	1a:2a	Oxidant (equiv)	Solvent	Additive	T (°C)	Yield[b] (%)
1	1:1	H_2O_2 (3.0)	EtOH	/	25	81
2	1:1	TBHP (3.0)	EtOH	/	25	68
3	1:1	BPO (3.0)	EtOH	/	25	61
4	1:1	IBX (3.0)	EtOH	/	25	33
5	1:1	DMP (3.0)	EtOH	/	25	27
6	1:1	DIB (3.0)	EtOH	/	25	26
7	1:1	SeO_2 (3.0)	EtOH	/	25	19
8	1:1	CrO_3 (3.0)	EtOH	/	25	11
9	1:1	OsO_4 (3.0)	EtOH	/	25	13
10	1:1	H_2O_2 (3.0)	CH_2Cl_2	/	25	73
11	1:1	H_2O_2 (3.0)	$CH_3COOC_2H_5$	/	25	71
12	1:1	H_2O_2 (3.0)	CH_3CN	/	25	65
13	1:1	H_2O_2 (3.0)	THF	/	25	67
14	1:1	H_2O_2 (3.0)	DMSO	/	25	40
15	1:1	H_2O_2 (3.0)	dioxane	/	25	50
16	1:1	H_2O_2 (3.0)	PEG-400	/	25	37
17	1:1	H_2O_2 (3.0)	H_2O	/	25	11
18	1:1	H_2O_2 (3.0)	H_2O	Tween 80	25	12
19	1:1	H_2O_2 (3.0)	H_2O	Bu_4NI	25	14
20	1:1	H_2O_2 (3.0)	EtOH	/	40	56
21	1:1	H_2O_2 (3.0)	EtOH	/	0	0
22	1:1	H_2O_2 (1.0)	EtOH	/	25	54
23	1:1	H_2O_2 (2.0)	EtOH	/	25	65
24	1:1	H_2O_2 (4.0)	EtOH	/	25	82
25	2:1	H_2O_2 (3.0)	EtOH	/	25	84
26	3:1	H_2O_2 (3.0)	EtOH	/	25	91
27	5:1	H_2O_2 (3.0)	EtOH	/	25	90

[a] Reaction condition: **1a** (1 mmol), **2a** (1 mmol) and oxidant (3 mmol) in 2 mL solvent at corresponding temperature, air, 3 h.
[b] Isolated yield.

With optimized conditions in hand, a series of oxidative amidations of pyrrolidine **2a** with various 2-oxoaldehydes was thus carried out. The results are summarized in Fig. 2. A host of oxanilic acids bearing either the electron-donating groups such as methyl and methoxy, or electron-withdrawing groups such as chloro and bromo, were well tolerated during the course of the reaction providing the desired oxamides **3ba**–**ha** in moderate to good yields. Besides, synthetically useful naphthyl and benzyl are tolerated in this transformation, giving **3ja**–**ka** in good to moderate yields. Notably, in addition to the aromatic systems, an aliphatic oxamide **3la** could also be obtained in an excellent yield.

To further define the scope of this transformation, a wide range of 2-oxoaldehydes and amines were reacted under the optimized reaction conditions (Fig. 3). Good to excellent yields of tertiary oxamides were obtained in most cases (**3ab**–**ad**, **bc**–**eb** and **hc**–**jb**). However, primary amines remained difficult substrates, giving secondary amides in only moderate yields (**3bb**, **hb** and **lb**). Interestingly, chiral oxamide could be synthesized from the corresponding chiral amine in moderate yield without detectable racemization when compared with the HPLC chromatograms of the racemic compounds (**3ec**). Furthermore, a variety of functional groups such as ether, ester, and halogen are well tolerated for this reaction.

A serious of control experiments has also been performed to explore the mechanism of this transformation (Scheme 2). When 1,1-diphenylethylene (a radical scavenger) was added to the reaction mixture, the oxidative amidation process was suppressed dramatically, which suggested that the oxidative amidation step may involve a radical pathway (Scheme 2a). When the reaction was conducted in the darkness, only 29% yield of **3aa** was obtained, which implies that the sunlight is likely to play an important role in the reaction process (Scheme 2b).

In Scheme 3, a plausible mechanism for the oxidative amidation reaction has been proposed. Initially, hydrogen peroxide can be transformed into hydroxyl radical under the triggering effect of sunlight (Scheme 3a). Then, the hydroxyl radical traps the H of **1a** to produce the acyl radical **4a**. Meanwhile, the aminyl radical **5a** is generated efficiently from **2a** with the assistance of the hydroxyl radical. Finally, the acyl radical **4a** and aminyl radical **5a** combine to result in the desired amide **3aa**.

The products prepared by this procedure are valuable precursors for the synthesis of heterocycles. For example, **3ac** could

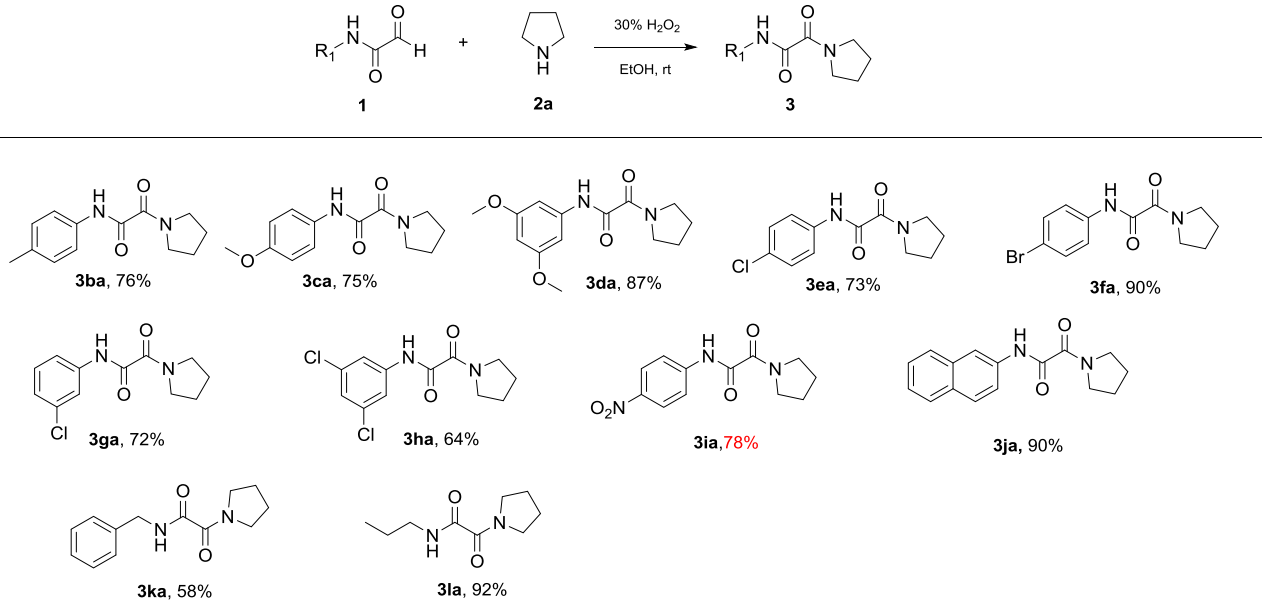


Fig. 2. Substrate scope of aldehydes in direct oxidative amidation with pyrrolidine using aqueous hydrogen peroxide as the oxidant. Reaction conditions: aldehyde (**1**, 3.0 mmol), pyrrolidine (**2**, 1.0 mmol), and 3.0 equiv of H_2O_2 (30% aqueous) in EtOH at room temperature for 2 h.

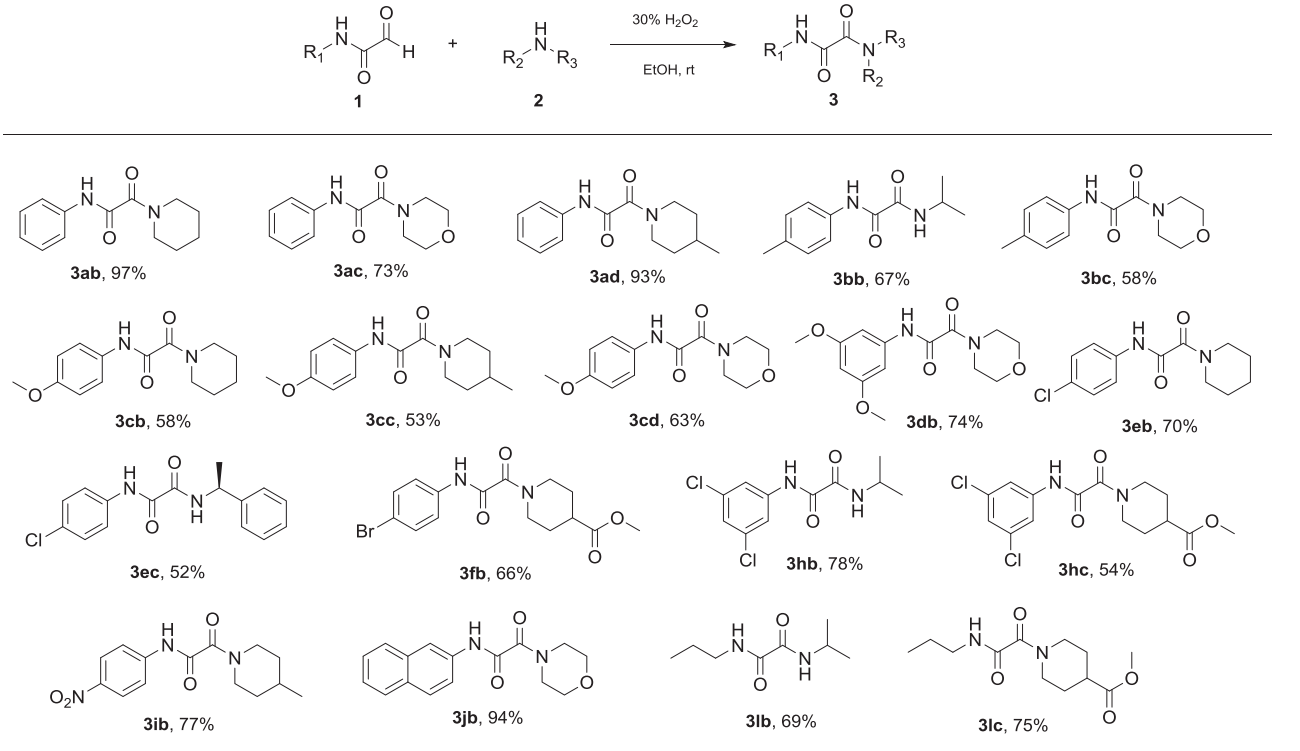
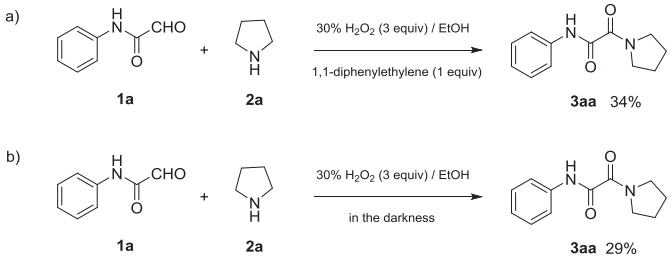


Fig. 3. H_2O_2 initiated amidation of various aldehydes with amines. Reaction conditions: 3.0 equiv of aldehyde, 1.0 equiv of amine, and 3.0 equiv of 30% H_2O_2 (aqueous) in EtOH at room temperature for 2 h.

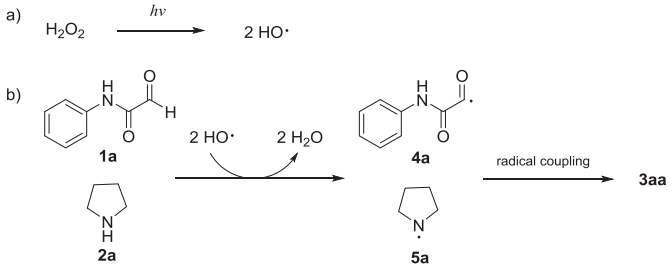
readily be reacted with phosphorus oxychloride to afford the interesting isatin **6** in good yield (Scheme 4).

3. Conclusion

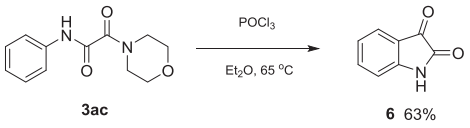
In this study, we have successfully demonstrated a new, efficient and metal-free synthesis of unsymmetrical oxamides via oxidative amidation of aldehydes. With amides mediated by hydrogen peroxide, this approach gives good yields of the product. The utilization of cheap aqueous hydrogen peroxide as the oxidant also provides a clean synthetic route with water being the sole byproduct. In view of the wide functional group tolerance and the mild reaction conditions, this protocol can be quite useful and potential widely adapted in synthetic chemistry.



Scheme 2. Control experiments for the reaction mechanism.



Scheme 3. A proposed mechanism accounting for the formation of **3aa**.



Scheme 4. Synthesis of isatin **6** from **3ac**.

4. Experimental section

4.1. General information

All the direct oxidative reactions of aldehydes with amines were carried out under an air atmosphere. ^1H and ^{13}C NMR spectra were measured on a Bruker Avance 400 or 600 MHz NMR spectrometer with $CDCl_3$ or DMSO-d_6 as solvent and recorded in ppm relative to an internal tetramethylsilane standard. Thin layer chromatography (TLC) characterization was performed with precoated silica gel GF254 (0.2 mm), while column chromatography characterization was performed with silica gel (100–200 mesh). Melting points were measured with YRT-3 melting point apparatus (Shantou Keyi Instrument & Equipment Co., Ltd., Shantou, China). High resolution mass spectroscopy data of the product were collected on a Waters Micromass GCT or a Bruker Apex IV FTMS instrument. The synthesis method of 2-Oxoaldehyde derivatives **1a**–**1l** were according to the reported procedure.[15] General chemicals were purchased from commercial suppliers and used without further purification.

4.2. General reaction procedure for the direct oxidative reactions of aldehydes with amines

2-Oxoaldehydes (3.0 mmol), amines (1.0 mmol), and 2 mL of ethanol were added to a reaction tube under air, and H_2O_2 (3.0 mmol, 30% aqueous solution) was dropped in over three minutes. The solution was then stirred at room temperature until the starting material was completely consumed (monitored by TLC). The mixture was diluted with water and extracted with ethyl acetate (20 mL × 3). The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated to dryness. The crude residue was purified by flash chromatography on silica (petroleum ether/ethyl acetate) to afford pure unsymmetrical oxamides **3**.

*4.2.1. 2-Oxo-N-phenyl-2-(pyrrolidin-1-yl)acetamide (**3aa**).* Pale yellow solid, mp 126–132 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.48 (s, 1H), 7.62 (d, J=7.6 Hz, 2H), 7.36 (t, J=7.6 Hz, 2H), 7.16 (t, J=7.6 Hz, 1H), 4.09 (t, J=6.8 Hz, 2H), 3.62 (t, J=6.8 Hz, 2H), 2.04–1.97 (m, 2H), 1.92–1.86 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 159.0, 158.1, 136.9, 128.9, 124.7, 119.7, 48.8, 48.2, 26.8, 23.3. ESI HRMS: calcd for $C_{12}H_{14}N_2O_2$+Na^+ 241.0947, found 241.0948. Elemental Analysis: C, 66.04; H, 6.47; N, 12.84, found C, 66.17; H, 6.41; N, 12.78.

*4.2.2. 2-Oxo-N-phenyl-2-(piperidin-1-yl)acetamide (**3ab**).* Yellow solid, mp 152–154 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.12 (s, 1H), 7.60 (d, J=8.0 Hz, 2H), 7.36 (t, J=7.6 Hz, 2H), 7.16 (t, J=7.2 Hz, 1H), 4.15–4.05 (m, 2H), 3.66–3.64 (m, 2H), 1.75–1.60 (m, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.6, 159.0, 136.9, 129.1, 125.0, 119.8, 47.7, 44.9, 26.8, 25.8, 24.4. ESI HRMS: calcd for $C_{13}H_{16}N_2O_2$+Na^+ 255.1104, found 255.1104. Elemental Analysis: C, 67.22; H, 6.94; N, 12.06, found C, 67.31; H, 7.01; N, 11.88.

*4.2.3. 2-Morpholino-2-oxo-N-phenylacetamide (**3ac**).* Pale yellow solid, mp 84–86 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ 9.29 (s, 1H), 7.60 (d, J=8.4 Hz, 2H), 7.36 (t, J=7.6 Hz, 2H), 7.17 (t, J=7.6 Hz, 1H), 4.31–4.29 (m, 2H), 3.78–3.75 (m, 4H), 3.73–3.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.5, 158.1, 136.7, 129.0, 125.1, 119.9, 66.9, 66.5, 47.2, 43.9. ESI HRMS: calcd for $C_{12}H_{14}N_2O_3$+Na^+ 257.0897, found 257.0899. Elemental Analysis: C, 61.53; H, 6.02; N, 11.96, found C, 61.60; H, 6.10; N, 11.80.

*4.2.4. 2-(4-Methylpiperidin-1-yl)-2-oxo-N-phenylacetamide (**3ad**).* Off-white solid, mp 118–120 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ 9.14 (s, 1H), 7.60 (d, J=7.8 Hz, 2H), 7.36 (t, J=7.8 Hz, 2H), 7.16 (t, 1H, J=7.8 Hz), 5.09–5.06 (m, 1H), 4.56–4.54 (m, 1H), 3.16–3.11 (m, 1H), 2.79–2.74 (m, 1H), 1.79–1.75 (m, 2H), 1.72–1.66 (m, 1H), 1.32–1.18 (m, 2H), 0.979 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.7, 159.1, 136.9, 129.0, 124.9, 119.8, 46.9, 44.2, 34.9, 33.8, 31.0, 21.5. ESI HRMS: calcd for $C_{14}H_{18}N_2O_2$+Na^+ 269.1260, found 269.1266. Elemental Analysis: C, 68.27; H, 7.37; N, 11.37, found C, 68.35; H, 7.32; N, 11.32.

*4.2.5. 2-Oxo-2-(pyrrolidin-1-yl)-N-(p-tolyl) acetamide (**3ba**).* White solid, mp 162–163 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ 9.40 (s, 1H), 7.50 (d, J=8.4 Hz, 2H), 7.16 (d, J=7.8 Hz, 2H), 4.09 (t, J=6.8 Hz, 2H), 3.61 (t, J=6.8 Hz, 2H), 2.33 (s, 3H), 2.01–1.98 (m, 2H), 1.91–1.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.0, 158.0, 134.9, 133.9, 129.5, 119.8, 48.7, 48.1, 26.6, 23.3, 20.8. ESI HRMS: calcd for $C_{13}H_{16}N_2O_2$+Na^+ 255.1104, found 255.1108. Elemental Analysis: C, 67.22; H, 6.94; N, 12.06, found C, 67.30; H, 6.89; N, 12.01.

*4.2.6. N1-Isopropyl-N2-(p-tolyl)oxalamide (**3bb**).* Off-white solid, mp 192–196 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 9.23 (s, 1H), 7.51 (d, J=8.0 Hz, 2H), 7.40 (s, 1H), 7.18 (d, J=8.0 Hz, 2H), 4.13–4.08 (m, 1H), 2.34 (s, 3H), 1.25 (d, J=6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 159.1, 157.5, 134.9, 133.9, 129.6, 119.8, 42.2, 22.3, 20.9. ESI HRMS: calcd for $C_{12}H_{16}N_2O_2$+Na^+ 243.1104, found 243.1106. Elemental Analysis: C, 65.43; H, 7.32; N, 12.72, found C, 65.52; H, 7.39; N, 12.54.

*4.2.7. 2-Morpholino-2-oxo-N-(p-tolyl)acetamide (**3bc**).* Pale yellow solid, mp 94–98 °C; ^1H NMR ($CDCl_3$, 600 MHz): δ 9.15 (s, 1H), 7.47 (d, J=8.4 Hz, 2H), 7.17 (d, J=8.4 Hz, 2H), 4.33 (t, J=4.8 Hz, 2H), 3.79–3.75 (m, 4H), 3.73 (t, J=4.8 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.2, 158.0, 135.0, 134.0, 129.6, 119.8, 67.2, 66.8, 47.3, 44.0, 20.9. ESI HRMS: calcd for $C_{13}H_{16}N_2O_3$+Na^+ 271.1053,

found 271.1058. Elemental Analysis: C, 62.89; H, 6.50; N, 11.28, found C, 62.96; H, 6.58; N, 11.12.

*4.2.8. N-(4-Methoxyphenyl)-2-oxo-2-(pyrrolidin-1-yl)acetamide (**3ca**).* White solid, mp 136–140 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.41 (s, 1H), 7.54 (d, J=9.6 Hz, 2H), 6.89 (d, J=8.4 Hz, 2H), 4.08 (t, J=7.2 Hz, 2H), 3.80 (s, 3H), 3.61 (t, J=7.2 Hz, 2H), 2.01–1.97 (m, 2H), 1.90–1.87 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 159.1, 157.8, 156.4, 130.1, 121.2, 113.8, 55.2, 48.6, 48.0, 26.6, 23.2. ESI HRMS: calcd for $C_{13}H_{16}N_2O_3$+Na^+ 271.1053, found 271.1056. Elemental Analysis: C, 62.89; H, 6.50; N, 11.28, found C, 63.02; H, 6.44; N, 11.20.

*4.2.9. N-(4-Methoxyphenyl)-2-oxo-2-(piperidin-1-yl)acetamide (**3cb**).* White solid, mp 92–94 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.15 (s, 1H), 7.53 (d, J=8.4 Hz, 2H), 6.88 (d, J=8.8 Hz, 2H), 4.10–4.00 (m, 2H), 3.80 (s, 3H), 3.70–3.63 (m, 2H), 1.70–1.60 (m, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 159.3, 157.9, 156.6, 130.0, 121.4, 114.0, 55.3, 47.7, 44.8, 26.7, 25.6, 24.4. ESI HRMS: calcd for $C_{14}H_{18}N_2O_3$+Na^+ 285.1210, found 285.1216. Elemental Analysis: C, 64.11; H, 6.92; N, 10.68, found C, 64.20; H, 6.99; N, 10.50.

*4.2.10. N-(4-Methoxyphenyl)-2-(4-methylpiperidin-1-yl)-2-oxoacetamide (**3cc**).* Pale brown liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.04 (s, 1H), 7.52 (d, J=8.8 Hz, 2H), 6.89 (d, J=8.8 Hz, 2H), 5.10 (d, J=12.8 Hz, 1H), 4.55 (d, J=12.8 Hz, 1H), 3.81 (s, 3H), 3.13 (t, J=12.8 Hz, 1H), 2.76 (t, J=12.8 Hz, 1H), 1.79–1.75 (m, 2H), 1.71–1.66 (m, 1H), 1.31–1.20 (m, 2H), 0.98 (d, J=6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.0, 158.1, 156.8, 129.9, 121.7, 114.1, 55.2, 46.8, 44.1, 34.6, 33.7, 30.9, 21.6. ESI HRMS: calcd for $C_{15}H_{20}N_2O_3$+Na^+ 299.1366, found 299.1369. Elemental Analysis: C, 65.20; H, 7.30; N, 10.14, found C, 65.28; H, 7.25; N, 10.09.

*4.2.11. N-(4-Methoxyphenyl)-2-morpholino-2-oxoacetamide (**3cd**).* Yellow solid, mp 89–91 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.13 (s, 1H), 7.51 (d, J=9.0 Hz, 2H), 6.90 (d, J=9.6 Hz, 2H), 4.33 (t, J=4.8 Hz, 2H), 3.81 (s, 3H), 3.78 (t, J=4.8 Hz, 2H), 3.76 (t, J=4.8 Hz, 2H), 3.73 (t, J=4.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.3, 157.9, 156.9, 129.8, 121.5, 114.2, 67.2, 66.7, 55.4, 47.2, 43.9. ESI HRMS: calcd for $C_{13}H_{16}N_2O_4$+Na^+ 287.1002, found 287.1004. Elemental Analysis: C, 59.08; H, 6.10; N, 10.60, found C, 59.17; H, 6.17; N, 10.42.

*4.2.12. N-(3,5-Dimethoxyphenyl)-2-oxo-2-(pyrrolidin-1-yl)acetamide (**3da**).* White solid, mp 126–130 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.43 (s, 1H), 6.86–6.85 (m, 2H), 6.28–6.27 (m, 1H), 4.08 (d, J=6.8 Hz, 2H), 3.80 (s, 6H), 3.61 (t, J=6.8 Hz, 2H), 2.02–1.97 (m, 2H), 1.92–1.87 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 161.1, 158.9, 158.0, 138.6, 97.9, 97.4, 55.4, 49.0, 48.4, 26.9, 23.4. ESI HRMS: calcd for $C_{14}H_{18}N_2O_4$+Na^+ 301.1159, found 301.1162. Elemental Analysis: C, 60.42; H, 6.52; N, 10.07, found C, 60.49; H, 6.60; N, 9.91.

*4.2.13. N-(3,5-Dimethoxyphenyl)-2-morpholino-2-oxoacetamide (**3db**).* White solid, mp 114–118 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.17 (s, 1H), 6.82–6.81 (m, 2H), 6.30–6.29 (m, 1H), 4.32 (t, J=4.8 Hz, 2H), 3.79 (s, 6H), 3.77–3.75 (m, 4H), 3.74–3.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 161.0, 158.8, 157.9, 138.6, 98.0, 97.6, 67.1, 66.7, 55.3, 47.3, 44.0. ESI HRMS: calcd for $C_{14}H_{18}N_2O_5$+Na^+ 317.1108, found 317.1109. Elemental Analysis: C, 57.14; H, 6.16; N, 9.52, found C, 57.23; H, 6.23; N, 9.34.

*4.2.14. N-(4-Chlorophenyl)-2-oxo-2-(pyrrolidin-1-yl)acetamide (**3ea**).* White solid, mp 191–194 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.51 (s, 1H), 7.58 (d, J=8.4 Hz, 2H), 7.32 (d, J=8.8 Hz, 2H), 4.07 (t, J=6.8 Hz, 2H), 3.61 (t, J=6.8 Hz, 2H), 2.04–1.97 (m, 2H), 1.92–1.86 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.6, 159.2, 135.8, 129.8, 128.9, 121.0, 48.9, 48.3, 26.8, 23.3. ESI HRMS: calcd for $C_{12}H_{13}ClN_2O_2$+Na^+ 275.0558, found 275.0560. Elemental Analysis: C, 57.04; H, 5.19; N, 11.09, found C, 57.13; H, 5.17; N, 11.06.

*4.2.15. N-(4-Chlorophenyl)-2-oxo-2-(piperidin-1-yl)acetamide (**3eb**).* Pale yellow solid, mp 122–125 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.22 (s, 1H), 7.56 (d, J=8.8 Hz, 2H), 7.31 (d, J=8.8 Hz, 2H), 4.10–4.08 (m, 2H), 3.66–3.63 (m, 2H) 1.71–1.68 (m, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.7, 159.2, 135.6, 129.9, 129.0, 121.1, 47.7, 44.7, 26.7, 25.7, 24.3. ESI HRMS: calcd for $C_{13}H_{15}ClN_2O_2$+Na^+ 289.0714, found 289.0716. Elemental Analysis: C, 58.54; H, 5.67; N, 10.50, found C, 58.61; H, 5.75; N, 10.40.

*4.2.16. (S)-N1-(4-Chlorophenyl)-N2-(1-phenylethyl) oxalamide (**3ec**).* Off-white solid, mp 181–184 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.25 (s, 1H), 7.76 (s, 1H), 7.57 (d, J=8.4 Hz, 2H), 7.37 (d, J=8.4 Hz, 2H), 7.35–7.29 (m, 5H), 5.13–5.10 (m, 1H), 1.60 (d, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 159.3, 159.0, 143.9, 136.9, 128.8, 128.5, 128.4, 127.1, 126.5, 122.1, 49.0, 21.8. ESI HRMS: calcd for $C_{16}H_{15}ClN_2O_2$+Na^+ 325.0714, found 325.0716. Elemental Analysis: C, 63.48; H, 4.99; N, 9.25, found C, 63.61; H, 4.97; N, 9.18.

*4.2.17. N-(4-Bromophenyl)-2-oxo-2-(pyrrolidin-1-yl)acetamide (**3fa**).* Pale brown solid, mp 192–194 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.50 (s, 1H), 7.53 (d, J=8.4 Hz, 2H), 7.47 (d, J=8.4 Hz, 2H), 4.07 (t, J=6.6 Hz, 2H), 3.61 (t, J=6.6 Hz, 2H), 2.03–1.98 (m, 2H), 1.92–1.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 158.7, 158.1, 136.0, 132.0, 121.2, 117.5, 48.9, 48.4, 26.8, 23.4. ESI HRMS: calcd for $C_{12}H_{13}BrN_2O_2$+Na^+ 319.0053, found 319.0064. Elemental Analysis: C, 48.50; H, 4.41; N, 9.43, found C, 48.59; H, 4.39; N, 9.40.

*4.2.18. Methyl 1-(2-((4-bromophenyl)amino)-2-oxoacetyl)piperidine-4-carboxylate (**3fb**).* Brown liquid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.19 (s, 1H), 7.51–7.46 (m, 4H), 4.96–4.94 (m, 1H), 4.39–4.36 (m, 1H), 3.72 (s, 3H), 3.49–3.45 (m, 1H), 3.08–3.04 (m, 1H), 2.67–2.62 (m, 1H), 2.05–2.03 (m, 2H), 1.89–1.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 174.2, 158.6, 158.0, 136.1, 131.9, 121.4, 117.6, 51.7, 45.8, 43.3, 40.5, 28.8, 27.8. ESI HRMS: calcd for $C_{15}H_{17}BrN_2O_4$+Na^+ 391.0264, found 391.0266. Elemental Analysis: C, 48.80; H, 4.64; N, 7.59, found C, 48.87; H, 4.72; N, 7.49.

*4.2.19. N-(3-Chlorophenyl)-2-oxo-2-(pyrrolidin-1-yl)acetamide (**3ga**).* White solid, mp 133–135 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.55 (s, 1H), 7.43 (d, J=8.4 Hz, 1H), 7.28 (d, J=7.8 Hz, 2H), 7.13 (d, J=7.8 Hz, 1H), 4.07 (t, J=7.2 Hz, 2H), 3.62 (t, J=7.2 Hz, 2H), 2.03–1.99 (m, 2H), 1.92–1.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 158.6, 158.1, 138.1, 134.7, 130.0, 124.9, 119.8, 117.8, 49.0, 48.5, 26.8, 23.3. ESI HRMS: calcd for $C_{12}H_{13}ClN_2O_2$+Na^+ 275.0558, found 275.0560. Elemental Analysis: C, 57.04; H, 5.19; N, 11.09, found C, 57.11; H, 5.27; N, 10.99.

*4.2.20. N-(3,5-Dichlorophenyl)-2-oxo-2-(pyrrolidin-1-yl)acetamide (**3ha**).* Off-white solid, mp 188–192 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.56 (s, 1H), 7.61–7.60 (m, 2H), 7.15–7.14 (m, 1H), 4.06 (t, J=7.2 Hz, 2H), 3.62 (t, J=7.2 Hz, 2H), 2.05–1.98 (m, 2H), 1.93–1.86 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 174.3, 159.8, 158.6, 138.8, 135.2, 124.6, 118.4, 48.7, 48.3, 26.6, 23.2. ESI HRMS: calcd for $C_{12}H_{12}Cl_2N_2O_2$+Na^+ 309.0168, found 309.0170. Elemental Analysis: C, 50.20; H, 4.21; N, 9.76, found C, 50.33; H, 4.19; N, 9.69.

*4.2.21. N1-(3,5-Dichlorophenyl)-N2-isopropyloxalamide (**3hb**).* Pale yellow solid, mp 164–166 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.48 (s, 1H), 7.64–7.63 (m, 2H), 7.36 (s, 1H), 7.18–7.17 (m, 1H), 4.13–4.10 (m, 1H), 1.27 (d, J=6.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 159.8, 158.6, 138.7, 135.3, 124.9, 118.1, 42.1, 22.3. ESI HRMS: calcd for

$C_{11}H_{12}Cl_2N_2O_2+Na^+$ 297.0168, found 297.0170. Elemental Analysis: C, 48.02; H, 4.40; N, 10.18, found C, 48.09; H, 4.48; N, 10.08.

*4.2.22. Methyl 1-(2-((3,5-dichlorophenyl)amino)-2-oxoacetyl)piperidine-4-carboxylate (**3hc**).* Off-white solid, mp 122–126 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.24 (s, 1H), 7.57–7.56 (m, 2H), 7.16 (s, 1H), 4.96–4.92 (m, 1H), 4.38–4.34 (m, 1H), 3.72 (s, 3H), 3.51–3.45 (m, 1H), 3.10–3.03 (m, 1H), 2.67–2.61 (m, 1H), 2.06–2.03 (m, 2H), 1.90–1.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 174.2, 159.9, 158.7, 138.7, 135.3, 124.9, 118.2, 51.9, 45.8, 43.3, 40.4, 28.8, 27.7. ESI HRMS: calcd for $C_{15}H_{16}Cl_2N_2O_4+Na^+$ 381.0379, found 381.0381. Elemental Analysis: C, 50.16; H, 4.49; N, 7.80, found C, 50.25; H, 4.47; Cl, N, 7.77.

*4.2.23. N-(4-Nitrophenyl)-2-oxo-2-(pyrrolidin-1-yl)acetamide (**3ia**).* Off-white solid, mp 216–219 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 9.85 (s, 1H), 8.25 (d, *J*=8.4 Hz, 2H), 7.82 (d, *J*=8.4 Hz, 2H), 4.08 (t, *J*=7.2 Hz, 2H), 3.63 (t, *J*=7.2 Hz, 2H), 2.04–2.01 (m, 2H), 1.94–1.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 158.3, 158.1, 144.0, 142.6, 125.1, 119.3, 49.0, 48.5, 26.9, 23.4. ESI HRMS: calcd for $C_{12}H_{13}N_3O_4+Na^+$ 286.0798, found 286.0802. Elemental Analysis: C, 54.75; H, 4.98; N, 15.96, found C, 54.82; H, 5.06; N, 15.80.

*4.2.24. 2-(4-Methylpiperidin-1-yl)-N-(4-nitrophenyl)-2-oxoacetamide (**3ib**).* Pale yellow solid, mp 242–244 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.62 (s, 1H), 8.25 (d, *J*=8.8 Hz, 2H), 7.79 (d, *J*=8.8 Hz, 2H), 5.07–5.03 (m, 1H), 4.56–4.53 (m, 1H), 3.20–3.13 (m, 1H), 2.83–2.76 (m, 1H), 1.82–1.78 (m, 2H), 1.76–1.71 (m, 1H), 1.35–1.17 (m, 2H), 0.99 (d, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.1, 159.5, 144.0, 142.8, 125.0, 119.5, 47.0, 44.3, 34.8, 33.8, 30.9, 21.5. ESI HRMS: calcd for $C_{14}H_{17}N_3O_4+Na^+$ 314.1111, found 314.1113. Elemental Analysis: C, 57.72; H, 5.88; N, 14.42, found C, 57.81; H, 5.95; N, 14.24.

*4.2.25. N-(Naphthalen-2-yl)-2-oxo-2-(pyrrolidin-1-yl)acetamide (**3ja**).* White solid, mp 169–170 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.64 (s, 1H), 8.36 (s, 1H), 7.84–7.79 (m, 3H), 7.54–7.41 (m, 3H), 4.14 (t, *J*=6.8 Hz, 2H), 3.65 (t, *J*=6.8 Hz, 2H), 2.05–2.00 (m, 2H), 1.95–1.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 158.9, 158.2, 134.4, 133.7, 130.8, 128.8, 127.7, 127.5, 126.5, 125.2, 119.6, 116.6, 49.0, 48.4, 26.8, 23.3. ESI HRMS: calcd for $C_{16}H_{16}N_2O_2+Na^+$ 291.1104, found 291.1105. Elemental Analysis: C, 71.62; H, 6.01; N, 10.44, found C, 71.75; H, 5.95; N, 10.36.

*4.2.26. 2-Morpholino-N-(naphthalen-2-yl)-2-oxoacetamide (**3jb**).* Pale brown solid, mp 112–116 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.40 (s, 1H), 8.32–8.31 (m, 1H), 7.85–7.80 (m, 3H), 7.52–7.44 (m, 3H), 4.38 (t, *J*=4.8 Hz, 2H), 3.80 (t, *J*=4.8 Hz, 2H), 3.79–3.76 (m, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 158.8, 158.2, 134.5, 133.6, 130.7, 128.8, 127.8, 127.5, 126.4, 125.3, 119.5, 116.5, 66.8, 66.3, 47.2, 43.9. ESI HRMS: calcd for $C_{16}H_{16}N_2O_3+Na^+$ 307.1053, found 307.1055. Elemental Analysis: C, 67.59; H, 5.67; N, 9.85, found C, 67.67; H, 5.62; N, 9.80.

*4.2.27. N-Benzyl-2-oxo-2-(pyrrolidin-1-yl)acetamide (**3ka**).* White solid, mp 77–79 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.91 (s, 1H), 7.36–7.29 (m, 5H), 4.48 (d, *J*=6.0 Hz, 2H), 4.03 (t, *J*=6.8 Hz, 2H), 3.56 (t, *J*=6.8 Hz, 2H), 2.00–1.94 (m, 2H), 1.89–1.83 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.4, 158.0, 137.4, 129.1, 128.6, 127.6, 127.4, 48,6, 47.8, 43.2, 26.7, 23.3. ESI HRMS: calcd for $C_{13}H_{16}N_2O_2+Na^+$ 255.1104, found 255.1111. Elemental Analysis: C, 67.22; H, 6.94; N, 12.06, found C, 67.35; H, 6.88; N, 11.98.

*4.2.28. 2-Oxo-N-propyl-2-(pyrrolidin-1-yl)acetamide (**3la**).* Pale yellow liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59 (s, 1H), 3.99 (t, *J*=6.8 Hz, 2H), 3.54 (t, *J*=6.8 Hz, 2H), 3.24 (q, *J*=6.8 Hz, 2H), 1.98–1.91 (m, 2H), 1.87–1.80 (m, 2H), 1.59–1.52 (m, 2H), 0.93 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.4, 159.2, 48.4, 47.5, 40.7, 26.6, 23.2, 22.3, 11.1. ESI HRMS: calcd for $C_9H_{16}N_2O_2+Na^+$ 207.1104, found 207.1105. Elemental Analysis: C, 58.67; H, 8.75; N, 15.21, found C, 58.75; H, 8.70; N, 15.16.

*4.2.29. N1-Isopropyl-N2-propyloxalamide (**3lb**).* White solid, mp 153–156 °C; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.49 (s, 1H), 7.30 (s, 1H), 4.08–4.02 (m, 1H), 3.28 (q, *J*=6.6 Hz, 2H), 1.62–1.56 (m, 2H), 1.25–1.21 (m, 6H), 0.97–0.93 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 160.0, 159.0, 41.9, 41.3, 22.4, 22.2, 11.2. ESI HRMS: calcd for $C_8H_{16}N_2O_2+Na^+$ 195.1104, found 195.1105. Elemental Analysis: C, 55.79; H, 9.36; N, 16.27, found C, 55.86; H, 9.44; N, 16.11.

*4.2.30. Methyl 1-(2-oxo-2-(propylamino)acetyl) piperidine-4-carboxylate (**3lc**).* Yellow liquid; ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.22 (s, 1H), 4.82–4.79 (m, 1H), 4.35–4.32 (m, 1H), 3.70 (s, 3H), 3.38–3.33 (m, 1H), 3.26 (q, *J*=6.6 Hz, 2H), 2.99–2.94 (m, 1H), 2.62–2.59 (m, 1H), 2.01–1.98 (m, 2H), 1.83–1.71 (m, 2H), 1.61–1.56 (m, 2H), 0.95 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 174.3, 159.8, 158.6, 51.9, 45.8, 43.2, 40.7, 40.4, 28.7, 27.7, 22.2, 11.1. ESI HRMS: calcd for $C_{12}H_{20}N_2O_4+Na^+$ 279.1315, found 279.1319. Elemental Analysis: C, 56.24; H, 7.87; N, 10.93, found C, 56.33; H, 7.94; N, 10.75.

4.3. The experiment to synthesis of 6

A mixture of 2-morpholino-2-oxo-*N*-phenylacetamide **3ac** (13 mg, 0.033 mmol), $POCl_3$ (1.0 ml) was stirred at room temperature for 5 min. Then, transfer the reaction liquid to 65 °C and stir overnight under argon. After disappearance of the reactant (monitored by TLC), the reaction liquid was poured into 20 ml ice water, extracted with ethyl acetate three times (3 × 25 mL). The organic layer was washed with water and saturated brine, dried over anhydrous Na_2SO_4 and evaporation. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate) to afford the product **6** as an orange solid (63% yield). Mp 200–202 °C (Lit[16] 202–203 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (s, 1H), 7.61–7.53 (m, 2H), 7.11 (t, *J*=7.2 Hz, 1H), 6.90 (d, *J*=8.0 Hz, 1H).

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