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Oxidative Coupling of Diazo and NH_4I: A Route to Primary Oxamates and α-Ketoamides

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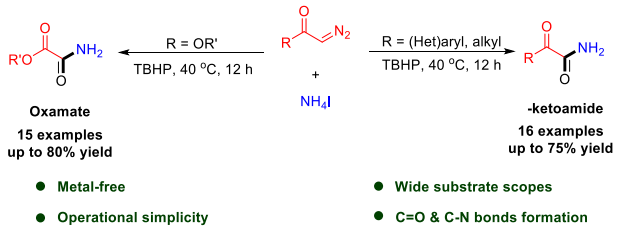
Supporting Information Placeholder



ABSTRACT: A simple and efficient method has been developed for the preparation of primary oxamates and α-ketoamides through the oxidative coupling of diazo compounds and NH_4I. Under the optimized reaction conditions, a range of diazo esters and α-diazoketones was explored, and the corresponding products were obtained in moderate to good yields. This protocol features metal free, mild conditions, wide substrate scopes and operational simplicity.

INTRODUCTION

Oxamates and α-ketoamides both contain amide groups and are ubiquitous in biologically active molecules as well as various pharmaceutical compounds.[1] Examples include the immunosuppressant drugs FK506 and rapamycin, which are T-cell proliferation blockers, and eurystatins **A** and **B**, which inhibit prolyl endopeptidase.[1e,1f] These compounds are also utilized as versatile building blocks in organic synthesis.[2] As a result of these numerous applications, oxamates and α-ketoamides have attracted considerable attention over the past several decades and a wide range of methods for their synthesis has been established. These traditional synthetic approaches are based on the acylation of appropriate amines, but suffer from the requirement for stoichiometric quantities of monoester oxaloyl chlorides or α-oxoyl chlorides (Scheme 1a).[3] The Pd-catalyzed double carbonylation of the corresponding starting materials with amines also provides an efficient means of generating oxamates and α-ketoamides (Scheme 1b).[4] The disadvantage of the latter strategy is that high pressure CO is required, while ethanol is usually used as a solvent for the preparation of oxamates[4a-4c] and the range of substrates is narrow. Other methods for the preparation of oxamates include the metal-free amidation reactions of glyoxalate esters with amines under oxidative conditions,[5a,5b] the *tert*-butyl hydroperoxide (TBHP)-promoted C=C bond cleavages of enamines[5c] and the aerobic esterification reactions of acetoacetamides.[5d] Although many such methods have been developed for the synthesis of oxamates, to the best of our knowledge, there have been few reports regarding the production of *primary* oxamates. In the case of α-ketoamides, synthetic methods proposed to date have largely focused on the preparation of secondary and tertiary α-ketoamides from alkenes,[6] alkynes,[7] aryl ethanes,[8] α-ketoaldehydes,[9] α-keto acids,[10] aryl methyl ketones,[11] 1-arylethanols,[12] α-hydroxy ketones[13] and other starting materials.[14] In contrast, there are only a handful of examples concerning the synthesis of primary α-ketoamides. As an example, Zhu and co-workers reported the $ZnCl_2$-promoted oxidative coupling of 4-methoxybenzaldehyde and 2-isocyano-2,4,4-trimethylpentane to generate a secondary α-ketoamide, followed by treatment with trifluoroacetic acid to provide the corresponding primary α-ketoamide.[15a] In addition, Wang's group established an efficient method for the construction of primary α-ketoamides via the electrochemical oxidation of aryl methyl ketones with ammonium acetate.[15b] Notably, Wang and Wu developed a method for synthesizing primary α-ketoamides from aryl methyl ketones.[11d,15c] Finally, the $Cu(OAc)_2$ or KBr-mediated aerobic oxidation of benzylimidates to primary α-ketoamides was demonstrated by Kumar.[15d,15e]

In general, the present methods for synthesizing primary oxamates and α-ketoamides suffer from several drawbacks, such as narrow scopes and the requirement to use harsh conditions and dangerous reagents. Thus, the development of green, more efficient synthetic pathways would be highly desirable. Herein, we report a novel synthetic strategy for the generation of both primary ox-

amates and α-ketoamides based on the oxidative coupling[16] of diazo compounds and NH_4I, using TBHP as the oxidant (Scheme 1c). In contrast to previous synthetic methods, our methodology does not involve an external catalyst because the NH_4I serves as both the source of ammonia and the catalyst for this transformation. Moreover, the reaction is performed under mild conditions and does not require an acidic or alkaline environment. The diazo compounds are readily prepared from the corresponding alcohols, phenols or carboxylic acids, such that the substrate scope of this reaction is very wide.

Scheme 1. Strategies for the Synthesis of Oxamates and α-ketoamides

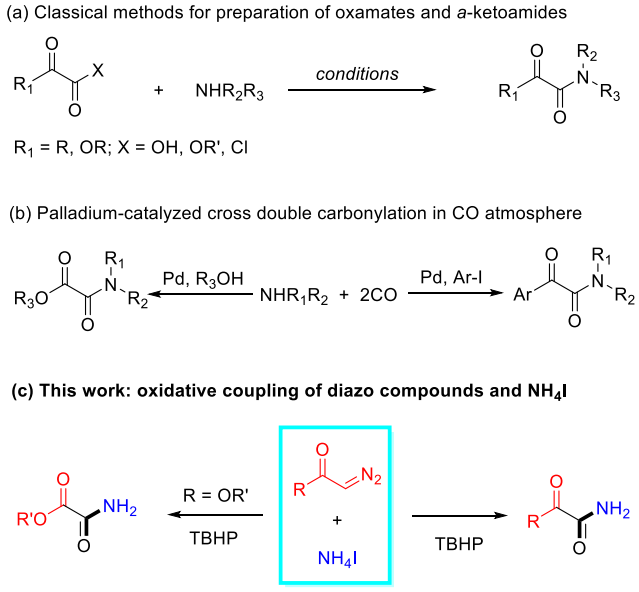
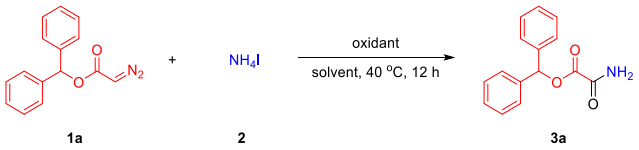


Table 1. Optimization of the Reaction Conditions[a]



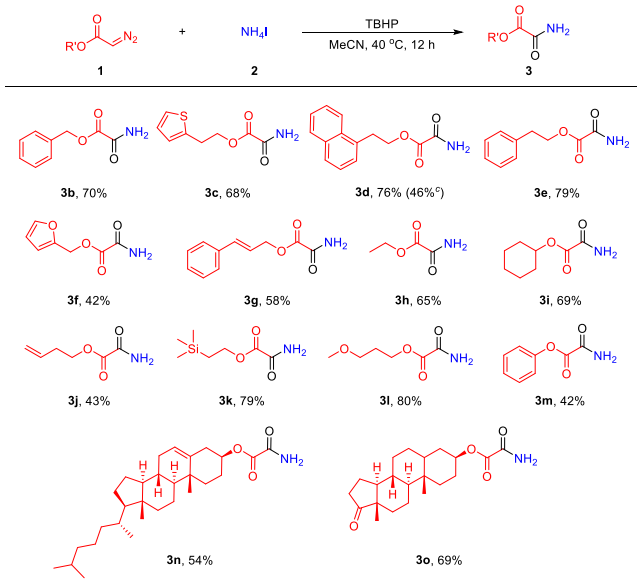
entry	oxidant	solvent	yield(%)[b]
1	TBHP	PE	< 5
2	TBHP	$MeNO_2$	< 5
3	TBHP	THF	53
4	TBHP	EA	69
5	TBHP	*i*-PrOH	51
6	TBHP	1,4-dioxane	72
7	**TBHP**	**MeCN**	**77**
8	TBHP	DMSO	51
9	TBHP	DMF	< 5
10	H_2O_2	MeCN	< 5
11	DTBP	MeCN	< 5
12	$K_2S_2O_8$	MeCN	< 5
13	TBPB	MeCN	< 5
14	BPO	MeCN	70
15	O_2	MeCN	< 5
16	air	MeCN	< 5
17[c]	none	MeCN	< 5
18[d]	TBHP	MeCN	< 5
19[e]	TBHP	MeCN	< 5
20[f]	TBHP	MeCN	< 5

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.8 mmol), TBHP (0.6 mmol, 70% in water), stirred in solvent (1.0 mL) for 12 h under air. [b] Isolated yields. [c] Under N_2. [d] NH_4Cl was used. [e] NH_4Br was used. [f] NH_4OAc was used.

RESULTS AND DISCUSSION

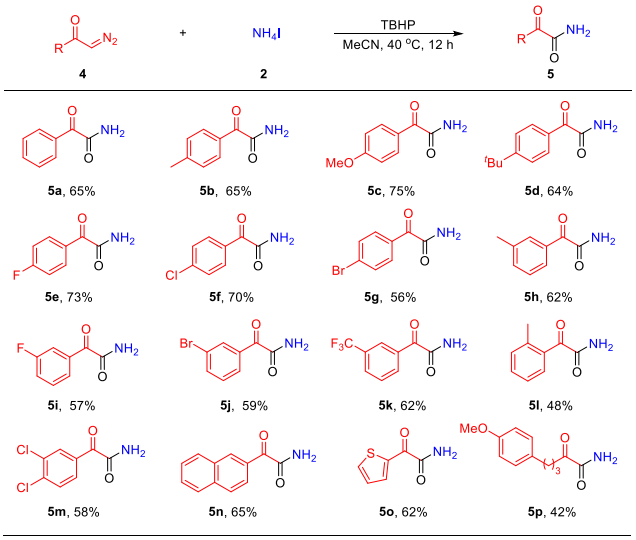
Initially, benzhydryl 2-diazoacetate **1a** and NH_4I were chosen as the model substrates to explore the formation of the oxamate **3a** using TBHP as the oxidant (Table 1). We screened a series of solvents (entries 1-9) and found that acetonitrile gave the best results, providing the desired product **3a** in a high 77% yield (entry 7). A control experiment also showed that the presence of the oxidant was essential for this transformation (entry 17). Compared to TBHP, other oxidants significantly reduced the yield of **3a** (entries 10-16). Various alternative nitrogen sources were also evaluated, by replacing NH_4I with NH_4Cl, NH_4Br and NH_4OAc, but resulted in the failure of the reaction (entries 18-20, for more details see Supporting Information).

Scheme 2. Scope of diazo esters[ab]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.8 mmol), TBHP (0.6 mmol, 70% in water), stirred in MeCN (1.0 mL) for 12 h under air. [b] Isolated yields. [c] 5.0 mmol scale.

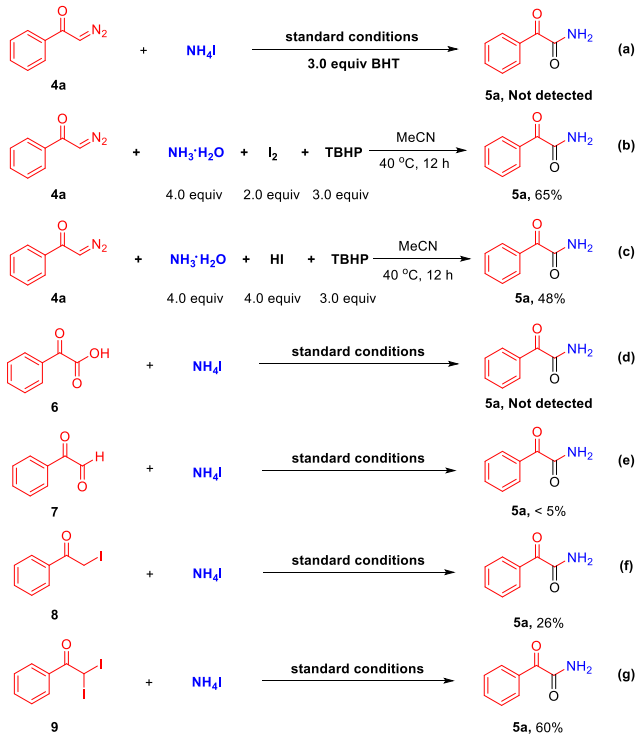
Scheme 3. Scope of α-diazoketones[ab]



[a] Reaction conditions: **4** (0.2 mmol), **2** (0.8 mmol), TBHP (0.6 mmol, 70% in water), stirred in MeCN (1.0 mL) for 12 h under air. [b] Isolated yields.

A variety of primary oxamate derivatives (**3a-3o**) were synthesized from diazoesters and NH_4I under the optimized reaction conditions, as shown in Scheme 2. The commercially available compound ethyl diazoacetate delivered the desired product **3h** in 65% yield. Diazoesters bearing heteroaromatic rings, such as thienyl and furyl moieties, were found to tolerate the reaction conditions, and gave the corresponding products **3c** and **3f** in 68% and 42% yields, respectively. Notably, substrates containing allylic groups also readily participated in this transformation to furnish the products **3g** and **3j** in moderate yields. A tetramethylsilane (TMS) group was also compatible in this oxidative environment, and provided the product **3k** with a good yield. In addition, a diazo ester prepared from phenol reacted efficiently, with a 42% yield of the final product **3m**. To further demonstrate the practicality of this transformation, diazo esters **1n** and **1o** (obtained from cholesterol and epiandrosterone) were used, and produced the corresponding primary oxamates **3n** and **3o** in 54% and 69% yields, respectively. To the best of our knowledge, it is difficult to prepare these two compounds by other methods.

Scheme 4. Mechanistic Studies

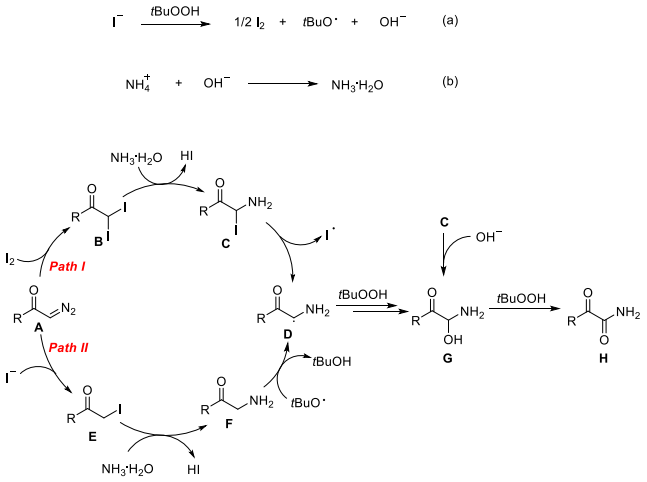


Next, a series of primary α-ketoamides were prepared using diazoketone as the substrate to explore the diversity of this strategy, as shown in Scheme 3. Interestingly, benzene rings having both electron-withdrawing and electron-donating groups were well tolerated, leading to the corresponding α-ketoamide products **5a-5m** in moderate to good yields. In addition, halogens such as F, Cl and Br at *para*- and *meta*- positions on these rings were compatible with this process and readily afforded the final products in good yields, thus providing opportunities for further synthetic transformations. It is noteworthy that 2-diazo-1-(3,4-dichlorophenyl)ethan-1-one, containing two chlorine atoms, was also found to be a suitable reactant, giving the desired product **5m** in 58% yield. As well, α-diazoketones bearing naphthalene or thiophene moieties delivered the corresponding products **5n** and **5o** in 65% and 62% yields, respectively. Notably, an alkyl-substituted α-diazoketone was also usable, such that the desired product **5p** was produced in 42% yield.

A series of experiments was conducted to clarify the mechanism of the reaction (Scheme 4). The compound 2,6-di-*tert*-butyl-4-methylphenol (BHT), a commonly used radical scavenger, was added to the reaction mixture and resulted in the complete inhibition of the formation of the α-ketoamide (Scheme 4a). This result suggested that a radical process might be involved in the reaction. Additional experiments were carried out as shown in Schemes 4b and 4c, and indicated that I_2, HI and $NH_3{\cdot}H_2O$ might be generated *in situ* in this system, and subsequently react with **4a** to deliver the desired product **5a**. Subsequently, 2-oxo-2-phenylacetic acid **6** and 2-oxo-2-phenylacetaldehyde **7** were utilized as substrates for this transformation. Unfortunately, no significant amount of the product **5a** was obtained in either case (Schemes 4d and 4e). In contrast, the use of 2-iodoacetophenone **8** or 2,2-diiodo-1-phenylethan-1-one **9** delivered the α-ketoamide **5a** in 26% and 60% yields, respectively,

indicating that these species might serve as reaction intermediates in this transformation (Schemes 4f and 4g).

Scheme 5. Proposed Reaction Mechanism



Based on the results from the above control experiments together with literature reports, two possible catalytic cycles for this transformation can be proposed, as presented in Scheme 5. Initially, both molecular iodine[17] and $NH_3{\cdot}H_2O$ are generated *in situ* under the optimized conditions (Scheme 5a and 5b). There are two possible pathways for this process and, at present, there is insufficient evidence to determine which the actual mechanism is. In path **I**, the diazo compound **A** interacts with I_2 to generate the intermediate **B**,[18] which is then attacked by $NH_3{\cdot}H_2O$ to deliver **C**. Next, intermediate **C** decomposes to intermediate **D**, which is oxidized to intermediates **G** and **H** successively.[8a,11d] **G** could also be generated from **C** through a simple S_N2 process.[19] In path **II**, intermediate **E** is produced by the insertion of iodide into the diazo compound **A**, and is subsequently attacked by $NH_3{\cdot}H_2O$ to generate intermediate **F**.[11a,b] The *tert*-butoxyl radical traps a hydrogen atom from **F** to afford the intermediate **D**.[8a,11d]

CONCLUSIONS

In summary, we have successfully developed an efficient method for building primary oxamates and α-ketoamides through the oxidative coupling of diazo compounds and NH_4I under transition-metal free conditions. This process simultaneously constructs one C–N bond and one C=O bond in a one pot system. The transformation permits the use of easily prepared or commercially available starting materials, wide substrate scopes and mild reaction conditions, and also offers operational simplicity. The exploration of diazo compounds for the synthesis of other functional skeletons is currently underway in our laboratory.

EXPERIMENTAL SECTION

General information. All manipulations were carried out under air atmosphere. Column chromatography was generally performed on silica gel (300-400 mesh) and reactions were monitored by thin layer chromatography (TLC) using UV light to visualize the course of the reactions. The ^{1}H NMR (400MHz), ^{13}C NMR (100 MHz) and ^{19}F NMR (376 MHz) data were recorded using DMSO-d6 or $CDCl_3$ as solvent at room temperature. The chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. ^{1}H NMR spectra was recorded with tetramethylsilane (δ = 0.00 ppm) as internal reference; ^{13}C NMR spectra was recorded with DMSO-d6 (δ = 39.50 ppm) or $CDCl_3$ (δ = 77.00 ppm) as internal reference. IR, MS and HRMS, were performed by the State-authorized Analytical Center in Soochow University.

General procedure for preparation of primary oxamates or primary *α*-ketoamides. Diazo compounds (0.2 mmol), NH_4I (116.0 mg, 0.8 mmol, 4.0 equiv) were added to test tube charged with stir bar. MeCN (1.0 mL), TBHP (84 μL, 0.6 mmol, 3.0 equiv, 70% in water) were added via syringe. The reaction mixture was heated at 40 °C in oil bath for 12 h, which was then quenched with saturated Na_2SO_3 solution and extracted with ethyl acetate (20 mL × 3). The organic layers were combined and dried with anhydrous Na_2SO_4. Removal of the organic solvent followed by flash column chromatographic purification afforded the desired products using petroleum and ethyl acetate.

Benzhydryl 2-amino-2-oxoacetate ***(3a)***. White solid (39.1 mg, 77% yield); purified by column chromatography on silica gel (PE/EtOAc = 3/1); mp: 182-183 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.38 (s, 1H), 8.08 (s, 1H), 7.48-7.46 (m, 4H), 7.40-7.36 (m, 4H), 7.34-7.28 (m, 2H), 6.90 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d6) δ 160.0, 158.7, 139.6, 128.6, 128.1, 126.7, 78.2. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{13}NO_3Na$ 278.0788; Found 278.0794. IR (neat, cm^{-1}): υ 3398, 3208, 2918, 2849, 1739, 1704, 1688, 1220.

Benzyl 2-amino-2-oxoacetate ***(3b)***. White solid (25.0 mg, 70% yield); purified by column chromatography on silica gel (PE/EtOAc = 3/1); mp: 133-134 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.28 (s, 1H), 7.99 (s, 1H), 7.54-7.27 (m, 5H), 5.23 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d6) δ 160.9, 158.8, 135.1, 128.5, 128.42, 128.40, 67.1. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_9H_9NO_3Na$ 202.0475; Found 202.0481. IR (neat, cm^{-1}): υ 3379, 3204, 2921, 2850, 1735, 1683, 1365, 1229.

2-(thiophen-2-yl)ethyl 2-amino-2-oxoacetate ***(3c)***. White solid (27.1 mg, 68% yield); purified by column chromatography on silica gel (PE/EtOAc = 3/1); mp: 109-111 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.22 (s, 1H), 7.96 (s, 1H), 7.37 (dd, *J* = 4.6, 1.7 Hz, 1H), 7.02 – 6.88 (m, 2H), 4.37 (t, *J* = 6.6 Hz, 2H), 3.20 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d6) δ 160.9, 158.7, 139.4, 127.1, 126.0, 124.6, 65.8, 28.3. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_8H_9NO_3SNa$ 222.0195; Found 222.0201. IR (neat, cm^{-1}): υ 3434, 3223, 2921, 2849, 1675, 1221, 1206, 956.

2-(naphthalen-1-yl)ethyl 2-amino-2-oxoacetate ***(3d)***. White solid (36.7 mg, 76% yield); purified by column chromatography on silica gel (PE/EtOAc = 3/1); mp: 145-147 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.23 (s, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 7.96 (s, 1H), 7.94 (s, 1H), 7.89-7.79 (m, 1H), 7.60-7.52 (m, 2H), 7.48-7.45 (m, 2H), 4.50 (t, *J* = 7.1 Hz, 2H), 3.47 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d6) δ 161.0, 158.8, 133.4, 133.3, 131.5, 128.7, 127.3, 127.1, 126.3, 125.7, 125.6, 123.5, 65.4, 31.1. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{13}NO_3Na$ 266.0788; Found 266.0780. IR (neat, cm^{-1}): υ 3345, 3175, 2921, 2850, 1694, 1240, 1216, 970., 46% yield for 5 mmol scale (559mg **3d** was ebtained).

Phenethyl 2-amino-2-oxoacetate ***(3e)***. White solid (30.4 mg, 79% yield); purified by column chromatography on silica gel (PE/EtOAc = 3/1); mp: 136-137 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.21 (s, 1H), 7.95 (s, 1H), 7.33-7.21 (m, 5H), 4.38 (t, *J* = 6.9 Hz, 2H), 2.97 (t, *J* = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d6) δ 161.0, 158.8, 137.5, 128.9, 128.4, 126.5, 66.1, 34.0. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{10}H_{11}NO_3Na$ 216.0631; Found 216.0632. IR (neat, cm^{-1}): υ 3381, 3189, 2964, 1737, 1682, 1235, 971, 820.

Furan-2-ylmethyl 2-amino-2-oxoacetate ***(3f)***. Light yellow solid (14.2 mg, 42% yield); purified by column chromatography on silica gel (PE/EtOAc = 4/1); mp: 113-115 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.28 (s, 1H), 7.98 (s, 1H), 7.73 (d, *J* = 1.0 Hz, 1H), 6.61 (d, *J* = 3.1 Hz, 1H), 6.61-6.49 (m, 1H), 5.21 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d6) δ 160.7, 158.6, 148.4, 144.1, 111.8, 110.9, 59.0. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_7H_7NO_4Na$ 192.0267; Found 192.0276. IR (neat, cm^{-1}): υ 3349, 3237, 2971, 1682, 1229, 1200, 1152, 931.

Cinnamyl 2-amino-2-oxoacetate ***(3g)***. White solid (23.6 mg, 58% yield); purified by column chromatography on silica gel (PE/EtOAc = 3/1); mp: 143-145 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.28 (s, 1H), 7.99 (s, 1H), 7.50-7.48 (m, 2H), 7.38-7.34 (m, 2H), 7.31-7.27 (m, 1H), 6.77 (d, *J* = 16.0 Hz, 1H), 6.45-6.38 (m, 1H), 4.86 (d, *J* = 5.6 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d6) δ 160.8, 158.9, 135.8, 134.2, 128.7, 128.2, 126.6, 122.7, 66.0. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{11}H_{11}NO_3Na$ 228.0631; Found 228.0637. IR (neat, cm^{-1}): υ 3398, 3214, 2921, 2850, 1681, 1252, 1207, 1180.

Ethyl 2-amino-2-oxoacetate ***(3h)***. White solid (15.0 mg, 65% yield); purified by column chromatography on silica gel (PE/EtOAc = 2/1); mp: 114-116 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.20 (s, 1H), 7.92 (s, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d6) δ 161.1, 159.1, 61.7, 13.8. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_4H_7NO_3Na$ 140.0318; Found 140.0316. IR (neat, cm^{-1}): υ 3374, 3201, 2989, 2941, 1732, 1682, 1238, 686.

Cyclohexyl 2-amino-2-oxoacetate ***(3i)***. White solid (23.3 mg, 69% yield); purified by column chromatography on silica gel (PE/EtOAc = 3/1); mp: 131-133 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.16 (s, 1H), 7.90 (s, 1H), 4.79-4.73 (m, 1H), 1.83-1.81 (m, 2H), 1.72-1.68 (m, 2H), 1.55-1.16 (m, 6H). ^{13}C NMR (100 MHz, DMSO-d6) δ 160.5, 159.3, 74.2, 30.8, 24.7, 23.1. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_8H_{13}NO_3Na$ 194.0788; Found 194.0790. IR (neat, cm^{-1}): υ 3388, 3227, 2945, 2927, 2860, 1735, 1692, 1226.

But-3-en-1-yl 2-amino-2-oxoacetate ***(3j)***. White solid (12.0 mg, 43% yield); purified by column chromatography on silica gel (PE/EtOAc = 3/1); mp: 81-82 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.19 (s, 1H), 7.93 (s, 1H), 5.86-5.75 (m, 1H), 5.30-4.90 (m, 2H), 4.21 (t, *J* = 6.7 Hz, 2H), 2.41 (q, *J* = 6.7 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d6) δ 161.0, 158.9, 134.1, 117.5, 64.6, 32.2. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_6H_9NO_3Na$ 166.0475; Found 166.0478. IR (neat, cm^{-1}): υ 3387, 3235, 2964, 1733, 1681, 1406, 1238, 687.

2-(trimethylsilyl)ethyl 2-amino-2-oxoacetate ***(3k)***. White solid (29.7 mg, 79% yield); purified by column chromatography on silica gel (PE/EtOAc = 3/1); mp: 73-76 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.15 (s, 1H), 7.89 (s, 1H), 4.30-4.22 (m, 2H), 1.07-0.98 (m, 2H), 0.04 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d6) δ 161.2, 159.1, 63.8, 16.6, -1.6. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_7H_{15}NO_3SiNa$ 212.0713; Found 212.0710. IR (neat, cm^{-1}): υ 3368, 3244, 2958, 2902, 1682, 1230, 1207, 1176.

3-methoxypropyl 2-amino-2-oxoacetate ***(3l)***. White solid (25.7 mg, 80% yield); purified by column chromatography on silica gel (PE/EtOAc = 2/1); mp: 76-79 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.20 (s, 1H), 7.93 (s, 1H), 4.20 (t, *J* = 6.4 Hz, 2H), 3.40 (t, *J* = 6.4 Hz, 2H), 3.23 (s, 3H), 1.91-1.84 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d6) δ 161.1, 158.9, 68.2, 63.0, 57.9, 28.1. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_6H_{11}NO_4Na$ 184.0580; Found 184.0587. IR (neat, cm^{-1}): υ 3380, 3214, 2874, 2809, 1682, 1235, 1129, 1097.

Phenyl 2-amino-2-oxoacetate ***(3m)***. Yellow solid (13.9 mg, 42% yield); purified by column chromatography on silica gel (PE/EtOAc = 3/1); mp: 130-131 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.50 (s, 1H), 8.17 (s, 1H), 7.49-7.45 (m, 2H), 7.34-7.30 (m, 1H), 7.26-7.24 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d6) δ 159.5, 158.2, 150.1, 129.7, 126.4, 121.4. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_8H_7NO_3Na$ 188.0318; Found 188.0323. IR (neat, cm^{-1}): υ 3412, 3240, 2921, 2850, 1760, 1683, 1206, 1176.

(3S,8S,9S,10R,13R,14S,17R)-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl 2-amino-2-oxoacetate **(3n).** White solid (49.3 mg, 54% yield); purified by column chromatography on silica gel (PE/EtOAc = 2/1); mp: 234-236 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.22 (s, 1H), 5.42 -5.40 (m, 1H), 4.82-4.73 (m, 1H), 2.56-2.49 (m, 1H), 2.42-2.37 (m, 1H), 2.03-0.82 (m, 38H), 0.68 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 158.7, 138.9, 123.4, 56.7, 56.1, 50.0, 42.3, 39.7, 39.5, 37.6, 36.8, 36.5, 36.2, 35.8, 31.9, 31.8, 28.2, 28.0, 27.3, 24.2, 23.8, 22.8, 22.5, 21.0, 19.2, 18.7, 11.8. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{29}H_{47}NO_3Na$ 480.3448; Found 480.3448. IR (neat, cm^{-1}): υ 3403, 3218, 2935, 2867, 1735, 1698, 1400, 1215.

(3S,8R,9S,10S,13S,14S)-10,13-dimethyl-17-oxohexadecahydro-1H-cyclopenta[a]phenanthren-3-yl-2-amino-2-oxoacetate ***(3o)***. White solid (49.4 mg, 69% yield); purified by column chromatography on silica gel (PE/EtOAc = 2/1); mp: 215-217 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 1H), 6.73 (s, 1H), 4.90-4.82 (m, 1H), 2.48-2.41 (m, 1H), 2.18-1.21 (m, 18H). 1.07-0.94 (m, 2H), 0.88-0.86 (m, 6H), 0.76-0.70 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d6) δ 219.6, 160.4, 159.2, 75.0, 53.6, 50.6, 47.1, 43.9, 36.0, 35.3, 35.2, 34.4, 33.2, 31.3, 30.3, 27.9, 26.7, 21.3, 20.1, 13.4, 11.9. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{21}H_{31}NO_4Na$ 384.2145; Found 384.2135. IR (neat, cm^{-1}): υ 3423, 3241, 2935, 2839, 1739, 1689, 1395, 1213.

2-oxo-2-phenylacetamide ***(5a)***. Light yellow solid (19.2 mg, 65% yield); purified by column chromatography on silica gel (PE/EtOAc = 5/1); mp: 82-84 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.33 (s, 1H), 7.99-7.97 (m, 3H), 7.74-7.71 (m, 1H), 7.61-7.57 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d6) δ 190.8, 167.2, 134.5, 132.7, 129.6, 128.9. HRMS (ESI-TOF) m/z: [M + MeOH + Na]$^+$ Calcd for

$C_9H_{11}NO_3Na$ 204.0631; Found 204.0635. IR (neat, cm^{-1}): υ 3428, 3203, 2921, 1679, 1657, 1228, 978, 683.

2-oxo-2-(p-tolyl)acetamide ***(5b)***. Light yellow solid (20.9 mg, 65% yield); purified by column chromatography on silica gel (PE/EtOAc = 5/1); mp: 127-129 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.28 (s, 1H), 7.94 (s, 1H), 7.88 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d6) δ 190.4, 167.3, 145.2, 130.3, 129.8, 129.5, 21.3. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_9H_9NO_2Na$ 186.0525; Found 186.0528. IR (neat, cm^{-1}): υ 3401, 3193, 2923, 1632, 1602, 1236, 770, 639.

2-(4-methoxyphenyl)-2-oxoacetamide ***(5c)***. Yellow solid (26.6 mg, 75% yield); purified by column chromatography on silica gel (PE/EtOAc = 5/1); mp: 130-131 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.24 (s, 1H), 7.98 (d, *J* = 8.8 Hz, 2H), 7.90 (s, 1H), 7.11 (d, *J* = 8.8 Hz, 2H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d6) δ 189.3, 167.5, 164.1, 132.2, 125.6, 114.3, 55.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_9H_9NO_3Na$ 202.0475; Found 202.0482. IR (neat, cm^{-1}): υ 3457, 3273, 3191, 2849, 1704, 1645, 1240, 800.

2-(4-(tert-butyl)phenyl)-2-oxoacetamide ***(5d)***. Light yellow solid (26.5 mg, 64% yield); purified by column chromatography on silica gel (PE/EtOAc = 5/1); mp: 51-53 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.28 (s, 1H), 7.92 (d, *J* = 8.2 Hz, 3H), 7.61 (d, *J* = 8.2 Hz, 2H), 1.31 (s, 9H). ^{13}C NMR (100 MHz, DMSO-d6) δ 190.5, 167.3, 157.7, 130.3, 129.7, 125.8, 35.0, 30.7. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{15}NO_2Na$ 228.0995; Found 228.0999. IR (neat, cm^{-1}): υ 3344, 3127, 2959, 2869, 1655, 1600, 1240, 984.

2-(4-fluorophenyl)-2-oxoacetamide ***(5e).*** Light yellow solid (24.0 mg, 73% yield); purified by column chromatography on silica gel (PE/EtOAc = 5/1); mp: 146-148 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.35 (s, 1H), 8.10 (dd, *J* = 8.6, 5.7 Hz, 2H), 8.03 (s, 1H), 7.42 (t, *J* = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d6) δ 189.1, 166.9 and 164.4 (d, J_{C-F} = 252.4 Hz), 166.7, 132.9 (d, J_{C-F} = 9.8 Hz), 129.6 (d, J_{C-F} = 2.8 Hz), 116.2 (d, J_{C-F} = 22.2 Hz). ^{19}F NMR (376 MHz, DMSO-d6) δ -103.47. HRMS (ESI-TOF) m/z: $[M + MeOH + Na]^+$ Calcd for $C_9H_{10}FNO_3Na$ 222.0537; Found 222.0537. IR (neat, cm^{-1}): υ 3451, 3288, 3106, 1715, 1662, 1575, 1224, 1159.

2-(4-chlorophenyl)-2-oxoacetamide ***(5f)***. Light yellow solid (25.5 mg, 70% yield); purified by column chromatography on silica gel (PE/EtOAc = 5/1); mp: 125-126 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.36 (s, 1H), 8.05-8.01 (m, 3H), 7.68-7.66 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d6) δ 189.4, 166.5, 139.4, 131.6, 131.5, 129.1. HRMS (ESI-TOF) m/z: $[M + MeOH + Na]^+$ Calcd for $C_9H_{10}{}^{35}ClNO_3Na$ 238.0241; Found 238.0235. $C_9H_{10}{}^{37}ClNO_3Na$ 240.0212; Found 240.0183. IR (neat, cm^{-1}): υ 3431, 3287, 3104, 1710, 1661, 1575, 1228, 1178.

2-(4-bromophenyl)-2-oxoacetamide ***(5g)***. Light yellow solid (25.2 mg, 56% yield); purified by column chromatography on silica gel (PE/EtOAc = 5/1); mp: 108-110 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.35 (s, 1H), 8.05 (s, 1H), 7.94-7.92 (m, 2H), 7.82-7.80 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d6) δ 189.6, 166.4, 132.1, 131.8, 131.6, 128.7. HRMS (ESI-TOF) m/z: $[M + MeOH + Na]^+$ Calcd for $C_9H_{10}{}^{79}BrNO_3Na$ 281.9736; Found 281.9738. $C_9H_{10}{}^{81}BrNO_3Na$ 283.9716; Found 283.9683. IR (neat, cm^{-1}): υ 3416, 3300, 3100, 2921, 1684, 1655, 1225, 1168.

2-oxo-2-(m-tolyl)acetamide ***(5h)***. Light yellow solid (20.0 mg, 62% yield); purified by column chromatography on silica gel (PE/EtOAc = 5/1); mp: 86-88 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.31 (s, 1H), 7.96 (s, 1H), 7.78-7.76 (m, 2H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d6) δ 191.0, 167.3, 138.4, 135.1, 132.8, 129.8, 128.9, 126.9, 20.8. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_9H_9NO_2Na$ 186.0525; Found 186.0530. IR (neat, cm^{-1}): υ 3435, 3230, 2922, 2853, 1686, 1602, 1257, 1170.

2-(3-fluorophenyl)-2-oxoacetamide ***(5i)***. Light yellow solid (19.0 mg, 57% yield); purified by column chromatography on silica gel (PE/EtOAc = 5/1); mp: 112-114 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.38 (s, 1H), 8.07 (s, 1H), 7.85-7.84 (m, 1H), 7.75-7.73 (m, 1H), 7.70-7.54 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d6) δ 189.2, 166.3, 162.0 (d, J_{C-F} = 245.9 Hz), 135.0 (d, J_{C-F} = 6.6 Hz), 131.3 (d, J_{C-F} = 7.8 Hz), 126.2 (d, J_{C-F} = 2.8 Hz), 121.5 (d, J_{C-F} = 21.4 Hz), 115.6 (d, J_{C-F} = 22.7 Hz). ^{19}F NMR (376 MHz, DMSO-d6) δ -111.77. HRMS (ESI-TOF) m/z: $[M + MeOH + Na]^+$ Calcd for $C_9H_{10}FNO_3Na$ 222.0537; Found 222.0537. IR (neat, cm^{-1}): υ 3412, 3289, 2920, 2850, 1715, 1669, 1246, 1171.

2-(3-bromophenyl)-2-oxoacetamide ***(5j)***. Light yellow solid (26.7 mg, 59% yield); purified by column chromatography on silica gel (PE/EtOAc = 5/1); mp: 90-92 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.37 (s, 1H), 8.11-8.05 (m, 2H), 7.99 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d6) δ 188.9, 166.1, 137.0, 134.8, 131.9, 131.2, 128.8, 122.0. HRMS (ESI-TOF) m/z: $[M + MeOH + Na]^+$ Calcd for $C_9H_{10}{}^{79}BrNO_3Na$ 281.9736; Found 281.9738. $C_9H_{10}{}^{81}BrNO_3Na$ 283.9716; Found 283.9682. IR (neat, cm^{-1}): υ 3397, 3226, 2923, 2852, 1659, 1222, 988, 757.

2-oxo-2-(3-(trifluoromethyl)phenyl)acetamide ***(5k)***. Yellow solid (26.7 mg, 62% yield); purified by column chromatography on silica gel (PE/EtOAc = 5/1); mp: 114-116 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.42 (s, 1H), 8.31 (s, 1H), 8.29 (s, 1H), 8.11 (d, *J* = 8.0 Hz, 2H), 7.85 (t, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d6) δ 188.7, 165.8, 133.7 (d, J_{C-F} = 6.7 Hz), 130.6 (q, J_{C-F} = 3.6 Hz), 130.4, 129.5 (q, J_{C-F} = 32.4 Hz), 126.0 (q, J_{C-F} = 4.0 Hz,), 123.68 (d, J_{C-F} = 272.4 Hz). ^{19}F NMR (376 MHz, DMSO-d6) δ -61.53. HRMS (ESI-TOF) m/z: $[M + MeOH + Na]^+$ Calcd for $C_{10}H_{10}F_3NO_3Na$ 272.0505; Found 272.0500. IR (neat, cm^{-1}): υ 3370, 3226, 2923, 2853, 1658, 1331, 1216, 1162.

2-oxo-2-(o-tolyl)acetamide ***(5l)***. Yellow solid (15.3 mg, 48% yield); purified by column chromatography on silica gel (PE/EtOAc = 5/1); mp: 109-110 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.28 (s, 1H), 7.93 (s, 1H), 7.71 (d, *J* = 7.2 Hz, 1H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 2H), 2.50 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d6) δ 193.6, 167.5, 139.3, 132.9, 132.3, 131.8, 131.7, 125.9, 20.6. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_9H_9NO_2Na$ 186.0525; Found 186.0515. IR (neat, cm^{-1}): υ 3418, 3306, 3209, 2936, 1721, 1676, 1232, 974.

2-(3,4-dichlorophenyl)-2-oxoacetamide ***(5m)***. Yellow solid (25.0 mg, 58% yield); purified by column chromatography on silica gel (PE/EtOAc = 5/1); mp: 162-164 °C;

^{1}H NMR (400 MHz, DMSO-d6) δ 8.39 (s, 1H), 8.19 (d, *J* = 1.8 Hz, 1H), 8.11 (s, 1H), 7.98 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d6) δ 187.7, 165.4, 137.3, 133.1, 131.8, 131.34, 131.32, 129.9. HRMS (ESI-TOF) m/z: [M + MeOH + Na]$^+$ Calcd for $C_9H_9Cl_2NO_3Na$ 271.9852, Found 271.9861. IR (neat, cm^{-1}): υ 3452, 3206, 2922, 2852, 1707, 1667, 1575, 1373, 1220.

2-(naphthalen-2-yl)-2-oxoacetamide ***(5n)***. Yellow solid (25.4 mg, 65% yield); purified by column chromatography on silica gel (PE/EtOAc = 5/1); mp: 173-176 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.68 (s, 1H), 8.43 (s, 1H), 8.21-8.19 (m, 1H), 8.11-8.00 (m, 4H), 7.73 (t, *J* = 7.4 Hz, 1H), 7.66 (t, *J* = 7.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d6) δ 190.9, 167.3, 135.6, 132.7, 131.9, 130.1, 129.9, 129.4, 128.7, 127.8, 127.3, 123.9. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{12}H_9NO_2Na$ 222.0525; Found 222.0523. IR (neat, cm^{-1}): υ 3405, 3201, 1692, 1663, 1593, 1277, 1264, 1124.

2-oxo-2-(thiophen-2-yl)acetamide ***(5o)***. Brown solid (18.9 mg, 62% yield); purified by column chromatography on silica gel (PE/EtOAc = 5/1); mp: 84-86 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.32 (s, 1H), 8.18-8.15 (m, 2H), 8.00 (s, 1H), 7.31-7.29 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d6) δ 180.5, 164.2, 138.7, 137.4, 137.1, 128.6. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_6H_5NO_2SNa$ 177.9933; Found 177.9934. IR (neat, cm^{-1}): υ 3447, 3274, 2921, 1703, 1643, 1569, 1501, 1242.

5-(4-methoxyphenyl)-2-oxopentanamide ***(5p)***. Yellow solid (18.6 mg, 42% yield); purified by column chromatography on silica gel (PE/EtOAc = 6/1); mp: 128-131 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 7.90 (s, 1H), 7.63 (s, 1H), 7.10 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 3.72 (s, 3H), 2.76 (t, *J* = 7.2 Hz, 2H), 2.51 (t, *J* = 7.2 Hz, 2H), 1.96-1.56 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d6) δ 199.7, 163.4, 157.5, 133.4, 129.2, 113.7, 54.9, 35.8, 33.3, 24.8. HRMS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for $C_{12}H_{15}NO_3Na$ 244.0944; Found 244.0939. IR (neat, cm^{-1}): υ 3411, 3280, 2939, 2839, 1659, 1513, 1247, 1176.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Reaction optimization, copies of ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

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