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Coupling of Methyl Ketones and Primary or Secondary Amines Leading to α-Ketoamides

Wei Wei,[†] Ying Shao,[‡] Huayou Hu,[§] Feng Zhang,[†] Chao Zhang,[†] Yuan Xu,[†] and Xiaobing Wan*[,†]

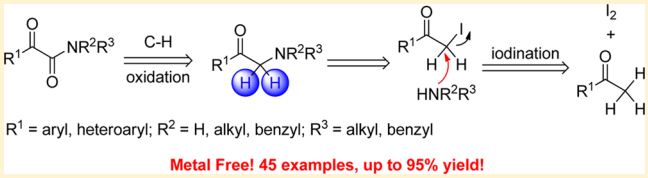
[†]Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, PR China

[‡]Jiangsu Province Key Laboratory of Fine Petrochemical Engineering, Changzhou University, Changzhou 213164, PR China

[§]Key Laboratory for Chemistry of Low-Dimensional Materials, School of Chemistry and Chemical Engineering, Huaiyin Normal University, Huaian 223300, PR China

Supporting Information

ABSTRACT: A metal-free oxidative coupling of methyl ketones and primary or secondary amines to α-ketoamides has been developed. Four intermediates, α-iodoketone, α-aminoketone, iminium intermediate, and α-hydroxy amine have been identified through a series of control experiments. The atom-economic methodology can be scaled-up, tolerates a variety of functional groups, and is operationally simple.

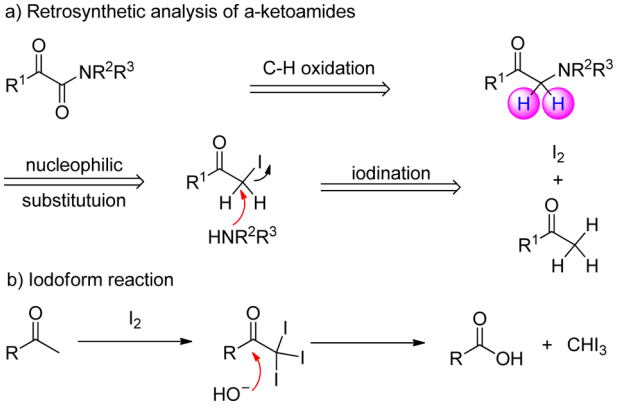


INTRODUCTION

The iodoform reaction, discovered in 1822, is one of the oldest reactions in organic chemistry.[1] While the iodoform reaction has been widely used to prepare carboxylic acids and identify CH_3CO groups, it is surprising that few expansions have been developed since its discovery. Herein, we combine the old iodoform reaction with a modern C−H oxidation[2] to provide a new strategy for α-ketoamides synthesis. α-Ketoamides are prevalent structural motifs found in numerous natural products, biologically relevant molecules, and marketed drugs.[3] They also serve as useful synthetic intermediates for further transformations.[4] As a result, the synthesis of α-ketoamides has attracted considerable interest.[5−13] Although much progress has been made in this field, the search for a simple and practical catalytic system remains a challenge for the synthetic chemist.

As shown in our retrosynthetic analysis (Scheme 1a), α-ketoamides could be synthesized from α-aminoketones through C−H oxidation, and α-aminoketone is the nucleophilic substitution product of amine and α-iodoketone reactants.[14] In turn, α-iodoketones can be formed by iodination of a methyl ketone.[15] It is well-known that nucleophilic attack by hydroxide on a carbonyl carbon atom was involved in the catalytic cycle of the iodoform reaction (Scheme 1b). In sharp contrast, nucleophilic attack by an amine on the iodomethyl, not the carbonyl group, is a key step in this pathway. Transition metal-catalyzed C−H oxidation is of both fundamental and industrial interest, enabling clean access to many functionalized chemicals.[2] However, despite their remarkable potential, the toxicity and expense of transition metals is a concern. Continuing our recent studies in TBAI (tetrabutylammonium iodide)-catalyzed chemical transformation,[16] we conceived of converting methyl ketone and amine to the corresponding α-ketoamides using a similar metal-free approach.

Scheme 1. Design for α-Ketoamides Synthesis



RESULTS AND DISCUSSION

Initially, we investigated the room temperature reaction of acetophenone **1a** with morpholine **2a** in the presence of 50 mol % TBAI in ^{i}PrOH for 13 h. The desired α-ketoamide **3a** was obtained in moderate yield (Table 1, entry 1). The use of KI under the same conditions lowered the yield (Table 1, entry 2). Finally, iodine was identified as the best catalyst for this reaction, affording α-ketoamide **3a** in excellent yield (Table 1, entry 3). No significant amount of product was observed in the absence of iodine or TBHP (Table 1, entries 4 and 5). The choice of oxidant was also crucial for this transformation. Other common oxidants (such as H_2O_2, *m*-CPBA, Oxone and O_2) suppressed the formation of desired α-ketoamide **3a** (Table 1, entries 6−9). Notably, no benzoic acid or 4-benzoylmorpholine

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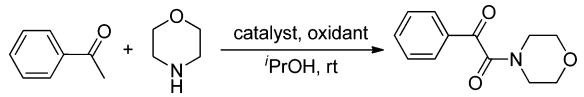
Table 1. Optimization of Reaction Conditions[a]



1a 2a 3a

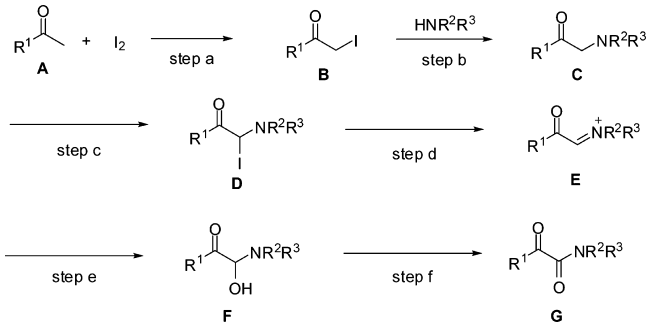
entry	catalyst	oxidant	yield
1	TBAI	TBHP	54%
2	KI	TBHP	40%
3	I_2	TBHP	90%
4	–	TBHP	N.O.[b]
5	I_2	–	<5%
6	I_2	H_2O_2	11%
7	I_2	*m*-CPBA	N.O.[b]
8	I_2	Oxone	13%
9	I_2	O_2	<5%
10	I_2	TBHP	82%[c]

[a]Reaction conditions: 0.5 mmol acetophenone **1a**, 2.0 mmol morpholine **2a**, 50 mol % catalyst, 3.0 mmol TBHP in 2.0 mL of ^{i}PrOH at room temperature for 13 h. [b]Not observed. [c]100 mmol acetophenone **1a** and 400 mmol morpholine **2a** were used.

(nucleophilic attack by morpholine on carbonyl group) were detected as a byproduct. The high selectivity could be attributed to the strong nucleophilicity of amines and superior leaving ability of iodide. Importantly, the reaction was scaled up to 100 mmol and retained its high yield (Table 1, entry 10). The mild conditions and cheap commercial available starting materials (catalyst, oxidant and reactant) make the methodology applicable in synthetic chemistry and drug discovery.

A proposed reaction mechanism, which differs from Ji's report,[7d] is shown in Scheme 2. In the first step, iodination of

Scheme 2. Proposed Reaction Mechanism



methyl ketone **A** forms α-iodoketone **B** (step a).[15] Subsequent nucleophilic substitution of amine to α-iodoketone **B** generates α-aminoketone **C** (step b).[14] Further iodination produces α-iodo-α-aminoketone **D** (step c). Ionization of **D** generates iminium-type intermediate **E** under the standard conditions (step d).[17] Nucleophilic attack by H_2O on the resulting **E** gives the α-hydroxy amine intermediate **F** (step e).[18] Finally, oxidation of **F** affords the desired α-ketoamide **G** (step f).[19]

A two-step one-pot synthesis of α-ketoamide **3b** was carried out to elucidate the mechanism. Treatment of 4′-bromoacetophenone **1b** with morpholine **2a** in the presence of 50 mol % iodine generated the α-aminoketone **4** (detected by LC–MS) after 1 h at ambient temperature. Subsequent addition of TBHP resulted in the desired α-ketoamide **3b** in 78% yield (Scheme 3a). When α-aminoketone **4** was subjected to the standard conditions, α-ketoamide **3b** was obtained in 81% yield (Scheme 3b). Notably, only trace amount of α-ketoamide **3b** was observed in the absence of iodine (Scheme 3c). We suspected α-aminoketone **4** is generated in situ by the nucleophilic substitution of morpholine **2a** on 1-(4-bromophenyl)-2-iodoethanone **5**. However, no 1-(4-bromophenyl)-2-iodoethanone **5** was observed by LC–MS during the reaction, which might be owing to the fast reaction of morpholine **2a** and 1-(4-bromophenyl)-2-iodoethanone **5**. As anticipated, when 1-(4-bromophenyl)-2-iodoethanone **5** was used in the standard conditions, a 76% yield of α-ketoamide **3b** was obtained (Scheme 3c). On the basis of the above results, both α-iodoketones and α-aminoketones are reaction intermediates in the formation of α-ketoamides.

Further investigations into the mechanism were performed. As shown in Scheme 4a, hydroxide anion is generated in situ from TBHP in the standard conditions.[20] Consequently, when an ^{18}O-labeled reaction was carried out, both **3b**-^{18}O and **3b** were obtained (Scheme 4b). Therefore, we believed the nucleophilic attack of a water molecule on the iminium-type intermediate, not by TBHP, is involved in the catalytic cycle. Notably, benzoylformaldehyde was also a suitable reaction partner, which suggested the α-hydroxy amine served as an intermediate in the transformation (Scheme 4c).

Next, a variety of substituted aryl methyl ketones were subjected to the standard conditions. Representative results are summarized in Figure 1. A host of aryl methyl ketones with *ortho*, *meta*, or *para* electron-donating or electron-withdrawing substituents reacted smoothly with morpholine **2a** in moderate to excellent yields. Interestingly, the presence of bromo and chloro substituents on the aromatic groups did not interfere with the C–H oxidation process, affording products **3b**, **3e** and **3m** that could be further functionalized by transition metal-catalyzed cross-coupling reactions. The reaction was also compatible with fluoro (**3d**), benzylic C–H (**3f**), trifluoromethyl (**3g**), nitriles (**3h**), esters (**3i**), alkyne (**3j**), sulfonate (**3k**), nitro (**3l** and **3o**), and ether (**3p**) groups. Even oxidative sensitive groups, such as C,C double bond (**3i**) and an unprotected hydroxyl group (**3n**), were tolerated in the transformation. Finally, steric effects did not significantly influence the reactivity of the reaction, with product **3q** being obtained in high yield.

Most recently, Ji and co-workers have developed an elegant copper-catalyzed oxidative coupling of methyl ketones and amines using molecular oxygen.[7d] In their work, the ketones are limited primarily to aryl methyl ketones. To further showcase the potential of our methodology, ketones with heteroaryl substituents were submitted to the optimized conditions. As shown in Figure 2, both 2-acetylthiophene and 2-acetyl-5-chlorothiophene were compatible reaction partners for this transformation, leading to products **6a** and **6b** in high yields. Thiazole (**6c**), pyrazine (**6d**) and furan (**6h**) were also tolerated in the α-ketoamide formation reaction. Finally, 2-acetylpyridine, 3-acetylpyridine, and 4-acetylpyridine afforded the desired α-ketoamide **6e–6g** in moderate yields.

To further define the scope of the α-ketoamide synthesis, we next applied this process to a series of amines as shown in Figure 3. Pyrrolidine and piperidine reacted well with acetophenone **1a** to afford **7a** and **7c** in 73 and 64% yields, respectively. Acyclic amines also worked well and gave the corresponding α-ketoamides in moderate to excellent yields (**7b**, **7d** and **7h**). A variety of functional groups, including ether (**7h**), pyridine (**7i**), ester (**7l**), and tertiary amine (**7i**), were unaffected in the reaction, and corresponding α-ketoamides

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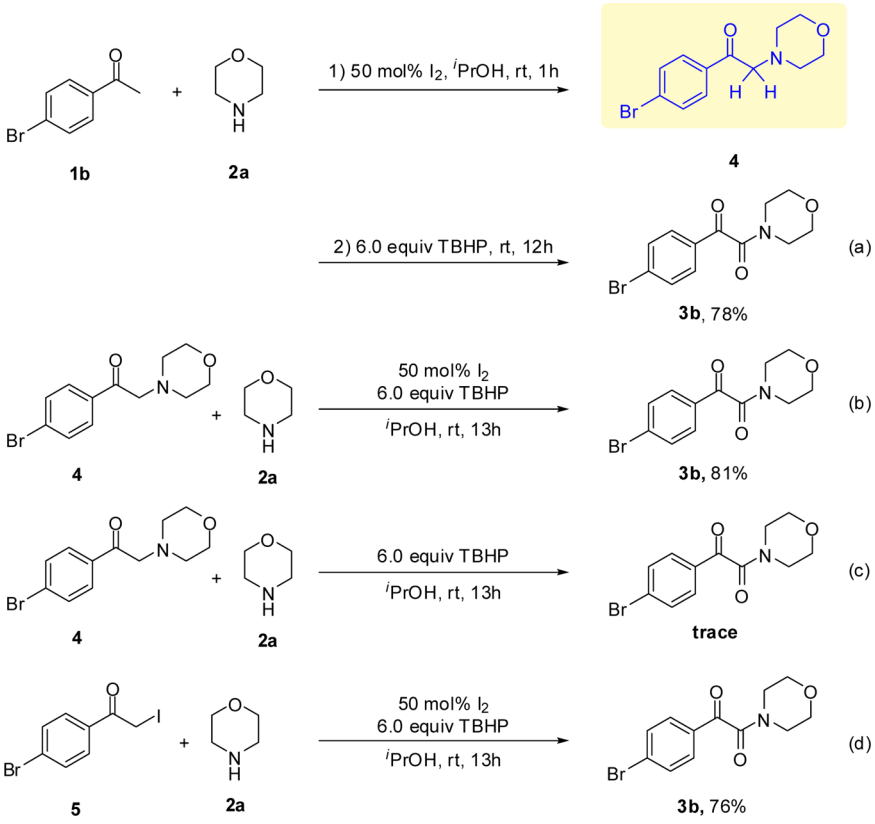
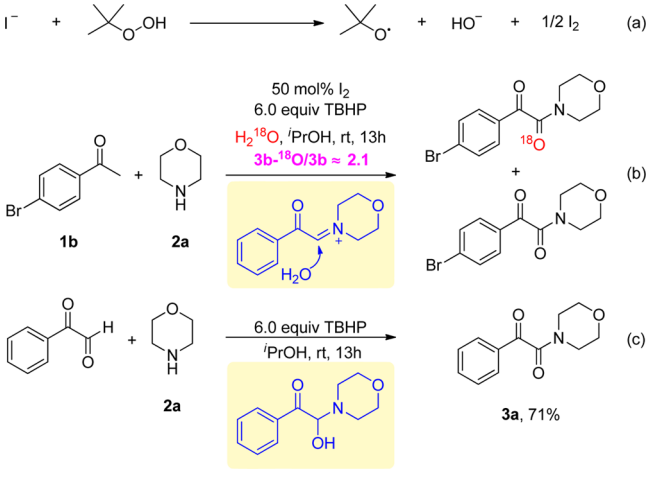
Scheme 3. Investigations into the Reaction Mechanism



Scheme 4. Investigation into the Reaction Mechanism



were obtained in high yields. Synthetically useful benzyl and tetrahydroisoquinoline are tolerated in the transformation, giving **7e**–**7g** in good yields. Notably, free hydroxyl (**7k**) and removable BocNH group (**7j**) were inert in the reaction, leading to expected α-ketoamides in satisfactory yields.

Next, primary amines were used as reaction partners for the synthesis of α-ketoamides. As shown in Figure 4, these reactions also tolerate a variety of aromatic substituents (electron-rich, electron-poor, and heteroaromatic), while potentially sensitive functional groups (double bond and benzylic C–H bond) are also unaffected by the reaction conditions.

CONCLUSIONS

In summary, we have described an oxidative coupling of methyl ketones with primary and secondary amines to give α-ketoamides in moderate to excellent yields. The reaction makes direct use of simple and abundant starting materials without requiring transition metal catalysts. In view of the wide functional group tolerance, the ease of conducting such reactions, and the mild reaction conditions, we envision this protocol will be widely adapted in synthetic chemistry.

EXPERIMENTAL SECTION

General Methods. 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 (400 MHz) and ^{13}C NMR (100 MHz) data were recorded on 400 M spectrometers using $CDCl_3$ as solvent at room temperature. The chemical shifts (δ) are reported in ppm and coupling constants (J) in Hz. ^{1}H NMR spectra were recorded with tetramethylsilane (δ = 0.00 ppm) as internal reference; ^{13}C NMR spectra were recorded with $CDCl_3$ (δ = 77.00 ppm) as internal reference.

General procedures for amides **3a**–**3q**, **6a**–**6h**, **7a**–**7l**, and **8a**–**8h**: Methyl ketone (0.5 mmol), amine (2.0 mmol), I_2 (0.25 mmol, 50 mol %), TBHP (6.0 equiv, 70% aqueous solution 401 uL), and 2.0 mL of ^{i}PrOH were added to a tube under air. The reaction mixture was stirred at room temperature or 0 °C for 13 h. The reaction mixture was quenched with saturated $Na_2S_2O_3$ solution, extracted repeatedly with ethyl acetate, and dried over Na_2SO_4. Removal of the organic solvent in a vacuum followed by flash silica gel column chromatographic purification (petroleum/ethyl acetate) afforded product.

1-Morpholino-2-phenylethane-1,2-dione (3a). Purified by flash column chromatography (EtOAc:hexane 1:5). Yellow oil (99 mg, 90% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98–7.95 (m, 2H),

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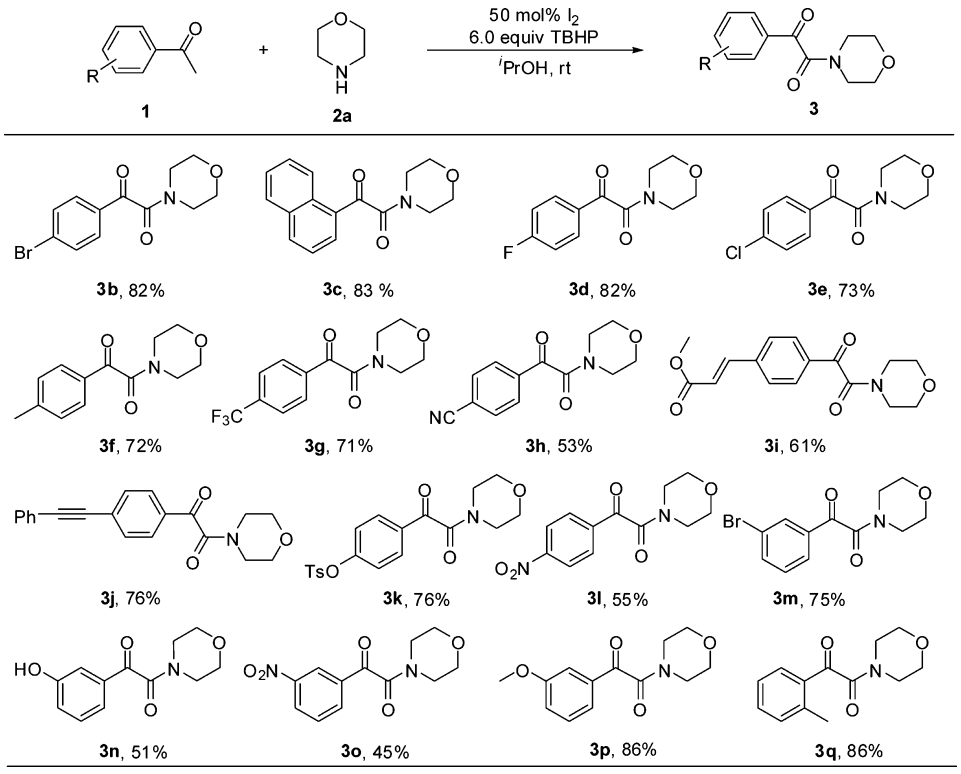

Figure 1. Scope of methyl ketones. Reaction conditions: 0.5 mmol ketones **1**, 2.0 mmol morpholine **2a**, 50 mol % iodine, 3.0 mmol TBHP in 2.0 mL of ^{i}PrOH at room temperature for 13 h.

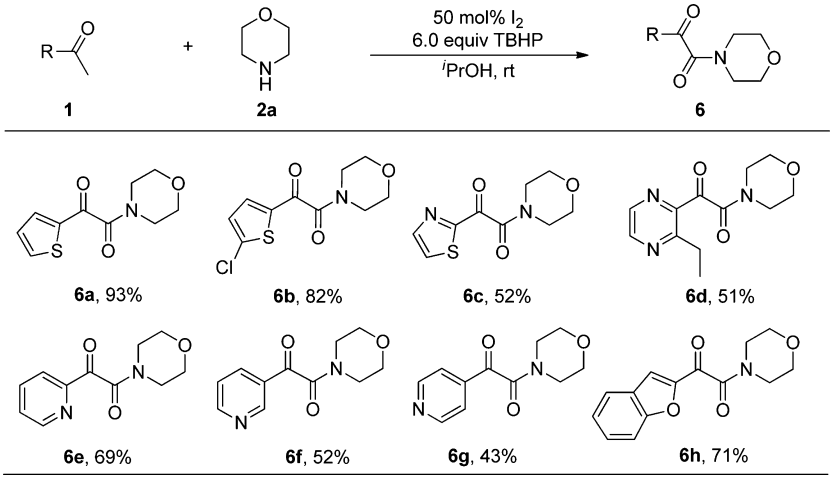

Figure 2. Scope of heteroaryl ketones. Reaction conditions: 0.5 mmol ketones **1**, 2.0 mmol morpholine **2a**, 50 mol % iodine, 3.0 mmol TBHP in 2.0 mL of ^{i}PrOH at room temperature for 13 h.

7.68−7.64 (m, 1H), 7.55−7.51 (m, 2H), 3.81 (t, J = 4.0 Hz, 2H), 3.79 (t, J = 4.0 Hz, 2H), 3.66 (t, J = 4.0 Hz, 2H), 3.39 (t, J = 4.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.0, 165.2, 134.8, 132.8, 129.4, 128.9, 66.5, 66.4, 46.0, 41.4; HRMS (TOF) m/z $[M + H]^+$ Calcd for $C_{12}H_{14}NO_3$ 220.0968, found 220.0975; IR (KBr, cm^{-1}) ν 1681, 1645.

Scale-up of Product 3a. Acetophenone (100.0 mmol), morpholine (400.0 mmol), I_2 (50.0 mmol, 50 mol %), TBHP (6.0 equiv, 70% aqueous solution 80.2 mL), and 400.0 mL of ^{i}PrOH, were added to a flask under air. The reaction mixture was stirred at room temperature for 13 h. Then, the reaction mixture was quenched with saturated $Na_2S_2O_3$ solution and then extracted three times with ethyl acetate. Removal of organic solvent got the raw product. Finally, flash silica gel column chromatographic purification (petroleum/ethyl acetate) afforded product **3a** in 82% yield.

1-(4-Bromophenyl)-2-morpholinoethane-1,2-dione (3b). Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (122 mg, 82% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (d, J = 8.6 Hz, 2H), 7.68 (d, J = 8.6 Hz, 2H), 3.79 (t, J = 4.0 Hz, 4H), 3.67 (t, J = 4.0 Hz, 2H), 3.38 (t, J = 4.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.8, 164.7, 132.3, 131.7, 130.9, 130.3, 66.5, 66.4, 46.1, 41.5; HRMS (TOF) m/z $[M]^+$ Calcd for $C_{12}H_{12}{}^{79}BrNO_3$ 297.0001, found 297.0007; Calcd for $C_{12}H_{12}{}^{81}BrNO_3$ 298.9980, found 299.0022; IR (KBr, cm^{-1}) ν 1676, 1628.

1-Morpholino-2-(naphthalen-1-yl)ethane-1,2-dione (3c). Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (112 mg, 83% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.25 (d, J = 8.7 Hz, 1H), 8.14 (d, J = 8.2 Hz, 1H), 8.05−8.03 (m, 1H), 7.93 (d, J = 8.1 Hz, 1H), 7.73−7.69 (m, 1H), 7.63−7.55 (m, 2H), 3.88−3.78 (m, 4H), 3.67 (t, J = 4.0 Hz, 2H), 3.44 (t, J = 4.0 Hz, 2H); ^{13}C NMR ($CDCl_3$,

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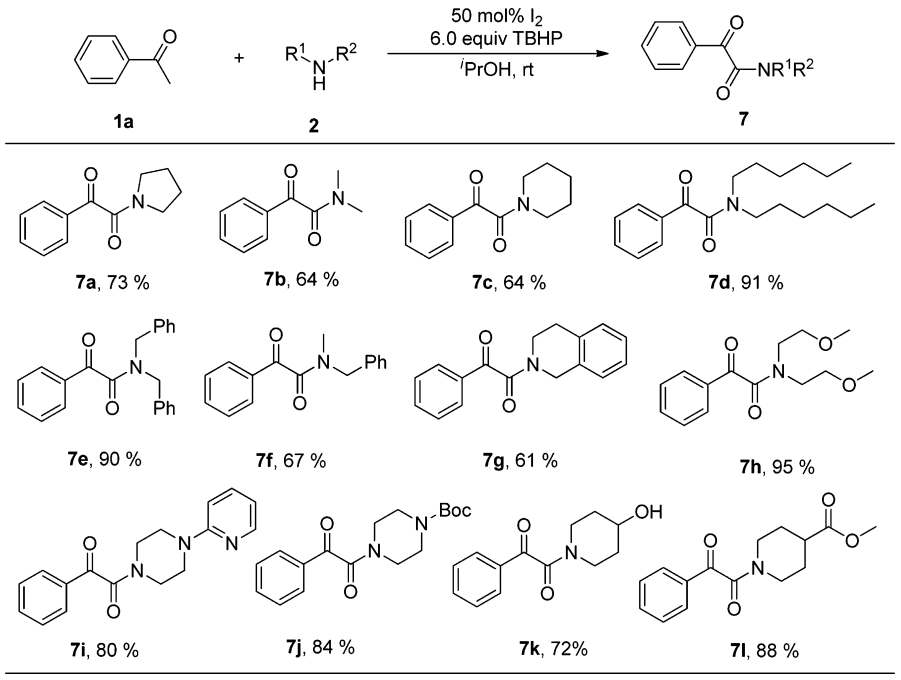

Figure 3. Scope of amines. Reaction conditions: 0.5 mmol acetophenone **1a**, 2.0 mmol amines **2**, 50 mol % iodine, 3.0 mmol TBHP in 2.0 mL of ^{i}PrOH at room temperature for 13 h.

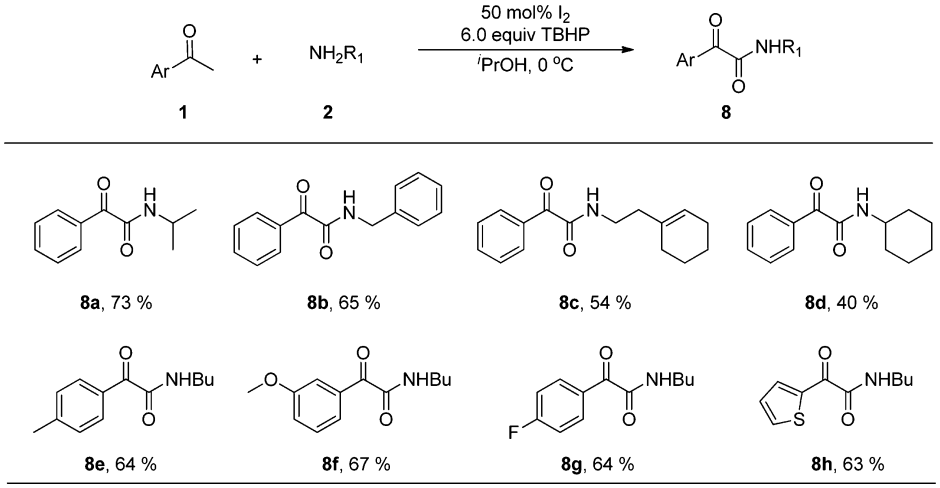

Figure 4. Scope of primary amines. Reaction conditions: 0.5 mmol methyl ketone **1**, 2.0 mmol amines **2**, 50 mol % iodine, 3.0 mmol TBHP in 2.0 mL of ^{i}PrOH at 0 °C for 13 h.

75 MHz) δ 193.4, 165.8, 136.0, 134.3, 133.8, 130.6, 129.3, 128.6, 128.1, 126.9, 125.5, 124.3, 66.41, 66.40, 46.1, 41.5; HRMS (TOF) m/z $[M + H]^+$ Calcd for $C_{16}H_{16}NO_3$ 270.1125, found 270.1136; IR (KBr, cm^{-1}) ν 1669, 1630.

1-(4-Fluorophenyl)-2-morpholinoethane-1,2-dione (3d). Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (97 mg, 82% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03−7.99 (m, 2H), 7.22−7.18 (m, 2H), 3.80−3.77 (m, 4H), 3.67 (t, J = 4.0 Hz, 2H), 3.39 (t, J = 4.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.2, 168.3, 164.9, 132.4, 132.3, 129.4, 116.4, 116.1, 66.5, 66.4, 46.1, 41.5; HRMS (TOF) m/z $[M]^+$ Calcd for $C_{12}H_{12}FNO_3$ 237.0801, found 237.0809; IR (KBr, cm^{-1}) ν 1672, 1633.

1-(4-Chlorophenyl)-2-morpholinoethane-1,2-dione (3e). Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (93 mg, 73% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93−7.90 (m, 2H), 7.52−7.50 (m, 2H), 3.82−3.77 (m, 4H), 3.67 (t, J = 4.0 Hz, 2H), 3.39 (t, J = 4.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.5, 164.7, 141.4, 131.3, 130.9, 129.3, 66.5, 66.4, 46.1, 41.5; HRMS (TOF) m/z $[M + H]^+$ Calcd for $C_{12}H_{13}{}^{35}ClNO_3$ 254.0578, found 254.0586; IR (KBr, cm^{-1}) ν 1676,1628.

1-Morpholino-2-p-tolylethane-1,2-dione (3f). Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (84 mg, 72% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 3.80−3.76 (m, 4H), 3.65 (t, J = 4.0 Hz, 2H), 3.37 (t, J = 4.0 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 190.8, 165.5, 146.1, 130.4, 129.7, 129.6, 66.53, 66.46, 46.1, 41.4, 21.8; HRMS (TOF) m/z $[M + H]^+$ Calcd for $C_{13}H_{16}NO_3$ 234.1125, found 234.1134; IR (KBr, cm^{-1}) ν 1675, 1645.

1-Morpholino-2-(4-(trifluoromethyl)phenyl)ethane-1,2-dione (3g). Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (102 mg, 71% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.0 Hz, 2H), 3.82−3.79 (m, 4H), 3.68 (t, J = 4.0 Hz, 2H), 3.41 (t, J = 4.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.6, 164.4, 135.9, 135.6, 135.5, 129.9, 126.03, 126.0, 125.96, 125.9, 124.6, 121.8, 66.6, 66.5, 46.2, 41.7; HRMS (TOF) m/z

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$[M + H]^+$ Calcd for $C_{13}H_{13}F_3NO_3$ 288.0842, found 288.0839; IR (KBr, cm^{-1}) ν 1681, 1630.

4-(2-Morpholino-2-oxoacetyl)benzonitrile (3h). Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (65 mg, 53% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 8.09 (d, J = 8.0 Hz, 2H), 7.84 (d, J = 8.0 Hz, 2H), 3.83−3.79 (m, 4H), 3.69 (t, J = 4.0 Hz, 2H), 3.41 (t, J = 4.0 Hz, 2H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 188.9, 163.9, 135.8, 132.7, 129.9, 117.7, 117.4, 66.5, 66.4, 46.1, 41.7; HRMS (TOF) m/z $[M + Na]^+$ Calcd for $C_{13}H_{12}N_2NaO_3$ 267.0740, found 267.0738; IR (KBr, cm^{-1}) ν 1686, 1643.

(*E*)-Methyl 3-(4-(2-morpholino-2-oxoacetyl)phenyl)acrylate (3i). Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (93 mg, 61% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.99 (d, J = 8.2 Hz, 2H), 7.72 (d, J = 16.1 Hz, 1H), 7.66 (d, J = 8.2 Hz, 2H), 6.56 (d, J = 16.1 Hz, 1H), 3.84 (s, 3H), 3.81−3.80 (m, 4H), 3.67 (t, J = 4.0 Hz, 2H), 3.40 (t, J = 4.0 Hz, 2H),; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.9, 166.4, 164.8, 142.5, 140.2, 133.7, 129.9, 128.3, 121.1, 66.5, 66.4, 51.7, 46.0, 41.4; HRMS (TOF) m/z $[M + H]^+$ Calcd for $C_{16}H_{18}NO_5$ 304.1179, found 304.1179; IR (KBr, cm^{-1}) ν 1725, 1667, 1641.

1-Morpholino-2-(4-(phenylethynyl)phenyl)ethane-1,2-dione (3j). Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (121 mg, 76% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.95 (d, J = 8.3 Hz, 2H), 7.66 (d, J = 8.3 Hz, 2H), 7.57−7.55 (m, 2H), 7.39−7.38 (m, 3H), 3.81−3.80 (m, 4H), 3.67 (t, J = 4.0 Hz, 2H), 3.40 (t, J = 4.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.1, 165.0, 132.0, 131.9, 131.7, 130.0, 129.5, 129.0, 128.4, 122.2, 94.0, 88.3, 66.6, 66.5, 46.1, 41.5; HRMS (TOF) m/z $[M]^+$ Calcd for $C_{20}H_{17}NO_3$ 319.1208, found 319.1223; IR (KBr, cm^{-1}) ν 1673, 1642.

4-(2-Morpholino-2-oxoacetyl)phenyl 4-methylbenzenesulfonate (3k). Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (148 mg, 76% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.94−7.91 (m, 2H), 7.75−7.71 (m, 2H), 7.35−7.33 (m, 2H), 7.18−7.14 (m, 2H), 3.81−3.76 (m, 4H), 3.65 (t, J = 4.0 Hz, 2H), 3.38 (t, J = 4.0 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.2, 164.6, 154.0, 145.9, 131.7, 131.4, 129.9, 128.2, 122.8, 66.5, 66.4, 46.1, 41.5, 21.6; HRMS (TOF) m/z $[M]^+$ Calcd for $C_{19}H_{19}NO_6S$ 389.0933, found 389.0930; IR (KBr, cm^{-1}) ν 1682, 1646.

1-Morpholino-2-(4-nitrophenyl)ethane-1,2-dione (3l). Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (73 mg, 55% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 8.37 (d, J = 8.0 Hz, 2H), 8.17 (d, J = 8.0 Hz, 2H), 3.83−3.81 (m, 4H), 3.70 (t, J = 4.0 Hz, 2H), 3.43 (t, J = 4.0 Hz, 2H),; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.6, 163.9, 151.0, 137.3, 130.7, 124.0, 66.6, 66.4, 46.2, 41.8; HRMS (TOF) m/z $[M + H]^+$ Calcd for $C_{12}H_{13}N_2O_5$ 265.0819, found 265.0824; IR (KBr, cm^{-1}) ν 1686, 1636.

1-(3-Bromophenyl)-2-morpholinoethane-1,2-dione (3m). Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (112 mg, 75% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.98−7.95 (m, 2H), 7.67−7.64 (m, 1H), 7.55−7.51 (m, 2H), 3.82−3.77 (m, 4H), 3.66 (t, J = 4.0 Hz, 2H), 3.39 (t, J = 4.0 Hz, 2H),; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.3, 164.4, 137.5, 134.6, 132.1, 130.5, 128.2, 123.1, 66.5, 66.4, 46.1, 41.5; HRMS (TOF) m/z $[M]^+$ Calcd for $C_{12}H_{12}{}^{79}BrNO_3$ 297.0001, found 297.0013; $C_{12}H_{12}{}^{81}BrNO_3$ 298.9980, found 298.9995; IR (KBr, cm^{-1}) ν 1677, 1634.

1-(3-Hydroxyphenyl)-2-morpholinoethane-1,2-dione (3n). Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (60 mg, 51% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.94 (brs, 1H), 7.43−7.41 (m, 1H), 7.36−7.29 (m, 2H), 7.09−7.06 (m, 1H), 3.81−3.77 (m, 4H), 3.66 (t, J = 4.0 Hz, 2H), 3.37 (t, J = 4.0 Hz, 2H),; ^{13}C NMR ($CDCl_3$,100 MHz) δ 190.9, 165.9, 157.1, 133.7, 130.3, 122.9, 121.5, 115.6, 66.5, 66.4, 46.3, 41.7; HRMS (TOF) m/z $[M + Na]^+$ Calcd for $C_{12}H_{13}NNaO_4$ 258.0737, found 258.0735; IR (KBr, cm^{-1}) ν 1681, 1630.

1-Morpholino-2-(3-nitrophenyl)ethane-1,2-dione (3o). Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (60 mg, 45% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 8.79−8.78 (m, 1H), 8.51−8.31 (m, 2H), 7.78−7.74 (m, 1H), 3.84−3.82 (m, 4H), 3.71 (t, J = 4.0 Hz, 2H), 3.46 (t, J = 4.0 Hz, 2H),; ^{13}C NMR ($CDCl_3$,100 MHz) δ 188.1, 163.8, 148.5, 135.1, 134.4, 130.3, 128.7, 124.4, 66.6, 66.5, 46.2, 41.9; HRMS (TOF) m/z $[M + H]^+$ Calcd for $C_{12}H_{13}N_2O_5$ 265.0819, found 265.0818; IR (KBr, cm^{-1}) ν 1685, 1645.

1-(3-Methoxyphenyl)-2-morpholinoethane-1,2-dione (3p). Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (107 mg, 86% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.52−7.50 (m, 2H), 7.45−7.41 (m, 1H), 7.22−7.19 (m, 1H), 3.87 (s, 3H), 3.81−3.78 (m, 4H), 3.66 (t, J = 4.0 Hz, 2H), 3.38 (t, J = 4.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.9, 165.2, 159.9, 134.1, 130.0, 122.6, 121.6, 112.6, 66.5 66.4, 55.4, 46.1, 41.4. HRMS (TOF) m/z $[M + H]^+$ Calcd for $C_{13}H_{16}NO_4$ 250.1074, found 250.1074; IR (KBr, cm^{-1}) ν 1681, 1646.

1-Morpholino-2-o-tolylethane-1,2-dione (3q). Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (100 mg, 86% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.73−7.71 (m, 1H), 7.52−7.48 (m, 1H), 7.35−7.31 (m, 2H), 3.80−3.76 (m, 4H), 3.67 (t, J = 4.0 Hz, 2H), 3.40 (t, J = 4.0 Hz, 2H), 2.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.9, 166.0, 141.4, 133.7, 132.51, 132.48, 131.2, 126.0, 66.42, 66.39, 46.0, 41.4, 21.6; HRMS (TOF) m/z $[M]^+$ Calcd for $C_{13}H_{15}NO_3$ 233.1052, found 233.1054; IR (KBr, cm^{-1}) ν 1673, 1629.

1-Morpholino-2-(thiophen-2-yl)ethane-1,2-dione (6a). Purified by column chromatography (EtOAc:hexane 1:5). Yellow oil (105 mg, 93% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.86−7.82 (m, 2H), 7.21−7.19 (m, 1H), 3.81−3.75 (m, 4H), 3.69 (t, J = 4.0 Hz, 2H), 3.50 (t, J = 4.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 182.7, 164.1, 140.0, 136.7, 136.1, 128.6, 66.6, 66.4, 46.2, 41.7; HRMS (TOF) m/z $[M + H]^+$ Calcd for $C_{10}H_{12}NO_3S$ 226.0532, found 226.0532; IR (KBr, cm^{-1}) ν 1651.

1-(5-Chlorothiophen-2-yl)-2-morpholinoethane-1,2-dione (6b). Purified by column chromatography (EtOAc:hexane 1:5). Yellow oil (106 mg, 82% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.67 (d, J = 4.1 Hz, 1H), 7.04 (d, J = 4.1 Hz, 1H), 3.78−3.74 (m, 4H), 3.69 (t, J = 4.0 Hz, 2H), 3.53 (t, J = 4.0 Hz, 2H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 181.2, 163.2, 142.7, 138.3, 135.9, 128.1, 66.6, 66.4, 46.3, 41.9; HRMS (TOF) m/z $[M + H]^+$ Calcd for $C_{10}H_{10}ClNO_3S$ 259.0070, found 259.0070; IR (KBr, cm^{-1}) ν 1640.

1-Morpholino-2-(thiazol-2-yl)ethane-1,2-dione (6c). Purified by column chromatography (EtOAc:hexane 1:5). Yellow oil (59 mg, 52% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 8.15 (d, J = 3.0 Hz, 1H), 7.87 (d, J = 3.0 Hz, 1H), 3.84−3.78 (m, 4H), 3.71 (t, J = 4.0 Hz, 2H), 3.42 (t, J = 4.0 Hz, 2H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 182.8, 163.8, 163.1, 146.0, 127.8, 66.34, 66.29, 46.1, 41.7; HRMS (TOF) m/z $[M + H]^+$ Calcd for $C_9H_{10}N_2O_3S$ 226.0412, found 226.0411; IR (KBr, cm^{-1}) ν 1686, 1647.

1-(3-Ethylpyrazin-2-yl)-2-morpholinoethane-1,2-dione (6d). Purified by column chromatography (EtOAc:hexane 1:5). Yellow oil (64 mg, 51% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 8.71 (d, J = 2.2 Hz, 1H), 8.55 (d, J = 2.2 Hz, 1H), 3.84−3.77 (m, 4H), 3.74−3.72 (m, 2H), 3.41−3.40 (m, 2H), 3.27 (q, J = 8.0 Hz, 2H), 1.35 (t, J = 8.0 Hz, 3H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 191.5, 166.4, 160.9, 147.0, 144.0, 141.3, 66.43, 66.38, 46.1, 41.6, 28.1, 12.6; HRMS (TOF) m/z $[M + H]^+$ Calcd for $C_{12}H_{15}N_3O_3$ 249.1133, found 249.1133; IR (KBr, cm^{-1}) ν 1701, 1643.

1-Morpholino-2-(pyridin-2-yl)ethane-1,2-dione (6e). Purified by column chromatography (EtOAc:hexane 1:5). Yellow oil (76 mg, 69% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 8.77−8.76 (m, 1H), 8.12−8.10 (m, 1H), 7.95−7.91 (m, 1H), 7.58−7.55 (m, 1H), 3.84−3.80 (m, 4H), 3.70 (t, J = 4.0 Hz, 2H), 3.36 (t, J = 4.0 Hz, 2H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 191.5, 166.3, 150.9, 149.8, 137.2, 128.1, 123.0, 66.3, 46.0, 41.4; HRMS (TOF) m/z $[M + H]^+$ Calcd for $C_{11}H_{13}N_2O_3$ 221.0921, found 221.0921; IR (KBr, cm^{-1}) ν 1702, 1641.

1-Morpholino-2-(pyridin-3-yl)ethane-1,2-dione (6f). Purified by column chromatography (EtOAc:hexane 1:5). Yellow oil (57 mg, 52% yield): ^1H NMR ($CDCl_3$, 400 MHz) δ 9.16−8.86 (m, 2H), 8.30−8.27 (m, 1H), 7.51−7.48 (m, 1H), 3.82−3.81 (m, 4H), 3.70 (t, J = 4.0 Hz, 2H), 3.44 (t, J = 4.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 189.3, 164.0, 154.7, 151.0, 136.6, 128.6, 123.8, 66.5, 66.4, 46.1, 41.7; HRMS (TOF) m/z $[M + H]^+$ Calcd for $C_{11}H_{13}N_2O_3$ 221.0921, found 221.0918; IR (KBr, cm^{-1}) ν 1683, 1646.

1-Morpholino-2-(pyridin-4-yl)ethane-1,2-dione (6g). Purified by column chromatography (EtOAc:hexane 1:5). Yellow oil (48 mg,

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43% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, J = 5.8 Hz, 2H), 7.78 (d, J = 5.8 Hz, 2H), 3.83−3.79 (m, 4H), 3.70 (t, J = 4.0 Hz, 2H), 3.42 (t, J = 4.0 Hz, 2H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 189.7, 163.8, 151.2, 138.9, 122.0, 66.7, 66.6, 46.2, 41.8; HRMS (TOF) m/z $[M]^+$ Calcd for $C_{11}H_{12}N_2O_3$ 220.0848, found 220.0848; IR (KBr, cm^{-1}) ν 1675, 1643.

1-(Benzofuran-2-yl)-2-morpholinoethane-1,2-dione (6h). Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (65 mg, 71% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76−7.74 (m, 2H), 7.63−7.61 (m, 1H), 7.56−7.52 (m, 1H), 7.37−7.34 (m, 1H), 3.81−3.78 (m, 4H), 3.71 (t, J = 4 Hz, 2H), 3.54 (t, J = 4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.7, 163.6, 156.4, 149.8, 129.6, 126.6, 124.4, 123.8, 118.8, 112.6, 66.7, 66.5, 46.3, 42.0; HRMS (TOF) m/z $[M + 1]^+$ Calcd for $C_{14}H_{14}NO_4$ 260, found 260; IR (KBr, cm^{-1}) ν 1655.

1-Phenyl-2-(pyrrolidin-1-yl)ethane-1,2-dione (7a). Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (74 mg, 73% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00−7.98 (m, 2H), 7.66−7.62 (m, 1H), 7.53−7.49 (m, 2H), 3.66 (t, J = 6.5 Hz, 2H), 3.42 (t, J = 6.5 Hz, 2H), 1.98−1.92 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.3, 164.7, 134.4, 132.5, 129.5, 128.7, 46.4, 44.9, 25.6, 23.7; ESI-MS m/z $[M + H]^+$ Calcd for $C_{12}H_{14}NO_2$ 204, found 204; IR (KBr, cm^{-1}) ν 1675, 1634.

***N*,*N*-Dimethyl-2-oxo-2-phenylacetamide (7b).** Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (57 mg, 64% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95−7.93 (m, 2H), 7.66−7.63 (m, 1H), 7.53−7.49 (m, 2H), 3.11 (s, 3H), 2.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.7, 166.9, 134.6, 132.8, 129.4, 128.9, 36.9, 33.8; HRMS (TOF) m/z $[M + Na]^+$ Calcd for $C_{10}H_{11}NNaO_2$ 200.0682, found 200.0670; IR (KBr, cm^{-1}) ν 1681, 1651.

1-Phenyl-2-(piperidin-1-yl)ethane-1,2-dione (7c). Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (70 mg, 64% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.96−7.94 (m, 2H), 7.66−7.63 (m, 1H), 7.54−7.50 (m, 2H), 3.71 (t, J = 5.0 Hz, 2H), 3.30 (t, J = 5.0 Hz, 2H), 1.72−1.68 (m, 4H), 1.57−1.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 191.9, 165.4, 134.6, 133.2, 129.5, 128.9, 47.0, 42.1, 26.1, 25.4, 24.3; ESI (TOF) m/z $[M + H]^+$ Calcd for $C_{13}H_{16}NO_2$ 218, found 218; IR (KBr, cm^{-1}) ν 1671, 1645.

***N*,*N*-Dihexyl-2-oxo-2-phenylacetamide (7d).** Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (144 mg, 91% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95−7.93 (m, 2H), 7.65−7.62 (m, 1H), 7.52−7.49 (m, 2H), 3.49 (t, J = 8.0 Hz, 2H), 3.15 (t, J = 8.0 Hz, 2H), 1.70−1.64 (m, 2H), 1.56−1.52 (m, 2H), 1.41−1.33 (m, 6H), 1.21−1.14 (m, 6H), 0.92 (t, J = 6.6 Hz, 3H), 0.82 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.5, 166.9, 134.4, 133.2, 129.5, 128.8, 47.5, 44.1, 31.4, 31.1, 28.4, 27.2, 26.6, 26.1, 22.5, 22.3, 13.9, 13.8; HRMS (TOF) m/z $[M + Na]^+$ Calcd for $C_{20}H_{31}NNaO_2$ 340.2247, found 340.2228; IR (KBr, cm^{-1}) ν 1682, 1644.

***N*,*N*-Dibenzyl-2-oxo-2-phenylacetamide (7e).** Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (148 mg, 90% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01−7.99 (m, 2H), 7.67−7.63 (m, 1H), 7.54−7.50 (m, 2H), 7.40−7.36 (m, 2H), 7.35−7.30 (m, 6H), 7.26−7.23 (m, 2H), 4.63 (s, 2H), 4.28 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.2, 167.3, 135.8, 134.7, 134.6, 133.2, 129.6, 128.9, 128.8, 128.7, 128.6, 128.1, 128.0, 127.8, 50.0, 45.9; HRMS (TOF) m/z $[M + Na]^+$ Calcd for $C_{22}H_{19}NNaO_2$ 352.1308, found 352.1310; IR (KBr, cm^{-1}) ν 1679, 1631.

***N*-Benzyl-*N*-methyl-2-oxo-2-phenylacetamide (7f).** Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (85 mg, 67% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00−7.95 (m, 2H), 7.64−7.60 (m, 1H), 7.51−7.47 (m, 2H), 7.37−7.36 (m, 2H), 7.32−7.24 (m, 3H), 4.72 (s, 1.08 H), 4.37 (s, 0.91 H), 2.98 (s, 1.37 H), 2.82 (s, 1.63 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.4, 191.3, 167.1, 166.9, 135.5, 134.7, 134.6, 134.6, 132.9, 132.8, 129.5, 129.4, 128.9, 128.8, 128.6, 128.6, 128.1, 128.0, 127.7, 127.6, 53.2, 49.5, 34.2, 31.1; HRMS (TOF) m/z $[M + Na]^+$ Calcd for $C_{16}H_{15}NNaO_2$ 276.0995, found 276.1012; IR (KBr, cm^{-1}) ν 1681, 1645.

***tert*-Butyl 4-(2-oxo-2-phenylacetyl)piperazine-1-carboxylate (7g).** Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (81 mg, 61% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.99−7.93 (m, 2H), 7.66−7.59 (m, 1H), 7.52−7.45 (m, 2H), 7.25−7.18 (m, 2.5H), 7.12−7.10 (m, 1H), 6.92−6.91 (m, 0.5H), 4.90 (s, 1.28H), 4.53 (s, 0.72H), 3.98 (t, J = 6.0 Hz, 0.7H), 3.60 (t, J = 6.0 Hz, 1.30H), 2.99 (t, J = 6.0 Hz, 0.70H), 2.84 (t, J = 6.0 Hz, 1.30H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.4, 191.2, 165.9, 165.6, 134.73, 134.68, 134.0, 133.3, 132.9, 132.8, 131.6, 131.4, 129.6, 129.5, 128.93, 128.9, 128.8, 128.7, 127.1, 126.7, 126.66, 126.5, 126.46, 125.9, 47.2, 43.4, 43.3, 39.2, 29.0, 28.1; HRMS (TOF) m/z $[M + Na]^+$ Calcd for $C_{17}H_{15}NNaO_2$ 288.0995, found 288.1001; IR (KBr, cm^{-1}) ν 1672, 1639.

***N*,*N*-Bis(2-methoxyethyl)-2-oxo-2-phenylacetamide (7h).** Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (126 mg, 95% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97−7.95 (m, 2H), 7.62−7.58 (m, 2H), 7.50−7.46 (m, 2H), 3.78 (t, J = 5.3 Hz, 2H), 3.66 (t, J = 5.4 Hz, 2H), 3.54 (t, J = 5.3 Hz, 2H), 3.44 (t, J = 5.4 Hz, 2H), 3.39 (s, 3H), 3.11 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.7, 167.4, 134.0, 133.2, 129.6, 128.4, 70.2, 70.0, 58.5, 58.2, 47.9, 44.9; HRMS (TOF) m/z $[M + Na]^+$ Calcd for $C_{14}H_{19}NNaO_4$ 288.1206, found 288.1189; IR (KBr, cm^{-1}) ν 1679, 1641.

1-Phenyl-2-(4-(pyridin-2-yl)piperazin-1-yl)ethane-1,2-dione (7i). Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (118 mg, 80% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.20−8.19 (m, 1H), 7.99−7.98 (m, 2H), 7.67−7.65 (m, 1H), 7.55−7.50 (m, 3H), 6.71−6.66 (m, 2H), 3.90 (t, J = 6.0 Hz, 2H), 3.68 (t, J = 6.0 Hz, 2H), 3.57 (t, J = 4.0 Hz, 2H), 3.49 (t, J = 4.0 Hz, 2H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 191.3, 165.5, 158.7, 147.9, 137.7, 134.9, 133.0, 129.6, 129.0, 114.2, 107.4, 45.47, 45.46, 45.1, 40.9; HRMS (TOF) m/z $[M + H]^+$ Calcd for $C_{17}H_{18}N_3O_2$ 296.1394, found 296.1393; IR (KBr, cm^{-1}) ν 1678, 1641.

***tert*-Butyl 4-(2-oxo-2-phenylacetyl)piperazine-1-carboxylate (7j).** Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (134 mg, 84% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97−7.95 (m, 2H), 7.69−7.65 (m, 1H), 7.55−7.51 (m, 2H), 3.75 (t, J = 4.0 Hz, 2H), 3.56 (t, J = 4.0 Hz, 2H), 3.44 (t, J = 4.0 Hz, 2H), 3.34 (t, J = 4.0 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.0, 165.4, 154.2, 134.8, 132.8, 129.5, 128.9, 80.4, 45.6, 41.0, 28.2; HRMS (TOF) m/z $[M + Na]^+$ Calcd for $C_{17}H_{22}N_2NaO_4$ 341.1472, found 341.1466; IR (KBr, cm^{-1}) ν 1677, 1650.

1-(4-Hydroxypiperidin-1-yl)-2-phenylethane-1,2-dione (7k). Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (84 mg, 72% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.93−7.92 (m, 2H), 7.67−7.64 (m, 1H), 7.54−7.50 (m, 2H), 4.07−3.95 (m, 2H), 3.50−3.44 (m, 2H), 3.18−3.12 (m, 1H), 2.69 (brs, 1H), 1.80−1.49 (m, 4H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 191.7, 165.4, 134.8, 132.8, 129.4, 129.0, 66.1, 43.0, 38.2; HRMS (TOF) m/z $[M + H]^+$ Calcd for $C_{13}H_{16}NO_3$ 234.1125, found 234.1120; IR (KBr, cm^{-1}) ν 1677, 1631.

Methyl 1-(2-oxo-2-phenylacetyl)piperidine-4-carboxylate (7l). Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (121 mg, 88% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95−7.93 (m, 2H), 7.67−7.63 (m, 1H), 7.54−7.50 (m, 2H), 4.46−4.43 (m, 1H), 3.69 (s, 3H), 3.58−3.55 (m, 1H), 3.13−3.06 (m, 2H), 2.66−2.61 (m, 1H), 2.06−2.04 (m, 1H), 1.91−1.68 (m, 3H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 191.4, 173.9, 165.2, 134.7, 132.8, 129.3, 128.9, 51.8, 45.0, 40.3, 40.2, 28.0, 27.4; HRMS (TOF) m/z $[M + H]^+$ Calcd for $C_{15}H_{18}NO_4$ 276.1230, found 276.1230; IR (KBr, cm^{-1}) ν 1733, 1679, 1642.

***N*-Isopropyl-2-oxo-2-phenylacetamide (8a).** Methyl ketones (0.5 mmol), amines (2.0 mmol), I_2 (0.25 mmol, 50 mol %), TBHP (6.0 equiv, 70% aqueous solution 401 uL), and 2.0 mL of ^{i}PrOH, were added to a tube under air. The reaction mixture was stirred at 0 °C for 13 h. The reaction mixture was quenched with saturated $Na_2S_2O_3$ solution, extracted repeatedly with ethyl acetate, and dried over Na_2SO_4. Then, removal of the organic solvent in a vacuum followed by flash silica gel column chromatographic purification afforded product (70 mg, 73% yield) as yellow solid with EtOAc/hexane (1:5) mixtures: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32−8.30 (m, 2H), 7.62−7.58 (m, 1H), 7.47 −7.43 (m, 2H), 7.05 (s, 1H), 4.22−4.10 (m, 1H), 1.25 (d, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$,75 MHz) δ 188.0, 160.9, 134.2, 133.3, 131.0, 128.3, 41.6, 22.3; ESI-MS m/z $[M + H]^+$ Calcd for $C_{11}H_{14}NO_2$ 192, found 192; IR (KBr, cm^{-1}) ν 1671,1643.

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***N*-Benzyl-2-oxo-2-phenylacetamide (8b).** Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (78 mg, 65% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.33−8.31 (m, 2H), 7.62−7.58 (m, 1H), 7.52 (s, 1H), 7.47−7.43 (m, 2H), 7.35−7.28 (m, 5H), 4.54 (d, J = 6.1 Hz, 2H). ^{13}C NMR ($CDCl_3$,75 MHz) δ 187.5, 161.6, 137.0, 134.4, 133.2, 131.1, 128.7, 128.4, 127.8, 127.7, 43.4; ESI-MS m/z [M + H]$^+$ Calcd for $C_{15}H_{14}NO_2$ 240, found 240; IR (KBr, cm^{-1}) ν 1683,1648.

***N*-(2-Cyclohexenylethyl)-2-oxo-2-phenylacetamide (8c).** Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (70 mg, 54% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32−8.30 (m, 2H), 7.63−7.59 (m, 1H), 7.48−7.45 (m, 2H), 7.13 (s, 1H), 5.51 (t, J = 3.7 Hz, 1H), 3.49−3.44 (m, 2H), 2.22 (t, J = 6.8 Hz, 2H), 2.01−1.96 (m, 4H), 1.64−1.53 (m, 4H). ^{13}C NMR ($CDCl_3$,75 MHz) δ 187.8, 161.7, 134.2, 133.9, 133.2, 131.0, 128.3, 123.9, 37.2, 37.1, 27.8, 25.1, 22.7, 22.2; ESI-MS m/z [M + H]$^+$ Calcd for $C_{16}H_{20}NO_2$ 258, found 258; IR (KBr, cm^{-1}) ν 1665.

***N*-Cyclohexyl-2-oxo-2-phenylacetamide (8d).** Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (46 mg, 40% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.32−8.29 (m, 2H), 7.59−7.57 (m, 1H), 7.47−7.43 (m, 2H), 7.08 (s, 1H), 3.87−3.84 (m, 1H), 1.99−1.95 (m, 2H), 1.76−1.62 (m, 3H), 1.38−1.21 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 188.1, 160. 9, 134.1, 133.3, 131.0, 128.3, 48.3, 32.5, 25.2, 24.6; ESI-MS m/z [M + H]$^+$ Calcd for $C_{14}H_{18}NO_2$ 232, found 232; IR (KBr, cm^{-1}) ν 1666.

***N*-Butyl-2-oxo-2-p-tolylacetamide (8e).** Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (70 mg, 64% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.24 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.20 (s, 1H), 3.41−3.37 (m, 2H), 2.41 (s, 3H), 1.60−1.56 (m, 2H), 1.43−1.36 (m, 2H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 187.4, 162.0, 145.4, 131.2, 130.8, 129.1, 39.0, 31.2, 21.7, 20.0, 13.6; ESI-MS m/z [M + H]$^+$ Calcd for $C_{13}H_{18}NO_2$ 220, found 220; IR (KBr, cm^{-1}) ν 1679.

***N*-Butyl-2-(3-methoxyphenyl)-2-oxoacetamide (8f).** Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (79 mg, 67% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.95−7.93 (m, 1H), 7.81 (s, 1H), 7.38−7.34 (m, 1H), 7.24 (s, 1H), 7.17−7.14 (m, 1H), 3.84 (s, 3H), 3.40−3.35 (m, 2H), 1.62−1.54 (m, 2H), 1.44−1.35 (m, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.6, 161.9, 159.3, 134.4, 129.3, 123.9, 121.1, 114.5, 55.2, 39.0, 31.2 19.9, 13.5; ESI-MS m/z [M + H]$^+$ Calcd for $C_{13}H_{18}NO_3$ 236, found 236; IR (KBr, cm^{-1}) ν 1662.

***N*-Butyl-2-(4-fluorophenyl)-2-oxoacetamide (8g).** Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (72 mg, 64% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.44 (d, J = 6.2 Hz, 2H), 7.22 (s, 1H), 7.15 (d, J = 6.2 Hz, 2H), 3.40−3.38 (m, 2H), 1.59−1.57 (m, 2H), 1.41−1.39 (m, 2H), 0.95 (t, J = 7.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 186.0, 168.2, 164.8, 161.5, 134.2, 134.1, 129.8, 115.8, 115.5, 39.1, 31.2, 20.0, 13.6; ESI-MS m/z [M + H]$^+$ Calcd for $C_{12}H_{15}FNO_2$ 224, found 224; IR (KBr, cm^{-1}) ν 1656.

***N*-Butyl-2-oxo-2-(thiophen-2-yl)acetamide (8h).** Purified by column chromatography (EtOAc:hexane 1:5). Yellow solid (67 mg, 63% yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.41 (d, J = 2.7 Hz, 1H), 7.83 (d, J = 2.7 Hz, 1H), 7.36 (s, 1H), 7.20−7.18 (m, 1H), 3.42−3.36 (m, 2H), 1.60−1.55 (m, 2H), 1.44−1.36 (m, 2H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.4, 160.6, 138.5, 137.8, 136.6, 128.0, 39.2, 31.1, 19.9, 13.6; ESI-MS m/z [M + H]$^+$ Calcd for $C_{12}H_{14}NO_2S$ 212, found 212; IR (KBr, cm^{-1}) ν 1685, 1648.

1-(4-Bromophenyl)-2-morpholinoethanone (4). A mixture of 2-bromo-1-(4-bromophenyl)ethanone (1 mmol), morpholine (2 equiv) in dichloromethane was heated at 25 °C for 6 h. Removal of the organic solvent in a vacuum followed by flash silica gel column chromatographic purification afforded product (260 mg, 92% yield) as yellow solid with EtOAc/hexane (1:5) mixtures: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (d, J = 8.0 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 3.77 (t, J = 4.0 Hz, 4H), 3.76 (s, 2H), 2.60 (t, J = 4.0 Hz, 4H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 195.2, 134.5, 131.8, 129.7, 128.5, 66.7, 64.8, 53.8; HRMS (TOF) m/z [M + H]$^+$ Calcd for $C_{12}H_{15}{}^{79}BrNO_2$ 284.0281, found 284.0281; $C_{12}H_{15}{}^{81}BrNO_2$ 284.0266, found 286.0262; IR (KBr, cm^{-1}) ν 1689.

1-(4-Bromophenyl)-2-iodoethanone (5). A mixture of 1-(4-bromophenyl)ethanone (1 mmol), CuO (1 equiv), and iodine (1 equiv) in methanol was heated at 65 °C for 1 h. Removal of the organic solvent in a vacuum followed by flash silica gel column chromatographic purification afforded product (292 mg, 90% yield) as colorless solid with EtOAc/hexane (1:20) mixtures: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 8.4 Hz, 2H), 4.32 (s, 2H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 191.8, 132.13, 132.08, 130.5, 129.1, 1.2; ESI-MS m/z [M + H]$^+$ Calcd for $C_8H_7{}^{79}BrIO$ 325, found 325; $C_8H_7{}^{81}BrIO$ 327, found 327; IR (KBr, cm^{-1}) ν 1688.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wanxb@suda.edu.cn.

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