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PAPER

# Copper-catalyzed aerobic oxidative synthesis of α-ketoamides from methyl ketones, amines and NIS at room temperature†

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A simple, efficient and practical copper-catalyzed aerobic oxidative synthesis of α-ketoamides from aryl methyl ketones, aliphatic amines and *N*-iodosuccinimide (NIS) has been developed. The one-pot reaction may proceed smoothly at room temperature in the open air. The possible mechanism for the formation of α-ketoamides was proposed. Molecular oxygen in air functions as both an oxidant and an oxygen source.

## Introduction

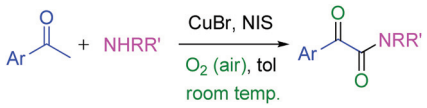
α-Ketoamides constitute key motifs in biologically active natural products.[1] They are also versatile intermediates in organic synthesis.[2] Representative methods for the construction of α-ketoamides include amidation of α-keto acids and α-keto acyl halides,[3] oxidation of α-hydroxyamides and α-aminoamides,[4] transition-metal-catalyzed double carbonylative amination of aryl halides,[5] and reaction of isocyanide with aromatic acyl chloride or anhydride followed by hydrolysis of the resulting α-ketoimidoyl chloride.[6] Nevertheless, most reactions are restricted by precursor availability, low yields, harsh conditions, multistep processes, and utilization of expensive transition-metal catalysts. Therefore, the development of mild, convenient and efficient methods toward α-ketoamides is still required.

Recently, aerobic oxidative reactions have been developed as novel, efficient and environmentally friendly methods to synthesize α-ketoamides, as demonstrated by Zhang and Jiao[7a,b] and Du and Ji.[7c] Molecular oxygen has been used as an ideal oxidant and oxygen source in organic synthesis because of its abundance, low cost, and lack of toxic byproducts.[8] Thus, dioxygen activation and the utilization of molecular oxygen for the construction of various oxygen-containing organic compounds have attracted great interest.[9] In our research on halogen activated organic reactions,[10] we reported halonium-initiated cascades leading to 3(2*H*)-furanones and dihydrofuropyridinones by using *N*-halosuccinimide as the electrophilic agent.[10a,b] Herein, we would like to report the most recent result, copper-catalyzed aerobic oxidative reactions of acetophenone, amines and NIS, giving access to α-ketoamides (Scheme 1).[11,12] The reaction proceeded efficiently at room temperature in the open air.

## Results and discussion

Initially, the model reaction of 4-bromoacetophenone (**1a**), piperidine (**2a**), and NIS was examined in the presence of a copper catalyst (Table 1). When CuBr (20% mol) was selected as the catalyst, the reaction in DMF at room temperature gave 1-phenyl-2-(piperidin-1-yl)ethane-1,2-dione (**3a**) in 53% yield (entry 1). With other solvents like THF, DCE, and MeCN, the yields were increased (Table 1, entries 2–4). Among the solvents screened, toluene was the most effective, affording **3a** in 95% yield (Table 1, entry 5). Comparatively, in the absence of NIS, product **3a** could not be obtained at all (Table 1, entry 6). In the absence of CuBr catalyst, the yield of **3a** was dramatically decreased to 55% under otherwise identical conditions (Table 1, entry 7). Decreasing the amount of CuBr catalyst to 10 mol% gave an unsatisfactory result (Table 1, entry 8). CuI exhibited the same reactivity (Table 1, entry 9). Cu(II) catalysts were also investigated, and proved to be effective (Table 1, entries 10–12). For example, with $CuBr_2$ (20 mol%) as the catalyst, the yield of **3a** reached up to 91% (Table 1, entry 11). Surprisingly, when NBS was used as the halogenation reagent, the yields of **3a** were fairly low (Table 1, entry 13).[13] The structure of **3a** was confirmed unambiguously by X-ray single crystal diffraction (Fig. 1).

With the optimized conditions in hand, the scope of the ketones was investigated (Table 2). Catalyzed by CuBr, aryl




**Scheme 1**

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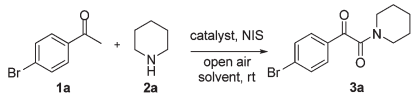
**Table 1** Optimization of the conditions




| Entry[a] | NXS | Catalyst | Solvent | Yield[b] (%) |
|---|---|---|---|---|
| 1 | NIS | CuBr (20%) | DMF | 53 |
| 2 | NIS | CuBr (20%) | THF | 56 |
| 3 | NIS | CuBr (20%) | DCE | 72 |
| 4 | NIS | CuBr (20%) | MeCN | 80 |
| **5** | **NIS** | **CuBr (20%)** | **Toluene** | **95** |
| 6 | — | CuBr (20%) | Toluene | 0 |
| 7 | NIS | — | Toluene | 55 |
| 8 | NIS | CuBr (10%) | Toluene | 52 |
| 9 | NIS | CuI (20%) | Toluene | 95 |
| 10 | NIS | $CuCl_2$ (20%) | Toluene | 90 |
| 11 | NIS | $CuBr_2$ (20%) | Toluene | 91 |
| 12 | NIS | $Cu(OAc)_2$ (20%) | Toluene | 85 |
| 13 | NBS | CuBr (20%) | Toluene | 11 |

[a] *Reaction conditions*: **1a** (1 mmol), **2a** (2.5 mmol), CuI (20 mol%), solvent (4 mL), room temperature, 35 h. [b] Yield of isolated product.

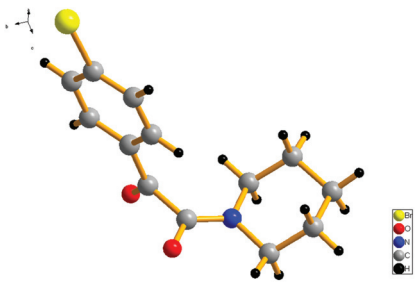
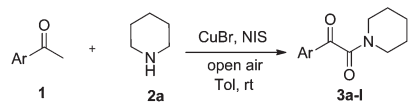


**Fig. 1** ORTEP drawing of **3a**.

**Table 2** Scope of ketones[a]




| Entry | Ar | 3 | Yield[b] (%) |
|---|---|---|---|
| 1 | 4-$BrC_6H_4$ | **3a** | 95 (94)[c] |
| 2 | 4-$BrC_6H_4$ (**1a**, 5 g) | **3a** | 89[d] |
| 3 | Ph | **3b** | 90 |
| 4 | 4-$CH_3OC_6H_4$ | **3c** | 40[e] |
| 5 | 4-$MeC_6H_4$ | **3d** | 83 |
| 6 | 2-$MeC_6H_4$ | **3e** | 89 (84)[d] |
| 7 | 4-$ClC_6H_4$ | **3f** | 94 |
| 8 | 4-$NO_2C_6H_4$ | **3g** | 91 (88)[d] |
| 9 | 3-$NO_2C_6H_4$ | **3h** | 92 |
| 10 | 2-Naphthyl | **3i** | 85 |
| 11 | 2-Pyridyl | **3j** | 90 |
| 12 | 2-Furyl | **3k** | 45 |
| 13 | 2-Thienyl | **3l** | 76 |

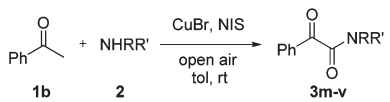
[a] *Reaction conditions*: **1** (1.0 mmol), **2a** (2.5 equiv.), CuBr (20%), NIS (1.2 equiv.), in toluene (4 mL), room temperature, 17–35 h. [b] Yield of isolated product. [c] Yields with $CuBr_2$ (20 mol%) as the catalyst. [d] The product was purified by recrystallization in a mixture of petroleum ether and ethyl ether. [e] Amide by-product **4a** was obtained (see Scheme 2).

methyl ketones containing both electron-withdrawing and electron-rich groups could react with piperidine smoothly, giving the desired products **3a–h** (Table 2, entries 1–9). A wide range of functionalities such as nitro and halogen groups were tolerated under the reaction conditions. 5 g-scale preparation of compound **3a** was achieved in 89% yield (entry 2). The naphthyl-substituted ketone was also tolerated in this transformation, generating **3i** in 85% yield (Table 2, entry 10). Heteroaryl methyl ketones such as 2-acetylpyridine, 2-acetylfuran and 2-acetylthiophene were compatible with this reaction, affording **3j–l** in moderate yields (Table 2, entries 11–13). Selected reactions with $CuBr_2$ as the catalyst were also conducted (Table 1, entries 1, 6 and 8) and comparable yields were attained.

The amine scope of the copper-catalyzed aerobic oxidative coupling leading to α-ketoamides was investigated (Table 3). The results indicate that secondary aliphatic amines (cyclic and acyclic) (Table 3, entries 1–6) and primary aliphatic amines (Table 3, entries 7–9) could be smoothly transformed into the desired products in moderate to high yields. However, reactions with aromatic amines, *e.g.* 4-methylaniline, did not occur (Table 3, entry 10). Notably, in the reactions of 1-(4-methoxyphenyl)ethanone with piperidine (Table 2, entry 2) and acetophenone with primary amines (Table 3, entries 7–9), the corresponding α-ketoamides were separated in fairly low yields. It was found that amide by-products were formed in the reactions. In isolated reactions, amides **4a** and **4b** were separated in 33% and 37% yields (Scheme 2).

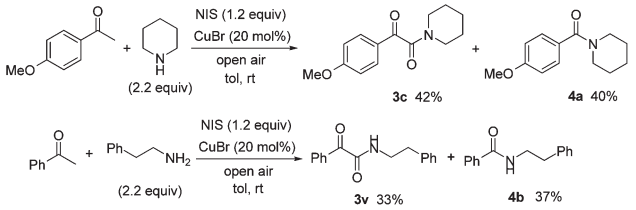
In order to elucidate the possible mechanism for the copper-catalyzed oxidative amidation reaction, several control experiments were carried out. Decreasing the amount of piperidine to 1.1 equiv. gave **3a** in 31% yield (Scheme 3). Obviously, 2.0 equiv. of amine were required, which was consistent with the possible mechanism described later. To judge the origin of the two oxygen atoms of the α-ketoamide, the reaction of 4-bromoacetophenone with piperidine was conducted under $N_2$ protection and in the open air, respectively (Scheme 4). In both cases, anhydrous toluene was used as the solvent and 4 Å MS were

**Table 3** Scope of amines[a]

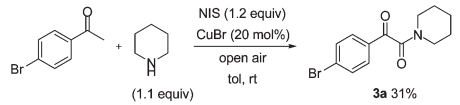



| Entry | Amine | 3 | Yield[b] (%) |
|---|---|---|---|
| 1 | Pyrrolidine | **3m** | 73 |
| 2 | Morpholine | **3n** | 84 |
| 3 | Dimethylamine (aq.) | **3o** | 45 |
| 4 | Diethylamine | **3p** | 75 |
| 5 | Dibutylamine | **3q** | 81 |
| 6 | *N*-Methylbenzylamine | **3r** | 73 |
| 7 | Benzylamine | **3s** | 42[c] |
| 8 | 4-Methylbenzylamine | **3t** | 40[c] |
| 9 | 2-Chlorobenzylamine | **3u** | 45[c] |
| 10 | 2-Phenylethylamine | **3v** | 33[c] |
| 11 | 4-Methylaniline | **3w** | n.r. |

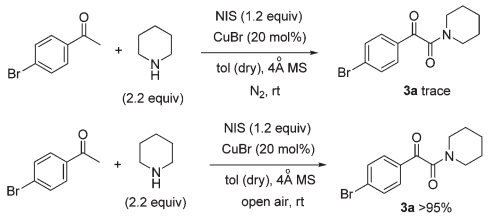
[a] *Reaction conditions*: **1a** (1.0 mmol), **2** (2.5 equiv.), CuBr (20 mol%), NIS (1.2 equiv.), in toluene (4 mL), room temperature, 17–35 h. [b] Yield of isolated product. [c] Amide by-products **4** were observed.



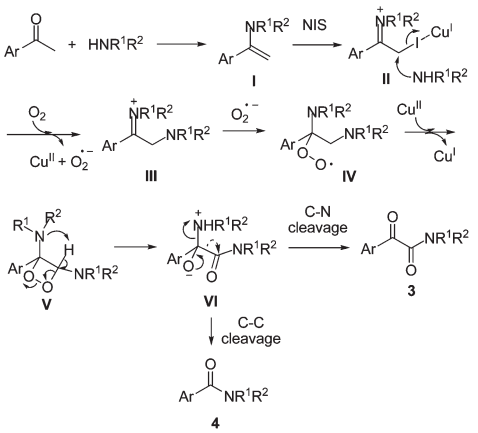

**Scheme 2** Amide by-products involved in the reactions.




**Scheme 3** Effect of amine amount on the reaction.




**Scheme 4** Effect of dioxygen (air) on the reaction.




**Scheme 5** Possible mechanism for the formation of α-ketoamides **3** and amide by-products **4**.

added to remove the water generated in the reaction system. As a result, the reaction under $N_2$ protection gave trace amounts of **3a**, while the reaction performed in the open air gave **3a** in >95% yield. The above experimental results indicate that dioxygen in the air was involved in the reaction leading to α-ketoamides.

Based on all the results described above and recent research by Zhang and Jiao,[7a,b] Du and Ji[7c] and Zhang and Wang, [12a] a possible mechanism for the formation of α-ketoamides is shown in Scheme 5. Firstly, enamine **I** is formed from aryl methyl ketone **1** and amine, followed by iodination to generate intermediate **II**.[12a,b] Nucleophilic substitution of excess amines gives α-amino substituted iminium **III**, in which CuBr facilitates the C–I bond cleavage.[14] Meanwhile, a superoxide radical ($O_2^{\cdot -}$) is generated from dioxygen in air during the oxidation of Cu(I) into Cu(II), which adds to the iminium **III** immediately to afford radical intermediate **IV**. Intramolecular cyclization gives key aminodioxetane intermediate **V**. During this process, Cu(II) was reduced to Cu(I) by single electron transfer (SET) to accomplish the catalytic cycle.[15] Ring-opening through O–O bond heterolysis leads to intermediate **VI**. C–N bond cleavage in **VI** furnishes the final α-ketoamide **3**. Alternatively, amide by-product **4** would be generated *via* C–C bond cleavage.[16]

## Conclusion

In summary, we have developed a simple, efficient and practical copper-catalyzed one-pot oxidative synthesis of α-ketoamides by the reaction of aryl methyl ketones, amines and NIS. A possible mechanism was proposed and the formation of the α-ketoamides and amide by-products was attributed to the different elimination fashion upon ring-opening of the four-membered aminodioxetane intermediates. The notable features of the reaction are cheap catalysts, readily available starting materials, mild conditions (*e.g.* room temperature) and utilization of air as the dioxygen source (instead of an $O_2$ balloon). Further work on halogen reagent-mediated organic reactions is ongoing in our laboratory.

## Experimental

### General methods

All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The products were purified by column chromatography over silica gel. $^1$H NMR and $^{13}$C NMR spectra were recorded at 25 °C on a Varian 500 MHz and 125 MHz, respectively, and TMS as the internal standard. Elemental analyses were measured on an E-2400 analyzer (Perkin-Elmer). Mass spectra were recorded on an Agilient 1100 LCMsD mass spectrometer.

### General procedure for the synthesis of 3 (3a as an example)

To a solution of acetophenone **1a** (0.117 mL, 1.0 mmol) in toluene (4 mL) was added NIS (270 mg, 1.2 mmol), CuBr (28.7 mg, 0.2 mmol) and piperidine (0.247 mL, 2.5 mmol). The mixture was stirred at room temperature for about 30 h. After the starting material **3a** was consumed as indicated by TLC, the reaction mixture was poured into water and then extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic phase was washed with water (3 × 10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, petroleum ether : ether = 6 : 1) to give **3a** (280 mg, 95%) as a white solid.

### Physical data of compounds isolated

**1-(4-Bromophenyl)-2-(piperidin-1-yl)ethane-1,2-dione (3a).** White solid. m.p. 87–89 °C. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 7.83–7.81 (d, $J$ = 8.5 Hz, 2H), 7.67–7.65 (d, $J$ = 8.5 Hz, 2H), 3.71–3.70 (d, $J$ = 5.5 Hz, 2H), 3.29–3.27 (t, $J$ = 5.5 Hz, 2H), 1.701–1.697 (d, $J$ = 2 Hz, 4H), 1.56 (s, 2H); $^{13}$C NMR

($CDCl_3$, 125 MHz, ppm): $\delta$ = 190.6, 164.7, 132.3, 131.9, 130.8, 130.0, 46.9, 42.1, 26.1, 25.3, 24.2. MS calcd *m/z* 295.0, found 296.0 $[(M + 1)]^+$. Anal. Calcd for $C_{13}H_{14}BrNO_2$: C, 52.72; H, 4.76; N, 4.73; Found: C, 52.60; H, 4.77; N, 4.72.

**1-Phenyl-2-(piperidin-1-yl)ethane-1,2-dione (3b).** White solid. m.p. 109–111 °C. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 7.96–7.95 (m, 2H), 7.66–7.63 (m, 1H), 7.53–7.50 (t, *J* = 7.5 Hz, 2H), 3.71 (s, 2H), 3.31–3.29 (t, *J* = 5.5 Hz, 2H), 1.71–1.70 (t, *J* = 3 Hz, 4H), 1.56–1.55 (d, *J* = 5.5 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 191.9, 165.4, 134.6, 133.2, 129.5, 129.0, 47.0, 42.1, 26.2, 25.4, 24.3. MS calcd *m/z* 217.1, found 218.1 $[(M + 1)]^+$. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.84; H, 6.96; N, 6.45; Found: C, 71.72; H, 6.95; N, 6.46.

**1-(4-Methoxyphenyl)-2-(piperidin-1-yl)ethane-1,2-dione (3c).** Yellowish oil. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 7.93–7.9 (m, 2H), 6.99–6.96 (m, 2H), 3.89 (s, 3H), 3.70–3.69 (d, *J* = 5.5 Hz, 2H), 3.30–3.28 (t, *J* = 5.5 Hz, 2H), 1.70–1.68 (t, *J* = 2.5 Hz, 4H), 1.55–1.53 (t, *J* = 5.5 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 190.6, 165.7, 164.7, 131.9, 126.2, 114.2, 55.5, 46.9, 42.0, 26.1, 25.4, 24.3. MS calcd *m/z* 247.1, found 248.1 $[(M + 1)]^+$. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66; Found: C, 68.11; H, 6.92; N, 5.67.

**1-(Piperidin-1-yl)-2-p-tolylethane-1,2-dione (3d).** Yellowish oil. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 7.85–7.83 (d, *J* = 8.5 Hz, 2H), 7.32–7.30 (d, *J* = 8.0 Hz, 2H), 3.70 (s, 2H), 3.29–3.27 (t, *J* = 5.5 Hz, 2H), 2.43 (s, 3H), 1.70–1.68 (t, *J* = 3 Hz, 4H), 1.55–1.53 (d, *J* = 5.5 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 191.6, 165.6, 145.8, 130.7, 129.63, 129.59, 46.9, 42.0, 26.1, 25.4, 24.3, 21.8. MS calcd *m/z* 231.1, found 232.1 $[(M + 1)]^+$. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06; Found: C, 72.79; H, 7.40; N, 6.05.

**1-(Piperidin-1-yl)-2-o-tolylethane-1,2-dione (3e).** Yellowish oil. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 7.72–7.71 (d, *J* = 8.0 Hz, 1H), 7.49–7.46 (m, 1H), 7.33–7.27 (m, 2H), 3.70–3.69 (d, *J* = 5.0 Hz, 2H), 3.32–3.29 (t, *J* = 5.5 Hz, 2H), 2.67 (s, 3H), 1.70–1.67 (t, *J* = 3 Hz, 4H), 1.57–1.55 (t, *J* = 5.5 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 193.8, 166.0, 141.4, 133.5, 132.7, 132.5, 131.5, 126.1, 47.0, 42.0, 26.0, 25.3, 24.3, 21.8. MS calcd *m/z* 231.1, found 232.1 $[(M + 1)]^+$. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06; Found: C, 72.79; H, 7.40; N, 6.05.

**1-(4-Chlorophenyl)-2-(piperidin-1-yl)ethane-1,2-dione (3f).** Yellowish oil. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 7.91–7.88 (d, *J* = 8.5 Hz, 2H), 7.50–7.47 (d, *J* = 8.5 Hz, 2H), 3.71–3.69 (t, *J* = 5.2 Hz, 2H), 3.30–3.27 (t, *J* = 5.6 Hz, 2H), 1.73–1.67 (m, 4H), 1.58–1.53 (m, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 190.5, 164.9, 141.2, 131.7, 130.9, 129.4, 47.1, 42.3, 26.3, 25.4, 24.4. MS calcd *m/z* 251.1, found 261.1 $[(M + 1)]^+$. Calcd for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.61; N, 5.56; Found: C, 52.61.85; H, 5.62; N, 5.55.

**1-(4-Nitrophenyl)-2-(piperidin-1-yl)ethane-1,2-dione (3g).** Yellow solid. m.p. 94–96 °C. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 8.37–8.35 (t, *J* = 7.5 Hz, 2H), 8.15–8.14 (d, *J* = 7.0 Hz, 2H), 3.74–3.73 (d, *J* = 5.5 Hz, 2H), 3.33–3.31 (t, *J* = 6.0 Hz, 2H), 1.73–1.72 (d, *J* = 3.0 Hz, 4H), 1.59–1.58 (d, *J* = 4.5 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 189.5, 164.0, 150.9, 137.5, 130.5, 124.0, 46.9, 42.3, 26.2, 25.3, 24.1. MS calcd *m/z* 262.1, found 263.1 $[(M + 1)]^+$. Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68; Found: C, 59.61; H, 5.39; N, 10.67.

**1-(3-Nitrophenyl)-2-(piperidin-1-yl)ethane-1,2-dione (3f).** Yellow solid. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 8.77 (s, 1H), 8.51–8.49 (m, 1H), 8.31–8.29 (d, *J* = 8.0 Hz, 1H), 7.79–7.76 (t, *J* = 8.0 Hz, 1H), 3.75–3.74 (d, *J* = 5.0 Hz, 2H), 3.36–3.34 (t, *J* = 5.5 Hz, 2H), 1.74–1.73 (d, *J* = 2.5 Hz, 4H), 1.61 (s, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 190.5, 164.9, 141.2, 131.7, 130.9, 129.4, 47.0, 42.2, 26.2, 25.4, 24.3. MS calcd *m/z* 262.1, found 263.1 $[(M + 1)]^+$. Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68; Found: C, 59.61; H, 5.39; N, 10.67.

**1-(Naphthalen-2-yl)-2-(piperidin-1-yl)ethane-1,2-dione (3i).** Yellowish solid. m.p. 80–82 °C. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 8.45 (s, 1H), 8.04–8.02 (m, 1 Hz, 1H), 7.98–7.96 (d, *J* = 8.0 Hz, 1H), 7.95–7.93 (d, *J* = 9.0 Hz, 2H), 7.89–7.87 (d, *J* = 8.0 Hz, 1H), 7.65–7.62 (t, *J* = 8.0 Hz, 1H), 7.58–7.55 (t, *J* = 8.0 Hz, 1H), 3.78–3.76 (t, *J* = 4.5 Hz, 2H), 3.33–3.31 (t, *J* = 5.5 Hz, 2H), 1.71 (s, 4H), 1.56–1.54 (t, *J* = 6.0 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 192.0, 165.4, 136.1, 132.7, 132.2, 130.4, 129.7, 129.2, 128.9, 127.8, 127.0, 123.4, 47.0, 42.1, 26.0, 25.3, 24.2. MS calcd *m/z* 267.1, found 268.1 $[(M + 1)]^+$. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24; Found: C, 76.31; H, 6.40; N, 5.25.

**1-(Piperidin-1-yl)-2-(pyridin-2-yl)ethane-1,2-dione (3j).** Yellowish oil. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 8.76–8.75 (d, *J* = 3.5 Hz, 1H), 8.12–8.11 (d, *J* = 8.0 Hz, 1H), 7.92–7.88 (m, 1H), 7.54–7.51 (m, 1H), 3.73 (s, 2H), 3.29–3.27 (t, *J* = 5.5 Hz, 2H), 1.72–1.64 (m, 4H), 1.59–1.53 (m, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 192.2, 166.2, 151.5, 150.0, 137.2, 127.9, 123.1, 47.0, 42.2, 25.9, 25.2, 23.8. MS calcd *m/z* 218.1, found 219.1 $[(M + 1)]^+$. Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84; Found: C, 65.97; H, 6.48; N, 12.83.

**1-(Furan-2-yl)-2-(piperidin-1-yl)ethane-1,2-dione (3k).** Yellowish oil. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 7.72–7.71 (m, 1H), 7.35–7.34 (m, 1H), 6.62–6.61 (m, 1H), 3.68–3.66 (t, *J* = 6.0 Hz, 2H), 3.39–3.37 (t, *J* = 6.0 Hz, 2H), 1.72–1.65 (m, 4H), 1.61–1.58 (m, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 178.9, 164.0, 150.2, 148.6, 121.9, 112.8, 47.0, 42.4, 25.6, 24.7, 23.9. MS calcd *m/z* 207.1, found 208.1 $[(M + 1)]^+$. Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76; Found: C, 63.66; H, 6.33; N, 6.75.

**1-(Piperidin-1-yl)-2-(thiophen-2-yl)ethane-1,2-dione (3l).** Yellowish oil. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 7.80–7.79 (m, 2H), 7.20–7.18 (m, 1H), 3.69–3.67 (t, *J* = 6.0 Hz, 2H), 3.39–3.37 (t, *J* = 5.5 Hz, 2H), 1.72 (s, 4H), 1.63–1.56 (m, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 183.9, 164.4, 140.5, 136.3, 1135.9, 128.2, 47.1, 42.4, 26.2, 25.4, 24.3. MS calcd *m/z* 223.1, found 224.1 $[(M + 1)]^+$. Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27; Found: C, 59.28; H, 5.86; N, 6.28.

**1-Phenyl-2-(pyrrolidin-1-yl)ethane-1,2-dione (3m).** Yellowish oil. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 8.00–7.99 (m, 2H),

7.66–7.62 (m, 1H), 7.53–7.49 (t, $J$ = 8.0 Hz, 2H), 3.68–3.65 (t, $J$ = 7.0 Hz, 2H), 3.44–3.42 (t, $J$ = 6.0 Hz, 2H), 1.99–1.93 (m, 4H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 191.6, 164.9, 134.6, 132.9, 129.9, 128.9, 46.6, 45.2, 25.9, 24.0. MS calcd $m/z$ 203.1, found 204.1 $[(M + 1)]^+$. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89; Found: C, 70.80; H, 6.44; N, 6.90.

**1-Morpholino-2-phenylethane-1,2-dione (3n).** Yellowish oil. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 7.97–7.96 (t, $J$ = 7.0 Hz, 2H), 7.68–7.65 (m, 1H), 7.55–7.52 (t, $J$ = 8.5 Hz, 2H), 3.82–3.79 (m, 4H), 3.67–3.65 (m, 2H), 3.40–3.38 (t, $J$ = 4.5 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 191.0, 165.2, 134.9, 132.8, 129.5, 129.0, 66.53, 66.45, 46.0, 41.4. MS calcd $m/z$ 219.1, found 220.1 $[(M + 1)]^+$. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39; Found: C, 65.81; H, 5.99; N, 6.38.

***N*,*N*-Dimethyl-2-oxo-2-phenylacetamide (3o).** Yellowish oil. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 7.96–7.94 (t, $J$ = 7.5 Hz, 2H), 7.66–7.63 (t, $J$ = 7.0 Hz, 1H), 7.53–7.50 (t, $J$ = 8.0 Hz, 2H), 3.13 (s, 3H), 2.97 (s, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 191.8, 167.0, 134.7, 132.9, 129.6, 129.0, 37.0, 33.9. MS calcd $m/z$ 177.1, found 178.1 $[(M + 1)]^+$. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 67.78; H, 6.26; N, 7.90; Found: C, 67.92; H, 6.25; N, 7.91.

***N*,*N*-Diethyl-2-oxo-2-phenylacetamide (3p).** Colorless oil. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 7.95–7.93 (m, 2H), 7.66–7.62 (m, 1H), 7.53–7.50 (m, 2H), 3.59–3.55 (m, 2H), 3.27–3.23 (m, 2H), 1.31–1.28 (m, 3H), 1.17–1.15 (m, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 191.6, 166.7, 134.6, 133.2, 129.6, 128.9, 42.1, 38.7, 14.1, 12.8. MS calcd $m/z$ 205.1, found 206.1 $[(M + 1)]^+$. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82; Found: C, 70.09; H, 7.36; N, 6.83.

***N*,*N*-Dibutyl-2-oxo-2-phenylacetamide (3q).** Colorless oil. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 7.94–7.93 (t, $J$ = 7.0 Hz, 2H), 7.65–7.62 (t, $J$ = 7.5 Hz, 1H), 7.52–7.49 (t, $J$ = 7.5 Hz, 2H), 3.51–3.48 (t, $J$ = 7.5 Hz, 2H), 3.17–3.13 (t, $J$ = 7.5 Hz, 2H), 1.70–1.64 (m, 2H), 1.57–1.51 (m, 2H), 1.44–1.40 (m, 2H), 1.21–1.16 (m, 2H), 1.01–0.98 (t, $J$ = 7.4 Hz, 3H), 0.83–0.80 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 191.6, 167.1, 134.5, 133.4, 129.6, 128.9, 47.4, 44.0, 30.6, 29.3, 19.9, 19.8, 13.8, 13.7. MS calcd $m/z$ 261.2, found 262.2 $[(M + 1)]^+$. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36; Found: C, 73.36; H, 8.86; N, 5.37.

***N*-Benzyl-*N*-methyl-2-oxo-2-phenylacetamide (3r).** Yellowish oil. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 8.00–7.96 (m, 4H), 7.66–7.63 (t, $J$ = 7.5 Hz, 2H), 7.53–7.50 (t, $J$ = 8.0 Hz, 4H), 7.39–7.25 (m, 10H), 4.74 (s, 2H), 4.40 (s, 2H), 3.00 (s, 3H), 2.85 (s, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 191.6, 167.3, 167.2, 135.8, 135.0, 134.8, 133.3, 133.1, 132.3, 130.9, 129.8, 129.1, 129.0, 128.91, 128.85, 128.7, 128.4, 128.2, 127.9, 127.8, 53.5, 49.9, 34.5, 31.4. MS calcd $m/z$ 253.1, found 254.1 $[(M + 1)]^+$. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53; Found: C, 75.71; H, 5.96; N, 5.67.

***N*-Benzyl-2-oxo-2-phenylacetamide (3s).** Colorless oil. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 8.37–8.35 (t, $J$ = 7.5 Hz, 2H), 7.64–7.61 (t, $J$ = 7.0 Hz, 1H), 7.50–7.47 (t, $J$ = 8.0 Hz, 2H), 7.43 (s, 1H), 7.38–7.29 (m, 4H), 4.58–4.57 (d, $J$ = 6.0 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 187.5, 161.5, 137.1, 134.4, 133.3, 131.2, 128.8, 128.5, 127.9, 127.8, 43.4. MS calcd $m/z$ 239.1, found 240.1 $[(M + 1)]^+$. Anal. Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85; Found: C, 75.16; H, 5.47; N, 5.86.

***N*-(4-Methylbenzyl)-2-oxo-2-phenylacetamide (3t).** Colorless oil. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 8.35–8.34 (t, $J$ = 7.0 Hz, 2H), 7.63–7.60 (t, $J$ = 7.5 Hz, 1H), 7.49–7.46 (t, $J$ = 7.5 Hz, 2H), 7.25 (s, 1H), 7.23–7.21 (d, $J$ = 8.0 Hz, 2H), 7.17–7.15 (d, $J$ = 8.0 Hz, 2H), 4.53–4.51 (d, $J$ = 6.0 Hz, 2H), 2.34 (s, 3H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 187.5, 161.4, 137.5, 134.4, 134.0, 133.3, 131.2, 129.4, 128.4, 127.9, 43.2, 21.1. MS calcd $m/z$ 253.1, found 254.1 $[(M + 1)]^+$. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53; Found: C, 75.74; H, 5.96; N, 5.34.

***N*-(2-Chlorobenzyl)-2-oxo-2-phenylacetamide (3u).** Yellowish oil. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 8.35–8.33 (m, 2H), 7.63–7.60 (t, $J$ = 7.5 Hz, 1H), 7.54 (s, 1H), 7.49–7.46 (t, $J$ = 8.0 Hz, 2H), 7.43–7.38 (m, 2H), 7.27–7.24 (m, 2H), 4.67–4.66 (d, $J$ = 6.0 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 187.4, 161.6, 134.6, 134.5, 133.8, 133.3, 131.5, 131.3, 130.2, 129.7, 129.3, 128.9, 128.5, 127.2, 43.4. MS calcd $m/z$ 253.1, found 254.1 $[(M + 1)]^+$. Anal. Calcd for $C_{15}H_{12}ClNO_2$: C, 65.82; H, 4.42; N, 5.12; Found: C, 65.71; H, 4.41; N, 5.13.

**2-Oxo-*N*-phenethyl-2-phenylacetamide (3v).** Colorless oil. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 8.31–8.29 (t, $J$ = 7.5 Hz, 2H), 7.63–7.60 (m, 1H), 7.48–7.45 (t, $J$ = 8.0 Hz, 2H), 7.34–7.31 (t, $J$ = 7.5 Hz, 2H), 7.26–7.24 (m, 4H), 7.12 (s, 1H), 3.68–3.64 (m, 2H), 2.93–2.90 (t, $J$ = 7.0 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 187.5, 161.5, 137.1, 134.4, 133.3, 131.2, 128.8, 128.5, 127.9, 127.8, 43.4. MS calcd $m/z$ 253.1, found 254.1 $[(M + 1)]^+$. Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53; Found: C, 75.92; H, 5.91; N, 5.52.

**(4-Methoxyphenyl)(piperidin-1-yl)methanone (4a).** Yellowish oil. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 7.37–7.35 (d, $J$ = 8.5 Hz, 2H), 6.91–6.89 (d, $J$ = 9.0 Hz, 2H), 3.86 (s, 3H), 3.83 (s, 2H), 1.68–1.67 (d, $J$ = 4.0 Hz, 2H), 1.59 (s, 4H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 190.6, 165.7, 164.7, 131.9, 126.2, 114.2, 55.5, 46.9, 42.0, 26.1, 25.4, 24.3. MS calcd $m/z$ 247.1, found 248.1 $[(M + 1)]^+$. Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39; Found: C, 71.13; H, 7.82; N, 6.38.

***N*-Phenethylbenzamide (4b).** Colorless oil. $^1$H NMR ($CDCl_3$, 500 MHz, ppm): $\delta$ = 7.70–7.68 (t, $J$ = 7.0 Hz, 2H), 7.50–7.47 (t, $J$ = 7.5 Hz, 1H), 7.42–7.39 (t, $J$ = 7.5 Hz, 2H), 7.35–7.33 (t, $J$ = 8.0 Hz, 2H), 7.27–7.24 (t, $J$ = 8.0 Hz, 3H), 6.11 (s, 1H), 3.75–3.71 (m, 2H), 2.96–2.93 (t, $J$ = 6.5 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz, ppm): $\delta$ = 167.5, 138.9, 134.7, 131.4, 128.8, 128.6, 126.8, 126.6, 41.1, 35.7. MS calcd $m/z$ 225.1, found 226.1 $[(M + 1)]^+$. Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22; Found: C, 79.79; H, 6.70; N, 6.23.

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