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Copper-Catalyzed Oxidative Synthesis of α-Ketoamides from Aryl Methyl Ketones and *N*-Bromobutanimide Using *N*,*N*-Dimethylformamide as Dimethylamine Source

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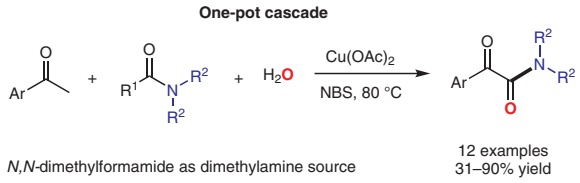

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Abstract A novel and practical $Cu(OAc)_2$-catalyzed oxidative synthesis of α-ketoamides from aryl methyl ketones and *N*-bromobutanimide (NBS) using *N*,*N*-dimethylformamide (DMF) as dimethylamine ($HNMe_2$) source and solvent has been developed under mild conditions. DMF was used as a $HNMe_2$ source and can be easily converted into $HNMe_2$ by acid hydrolysis. The mechanistic studies indicate that $Cu(OAc)_2$ plays a dual role in providing both catalyst and oxidant.

Key words dimethylamine, α-ketoamides, *N*-bromobutanimide, aryl methyl ketones, *N*,*N*-dimethylformamide

The α-ketoamides is a key structural unit in a number of biologically active natural compounds, drugs and drug candidates such as oxerin receptor agonist, cytokine inhibitor, RARγagonist, eurystatin A and B, and poststatin (Figure 1).[1–5] Because of their importance, the synthesis of α-ketoamides have attracted significant attention in recent years. So far, a wide variety of synthetic methodologies for constructing α-ketoamides have been developed towards achieving high efficiency and novelty.[6] Several oxidative amidation methods have been described for the preparation of α-ketoamides. The common routes involve Cu-catalyzed oxidative amidation of aryl acetaldehydes,[7] aryl methyl ketones,[8–11] or 1-arylethanols,[12] Cu-catalyzed oxidative amidation–diketonization of terminal alkynes,[13–15] the halogen-catalyzed oxidative amidation of aryl methyl ketones,[16,17] alkynes,[18] or terminal alkenes,[19] the TBAI-catalyzed decarbonylative amidation of aryl methyl ketones[20] or ethyl arenes,[21] and the benzoic acid assisted iodine-catalyzed decarbonylative oxidative amidation of aryl methyl ketones.[22] Among them, aryl methyl ketones as starting materials are widely used in the synthesis of α-ketoamides. However, the most commonly used oxidants in these reactions are TBHP or Cu(I)/oxygen combination. Therefore, in this work, we focused on developing a new oxidative reagent and masked amine sources reagent combination for the synthesis of α-ketoamides.

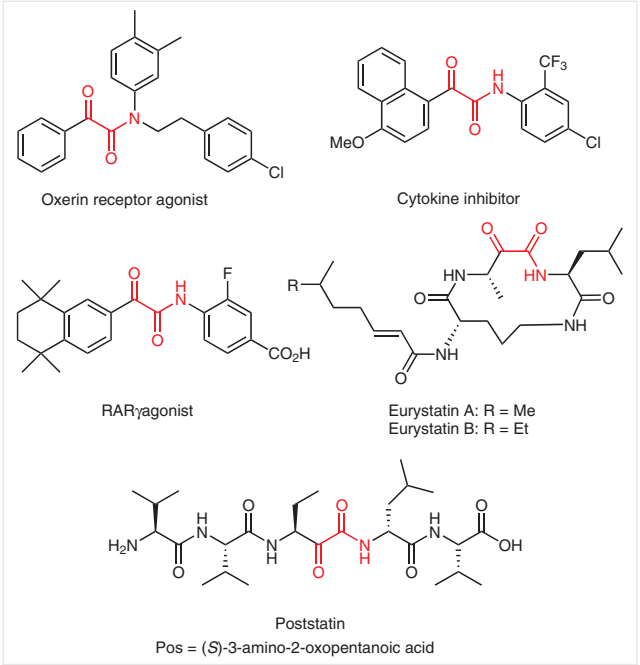

Figure 1 Biologically active molecules

N-Dimethylformamide (DMF) has been widely used as a multifunctional reagent in organic synthesis. For example, DMF can participate in many reactions as a dehydrating agent, as a catalyst, as a reducing agent, or even as a source for various units (O, –CO, $–NMe_2$, $–CONMe_2$, –Me, –CHO, etc.).[23] Inspired by these aspects, we became interested in the possibility of preparing α-ketoamides using DMF as di-

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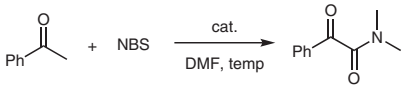
alkylamine source. For example, recently, Li and co-workers have developed a copper-catalyzed oxidative C–H amination of benzoxazoles using DMF as a dimethylamine source.[24] Yang et al. reported a zinc-catalyzed reductive amination of carbonyl compounds with DMF as $HNMe_2$ source.[25] Herein, in this context, we show a concise and efficient synthetic approach for preparing α-ketoamides through a Cu-catalyzed oxidative reaction of aryl methyl ketones and NBS using DMF as dialkylamine source and as a solvent. This protocol provides not only a new strategy to construct α-ketoamides but also extends the application range of DMF as dialkylamine source. The mechanistic studies indicate that the copper catalyst plays a dual role in providing both catalyst and oxidant.

The reaction of acetophenone (**1a**) with NBS was chosen as a model reaction for optimization of the reaction conditions (Table 1). First, several Cu catalysts were investigated by using DMF as the dimethylamine source and solvent at 80 °C (Table 1, entries 1–5). The reaction with $Cu(OAc)_2$ as the catalyst in DMF gave *N*,*N*-dimethyl-2-oxo-2-phenylacetamide (**2a**) in 84% yield. $CuBr_2$ exhibited the same reactivity. When $Cu(OTf)_2$ was selected as the catalyst, the yields decreased. Besides Cu(II) catalysts, both Cu(I) catalysts like CuBr and CuI proved to be suitable, giving **2a** in moderate yields. No reaction occurred in DMF at 80 °C, by the utilization of $FeSO_4$, and AgOTf as the catalyst (Table 1, entries 6 and 7). However, when the reaction temperature was lowered to 60 °C, only 52% of **2a** was observed (Table 1, entry 8). Additionally, the yield decreased significantly to 43%, when the quantity of the catalyst was reduced to 20 mol% (Table 1, entry 9). When toluene was selected as the solvent, the yields decreased (Table 1, entry 10).

With the optimal conditions established above (Table 1, entry 1), the scope of the ketones was investigated (Table 2). Catalyzed by $Cu(OAc)_2$, aryl methyl ketones containing both electron-donating and electron-withdrawing groups could react with piperidine smoothly, giving the desired products **2a–h** in moderate yields (76–90%, Table 2, entries 1–8). It is noteworthy that an electron-donating substituent on the benzene ring proceeded more efficiently than an electron-withdrawing substituent on the benzene ring. In addition, the naphthyl-substituted ketone also provided the target product **2i** in 81% yield (Table 2, entry 9). Encouraged by the results obtained with aryl methyl ketones, we turned our attention to the heteroaryl methyl ketones. The heterocycles, including furan **1j** and thiophene **1k**, were converted into the corresponding products **2j** and **2k** in 76% and 72% yields, respectively (Table 2, entries 10 and 11). Nevertheless, when 2-acetyl pyridine was used as substrates, none of the desired products was detected.

Then, we examined the efficacy of another amine source (Table 3). As a result, *N*,*N*-diethylformamide (DEF) is also efficient in the explored reactions, giving the corresponding products **2m** in 31% yield. Nevertheless, no reaction occurred with piperidine-1-carbaldehyde or morpholine-4-carbaldehyde as the amine source and solvent. In addition, we use *N*,*N*-diphenylformamide as an aromatic amine source. As a result, the target product **2p** was not ob-

Table 1 Optimization of the Reaction Conditions[a]

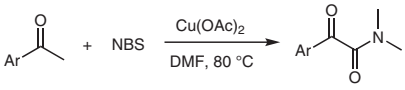


1a **2a**

Entry	Catalyst (equiv)	Temp (°C)	Yield of **2a** (%)[b]
1	$Cu(OAc)_2$ (1.2)	80	84
2	$CuBr_2$ (1.2)	80	81
3	$Cu(OTf)_2$ (1.2)	80	47
4	CuBr (1.2)	80	78
5	CuI (1.2)	80	80
6	AgOTf (1.2)	80	0
7	$FeSO_4$ (1.2)	80	0
8	$Cu(OAc)_2$ (1.2)	60	52
9	$Cu(OAc)_2$ (0.2)	80	43
10	$Cu(OAc)_2$ (1.2)	80	40[c]

[a] Reaction conditions: **1a** (1.0 mmol), NBS (1.2 mmol), with catalyst (1.2 equiv) in DMF (2 mL).
[b] Isolated yield.
[c] DMF (5 mmol) in toluene (2 mL).

Table 2 Substrate Scope of Aryl Methyl Ketones[a]



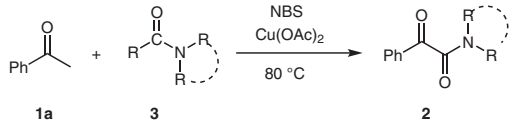
1 **2**

Entry	**1**	Ar	**2**	Yield (%)[b]
1	**1a**	Ph	**2a**	84
2	**1b**	4-$MeOC_6H_4$	**2b**	87
3	**1c**	4-MeC_6H_4	**2c**	90
4	**1d**	2-MeC_6H_4	**2d**	86
5	**1e**	4-BrC_6H_4	**2e**	81
6	**1f**	4-ClC_6H_4	**2f**	80
7	**1g**	4-$O_2NC_6H_4$	**2g**	79
8	**1h**	3-$O_2NC_6H_4$	**2h**	76
9	**1i**	2-naphthyl	**2i**	81
10	**1j**	2-thienyl	**2j**	76
11	**1k**	2-furyl	**2k**	72

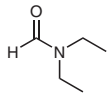
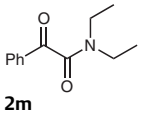
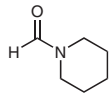
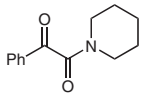
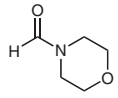
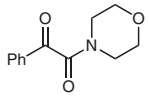
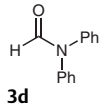
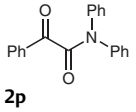
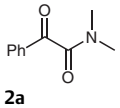
[a] Reaction conditions: **1** (1.0 mmol), NBS (1.2 mmol), $Cu(OAc)_2$ (1.2 mmol) in DMF (2 mL) at 80 °C.
[b] Isolated yield.

served. Interestingly, *N*,*N*-dimethylacetamide (DMA) was used instead of DMF under otherwise the same conditions, and product **2a** was also produced in 78% yield.

Table 3 Substrate Scope of Amides[a]



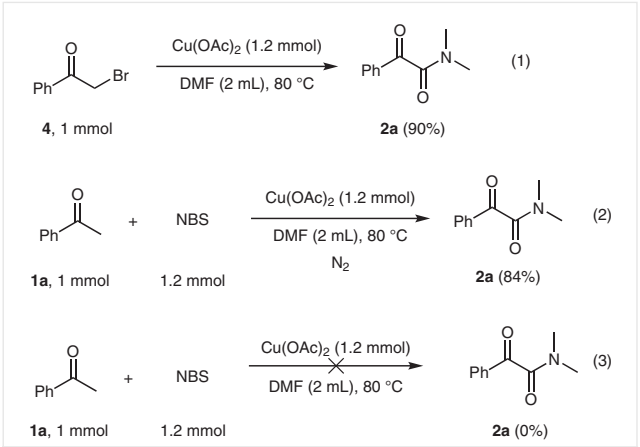
1a **3** **2**

Entry	3	2	Yield (%)[b]
1	 **3a**	 **2m**	31
2	 **3b**	 **2n**	0
3	 **3c**	 **2o**	0
4	 **3d**	 **2p**	0[c]
5	 **3e**	 **2a**	78

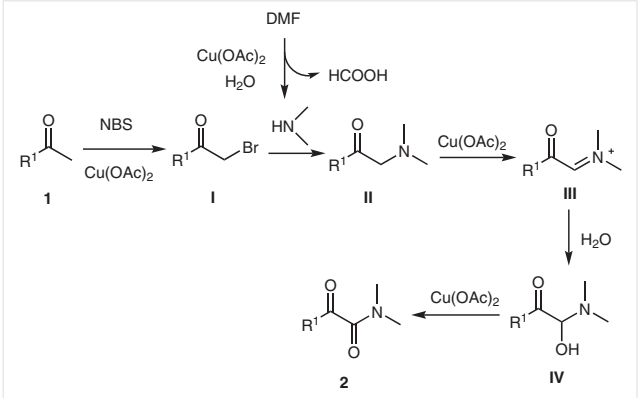
[a] Reaction conditions: **1a** (1.0 mmol), NBS (1.2 mmol), $Cu(OAc)_2$ (1.2 mmol) in **3** (2 mL) at 80 °C.
[b] Isolated yield.
[c] *N*,*N*-Diphenylformamide (5 mmol) in toluene (2mL).

To gain insight into the mechanism, several control experiments were performed (Scheme 1). The reaction of α-bromoacetophenone (**4**) and $Cu(OAc)_2$ was conducted in DMF at 80 °C and gave product **2a** in 90% yield (Scheme 1, eq. 1). The results indicate that the α-bromoacetophenone might be involved in the mechanism. To explore the origin of the two oxygen atoms of the α-ketoamide, the reaction under N_2 protection gave **2a** in 84% yield (Scheme 1, eq. 2), while the reaction performed in anhydrous DMF (Scheme 1, eq. 3), no **2a** could be observed. Thus, the results indicate that water is crucial for the reaction to proceed.

On the basis of all the results described above, a possible mechanism for the formation of α-ketoamides is shown in Scheme 2. First, in the presence of $Cu(OAc)_2$, aryl methyl ketones **1** and NBS react to form α-bromoketone **I**. At the same time, catalyzed by $Cu(OAc)_2$, DMF is hydrolyzed to give dimethylamine and formic acid.[25] Then, α-aminomethyl ketone **II** is formed via nucleophilic substitution of **I** by the dimethylamine. Finally, α-aminomethyl ketone **II** could be oxidized to iminium **III** by $Cu(OAc)_2$.[26,27] Followed by the nucleophilic substitution attack of **III** by H_2O leads to the formation of intermediate **IV**, which is further oxidized to afford the desired α-ketoamides **2**.



Scheme 1 Control experiments



Scheme 2 Proposed mechanism

In conclusion, we have successfully developed a novel and atom-efficient copper-catalyzed one-pot oxidative synthesis of α-ketoamides by the reaction of aryl methyl ketones and NBS using *N*,*N*-dimethylformamide as dimethylamine, in which $Cu(OAc)_2$ plays a dual role in providing both catalyst and oxidant.[28] The mechanistic studies indicate that H_2O plays an important role in the reaction. The reaction features mild conditions, a broad substrate scope, and atom efficiency.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691568.

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(28) **General Procedure for the Preparation of α-Ketoamides 2 – Synthesis of Compound 2a**

To a solution of acetophenone (0.12 mL, 1.0 mmol) and $Cu(OAc)_2$ (218 mg, 1.2 mmol) in DMF (2 mL). NBS (213 mg, 1.2 mmol) was then added to the flask in succession. The reaction mixture was stirred at 80 °C for 12 h. After the starting material **1a** 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/ethyl acetate = 2:1) to give **2a** (148 mg, 84%) as a white solid.

***N,N*-Dimethyl-2-oxo-2-phenylacetamide (2a)**

Yellow solid-liquid mixtures (148 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.96 (s, 3 H), 3.12 (s, 3 H), 7.50–7.53 (t, *J* = 7.5 Hz, 2 H), 7.63–7.66 (t, *J* = 7.5 Hz, 1 H), 7.94–7.95 (t, *J* = 7.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 33.9, 37.0, 128.9, 129.6, 132.9, 134.7, 166.9, 191.7. MS: *m/z* calcd: 177.0; found: 178.1 [M + 1]$^+$. Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.69; H, 6.27; N, 7.89.

2-(4-Methoxyphenyl)-*N,N*-dimethyl-2-oxoacetamide (2b)

Colourless oil (180 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.95 (s, 3 H), 3.11 (s, 3 H), 3.89 (s, 3 H), 6.96–6.98 (m, 2 H), 7.90–7.92 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 33.8, 37.0, 55.5, 114.2, 126.0, 132.0, 164.7, 167.2, 190.4. MS: *m/z* calcd: 207.0; 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, 63.88; H, 6.33; N, 6.77.

***N,N*-Dimethyl-2-oxo-2-(*p*-tolyl)acetamide (2c)**

Colourless oil (171 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 2.95 (s, 3 H), 3.11 (s, 3 H), 7.30–7.31 (d, *J* = 8.0 Hz, 2 H), 7.83–7.84 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.8, 33.8, 37.0, 129.6, 129.7, 130.5, 145.9, 167.1, 191.5. MS: *m/z* calcd: 191.0; found: 192.4 [M + 1]$^+$. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.00; H, 6.84; N, 7.31.

***N,N*-Dimethyl-2-oxo-2-(*o*-tolyl)acetamide (2d)**

Solid-liquid mixtures (164 mg, 86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.65 (s, 3 H), 2.96 (s, 3 H), 3.09 (s, 3 H), 7.25–7.31 (m, 2 H), 7.43–7.46 (t, *J* = 7.5 Hz, 1 H), 7.66–7.68 (d, *J* = 7.5 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.7, 33.9, 36.9, 126.1, 132.5, 132.6, 133.6, 141.4, 167.7, 193.6. MS: *m/z* calcd 191.0; found: 192.5 [M + 1]$^+$. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.20; H, 6.86; N, 7.31.

2-(4-Bromophenyl)-*N,N*-dimethyl-2-oxoacetamide (2e)

Solid-liquid mixtures (206 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.96 (s, 3 H), 3.12 (s, 3 H), 7.65–7.66 (d, *J* = 8.0 Hz, 2 H), 7.81–7.82 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.0, 37.0, 131.0, 131.9, 132.3, 132.6, 166.3, 190.5. MS: *m/z* calcd: 254.9; found: 256.7 [M + 1]$^+$. Anal. Calcd for $C_{10}H_{10}BrNO_2$: C, 46.90; H, 3.94; N, 5.47. Found: C, 47.00; H, 3.93; N, 5.48.

2-(4-Chlorophenyl)-*N,N*-dimethyl-2-oxoacetamide (2f)

Solid-liquid mixtures (168 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.97 (s, 3 H), 3.12 (s, 3 H), 7.48–7.50 (d, *J* = 8.5 Hz, 2 H), 7.89–7.90 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.0, 37.0, 129.3, 130.9, 132.5, 141.2, 166.4, 190.2. MS: *m/z* calcd: 211.0; found: 212.3 [M + 1]$^+$. Anal. Calcd for $C_{10}H_{10}ClNO_2$: C, 56.75; H, 4.76; N, 6.62. Found: C, 56.82; H, 4.75; N, 6.61.

***N,N*-Dimethyl-2-(4-nitrophenyl)-2-oxoacetamide (2g)**

Light yellow solid-liquid mixtures (175 mg, 79%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.01 (s, 3 H), 3.15 (s, 3 H), 8.14–8.16 (m, 2 H), 8.34–8.36 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.2, 37.0, 124.0, 130.7, 137.4, 151.0, 165.5, 189.2. MS: *m/z* calcd: 222.0; found: 223.4 [M + 1]$^+$. Anal. Calcd for $C_{10}H_{10}N_2O_4$:

C, 54.05; H, 4.54; N, 12.61. Found: C, 54.15; H, 4.55; N, 12.62.

***N,N*-Dimethyl-2-(3-nitrophenyl)-2-oxoacetamide (2h)**

Light yellow solid-liquid mixtures (168 mg, 76%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.03 (s, 3 H), 3.17 (s, 3 H), 7.73–7.76 (t, *J* = 7.5 Hz, 1 H), 8.30–8.32 (d, *J* = 7.5 Hz, 1 H), 8.49–8.50 (d, *J* = 8.0 Hz, 1 H), 8.78 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.3, 37.0, 124.4, 128.6, 130.2, 134.4, 135.1, 148.4, 165.3, 188.6. MS: *m/z* calcd: 222.0; found: 223.2 $[M + 1]^+$. Anal. Calcd for $C_{10}H_{10}N_2O_4$: C, 54.05; H, 4.54; N, 12.61. Found: C, 53.93; H, 4.53; N, 12.62.

***N,N*-Dimethyl-2-(naphthalen-1-yl)-2-oxoacetamide (2i)**

Solid-liquid mixtures (183 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.00 (s, 3 H), 3.18 (s, 3 H), 7.56–7.59 (m, 1 H), 7.63–7.66 (m, 1 H), 7.88–7.90 (d, *J* = 8.5 Hz, 1 H), 7.93–7.98 (m, 2 H), 8.02–8.04 (m, 1 H), 8.43 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.0, 37.1, 123.5, 127.0, 127.8, 129.0, 129.3, 129.8, 130.3, 132.3, 132.9, 136.2, 167.1, 191.8. MS: *m/z* calcd: 227.0; found: 228.3 $[M + 1]^+$. Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.89; H, 5.78; N, 6.15.

***N,N*-Dimethyl-2-oxo-2-(thiophen-2-yl)acetamide (2j)**

Light yellow oil (139 mg, 76%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.04 (s, 3 H), 3.10 (s, 3 H), 7.18–7.19 (t, *J* = 4.5 Hz, 1 H), 7.79–7.82 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.3, 37.2, 128.5, 136.1, 136.4, 140.2, 165.7, 183.4. MS: *m/z* calcd: 183.0; found: 184.5 $[M + 1]^+$. Anal. Calcd for $C_8H_9NO_2S$: C, 52.44; H, 4.95; N, 7.64. Found: C, 52.33; H, 4.94; N, 7.65.

2-(Furan-2-yl)-*N,N*-dimethyl-2-oxoacetamide (2k)

Light yellow oil (120 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.04 (s, 3 H), 3.09 (s, 3 H), 6.61 (s, 1 H), 7.38 (s, 1 H), 7.72 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.5, 37.2, 112.8, 122.4, 148.7, 150.1, 165.3, 178.4. MS: *m/z* calcd: 167.0; found: 168.2 $[M + 1]^+$. Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.59; H, 5.42; N, 8.37.

***N,N*-Diethyl-2-oxo-2-phenylacetamide (2m)**

Yellow solid-liquid mixtures (63 mg, 31%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.14–1.17 (m, 3 H), 1.28–1.30 (m, 3 H), 3.22–3.26 (m, 2 H), 3.54–3.59 (m, 2 H),7.49–7.52 (m, 2 H), 7.62–7.65 (m, 1 H), 7.93–7.95 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.8, 14.0, 38.7, 42.0, 128.9, 129.5, 133.1, 134.5, 166.6, 191.5. MS: *m/z* calcd: 205.1; found: 206.4 $[M + 1]^+$. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.31; H, 7.36; N, 6.83.