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Microwave-assisted direct oxidative synthesis of α-ketoamides from aryl methyl ketones and amines by a water soluble Cu(I)-complex

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A stable and isolable [bis[(tetrabutylammonium) di-μ-iodo-diiododicuprate(I)] complex has been identified for the direct oxidative synthesis of α-ketoamides from substituted aryl methyl ketones and secondary amines in the presence of molecular oxygen. Gratifyingly, this Cu(I) complex acts as an effective catalytic system with enhanced solubility in both water and organic solvents. These reactions were effectively accelerated by microwave irradiation in water and were applied for the synthesis of a variety of substituted α-ketoamides with good yields. It was interesting to note that, in these optimized microwave reaction times, α-ketoamides were the exclusive products and amide byproducts observed in previous reports were not formed.

This article is dedicated to Dr Ahmed Kamal on the occasion of his 60th birthday.

Introduction

α-Ketoamides occur in a wide range of biologically active molecules such as FK506 (tacrolimus),[1] varespladib,[2] didemnidines A and B,[3] leptoclinidamines A–C,[4] Boceprevir,[5] telaprevir,[6] rapamycin (sirolimus),[7] and cyclotheonamide.[8] Besides their significant biological and pharmacological profile, they also serve as versatile synthetic intermediates and precursors for a variety of transformations in organic synthesis.[9,10] Their vista also expands into the synthesis of 2-oxazolidin-4-ones,[11] *cis*- and *trans*-isomers of β-lactam,[12] chiral α-hydroxyamides,[13] 2-oxindoles,[14] etc. Consequently, several synthetic methodologies have been developed to access α-ketoamides, each enabling greater scope in terms of coupling partners and milder reaction conditions.[15] Despite the utility of such processes, there is still a great demand for the development of milder, environment friendly and efficient methodologies to access these biologically important scaffolds.

The activation and utilization of molecular oxygen as an oxygen source as well as oxidant in synthetic organic chemistry, has attracted great interest in academia and industrial scenarios owing to its low cost, and environmentally benign features. The recently developed aerobic oxidative reactions employing molecular oxygen, offer particularly appealing approaches to α-ketoamides. Representative examples of such transformations include the oxidative amidation-diketonization of terminal alkynes,[16] coupling of aryl acetaldehydes and aryl methyl ketones with amines,[17] direct oxidation of arylacetamides,[18] oxidative amidation of 2,2-dibromo-1-aryl and hetero aryl ethanones,[19] oxidative cleavage of α-arylamino amides,[20] aerobic oxidative cross-dehydrogenative coupling (CDC) of amines with α-carbonyl aldehydes,[21] aerobic oxidative coupling of aryl methyl ketones with formamides,[22] and C=C bond activation of enaminones.[23] As ketones are extremely versatile building blocks and have been widely used in organic synthesis, numerous strategies for the direct oxidative transformation of ketones with molecular oxygen have been investigated.[24]

Eventhough, Cu(I) catalyzed synthesis of α-Ketoamides in neat conditions was reported previously,[17a] it cannot be applied to solid substrates such as tetrahydro-β-carbolines. Moreover, despite the predominant utility of Cu(I) halides in organic reactions, their poor solubility in water and most organic solvents can cause issues with catalyst activity, reliability and reproducibility. Recently, there have been increased efforts to minimize the use of organic solvents and to develop new protocols using water as a reaction medium.[25] In this regard, we have identified a stable and isolable Cu(I) complex i.e., [bis[(tetrabutylammonium) di-μ-iodo-diiododicuprate(I)],[26] with enhanced solubility in water and organic solvents to overcome these drawbacks. As shown in **Figure 1**, this Cu(I) complex (**B**) is comparatively more water soluble than copper iodide (**A**). This catalyst is a stable crystalline solid in which the $[Cu_2I_4]^{2-}$ anion is a centrosymmetric dimer containing three-coordinated Cu(I). Recently, the utility of this Cu(I) double salt has been explored

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as a superior catalyst for C–N and C–O couplings compared to traditional copper salts.[27]

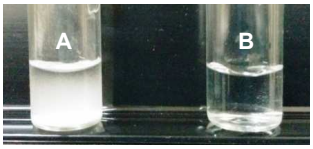


FIGURE 1. Solubility of equimolar concentrations of CuI (**A**) and bis[(tetrabutylammonium) di-μ-iodo-diiododicuprate(I) complex (**B**) in H_2O.

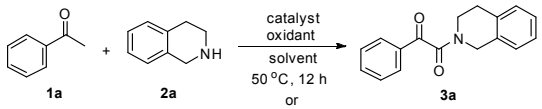
Microwave-assisted (MWA) approaches have been applied in a variety of synthetic transformations, owing to their time as well as energy-saving aspects in comparison to thermal reactions and also due to the avoidance of decomposition of reactants and products. In continuation of our earlier efforts in the field of biologically relevant β-carbolines and their novel strategies,[28] we have attempted to develop a green protocol for their synthesis. Herein, we report a novel and efficient microwave assisted Cu(I)-catalyzed direct oxidative synthesis of α-ketoamides in the presence of molecular oxygen from readily available substituted aryl methyl ketones and secondary amines. To the best of our knowledge, this is the first report on the synthesis of the β-carboline based 1-phenyl-2-(1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl)ethane-1,2-diones.

Results and Discussion

Initially, the bis[(tetrabutylammonium) di-μ-iodo-diiododicuprate(I) complex is prepared from CuI (Copper iodide) and TBAI (n-tetrabutylammonium iodide) in THF followed by crystallization.[27] Next, acetophenone (**1a**) and 1,2,3,4-tetrahydroisoquinoline (**2a**) were chosen as model substrates to examine the catalytic activity of the synthesized complex at 50 °C for 12 h in water (**Table 1**). Among the oxidants, molecular oxygen was found to be the most effective oxidant when compared to oxone, $K_2S_2O_8$, IBX, TBHP, NBS and NIS (all at 3 mmol) to afford the desired product **3a** (78% yield, entry 8, Table 1). Then, a range of solvents were screened which indicated that water was the best choice. However, **3a** was obtained in 71% yield even under solvent free conditions (entry 13, Table 1). Interestingly, when the individual components of the dimeric salt i.e., CuI and TBAI were tested under molecular oxygen in water, **3a** was produced in only 33% and 59% (entry 14 and 15, Table 1) respectively. The yield was only 70% when the catalyst loading was reduced to 10 mol%, even after 20 h (entry 16, Table 1). Notably, a 61% yield could also be obtained even under an air atmosphere (entry 17, Table 1). No desired product was observed in the absence of molecular oxygen or catalyst (entries 18 and 19, Table 1). Incidentally, when the reaction was carried out at room temperature for 18 h, **3a** was isolated in only 66% yield (entry 20, Table 1).

In order to rapidly access α-ketoamides, we explored microwave technology for the acceleration of the reaction of acetophenone (**1a**) with 1,2,3,4-tetrahydroisoquinoline (**2a**) at the optimized reaction conditions obtained in conventional heating (entry 8, Table 1). By using bis[(tetrabutylammonium) di-μ-iodo-diiododicuprate(I) complex in water, in a microwave vial purged with oxygen at 60 °C, a conversion of 83% was observed after only 10 min, (see SI). Compared to thermal reactions (50 °C), microwave irradiation (60 °C) gave better yield of **3a** (78% and 83% respectively) and significantly reduced the reaction times from 12 h to 10 min. Thus, the microwave conditions were employed subsequently for all further reactions.

TABLE 1. Screening of the direct oxidative coupling reaction conditions[a]



entry	catalyst	oxidant	solvent	yield (%)[b]
1	$(nBu_4N^+)_2(Cu_2I_4)^=$	oxone	water	<5
2	$(nBu_4N^+)_2(Cu_2I_4)^=$	$K_2S_2O_8$	water	<5
3	$(nBu_4N^+)_2(Cu_2I_4)^=$	IBX	water	10
4	$(nBu_4N^+)_2(Cu_2I_4)^=$	TBHP	water	18
5	$(nBu_4N^+)_2(Cu_2I_4)^=$	H_2O_2	water	15
6	$(nBu_4N^+)_2(Cu_2I_4)^=$	NBS	water	29
7	$(nBu_4N^+)_2(Cu_2I_4)^=$	NIS	water	32
8	**$(nBu_4N^+)_2(Cu_2I_4)^=$**	**O_2**	**water**	**78, 83[c]**
9	$(nBu_4N^+)_2(Cu_2I_4)^=$	O_2	isopropanol	46
10	$(nBu_4N^+)_2(Cu_2I_4)^=$	O_2	CH_3CN	16
11	$(nBu_4N^+)_2(Cu_2I_4)^=$	O_2	toluene	43
12	$(nBu_4N^+)_2(Cu_2I_4)^=$	O_2	THF	65
13	$(nBu_4N^+)_2(Cu_2I_4)^=$	O_2	neat	71
14	CuI	O_2	water	33
15	TBAI	O_2	water	59
16	$(nBu_4N^+)_2(Cu_2I_4)^=$	O_2	water	70[d]
17	$(nBu_4N^+)_2(Cu_2I_4)^=$	O_2	water	61[e]
18	$(nBu_4N^+)_2(Cu_2I_4)^=$	N_2	water	0
19	-	O_2	water	0
20	$(nBu_4N^+)_2(Cu_2I_4)^=$	O_2	water	66[f]

[a]Reaction conditions: **1a** (1 mmol), **2a** (2 mmol), catalyst (20 mol%), oxidant (3 mmol) solvent (2 mL), 50 °C, 12 h. [b]Isolated yields. [c]Reaction carried out in a microwave vial purged with oxygen, 60 °C, 10 min. [d]Catalyst (10 mol%), 20 h. [e]Under air. [f]At room temperature for 18 h.

Under these optimized reaction conditions, the scope and limitations of substituted aryl methyl ketones and secondary amines in the direct oxidative coupling reactions were investigated and the results were summarized in **Table 2**. Substituents at different positions of the arene group in the ketones and their electronic nature did not affect the efficiency of the reaction; both electron-donating and electron with-drawing groups could afford the corresponding products in good yields (**3a–3ac**). Acetophenone (**1a**) reacted remarkably well with piperidine **(2b)**, morpholine **(2c)**, 1-boc-piperazine **(2d)**, pyrrolidine **(2e)**, bis(2-methoxyethyl)amine **(2f)**, dimethylamine **(2g)**, 7-bromo-1,2,3,4-tetrahydroisoquinoline **(2h)** and 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole **(2i)** to form the corresponding α-

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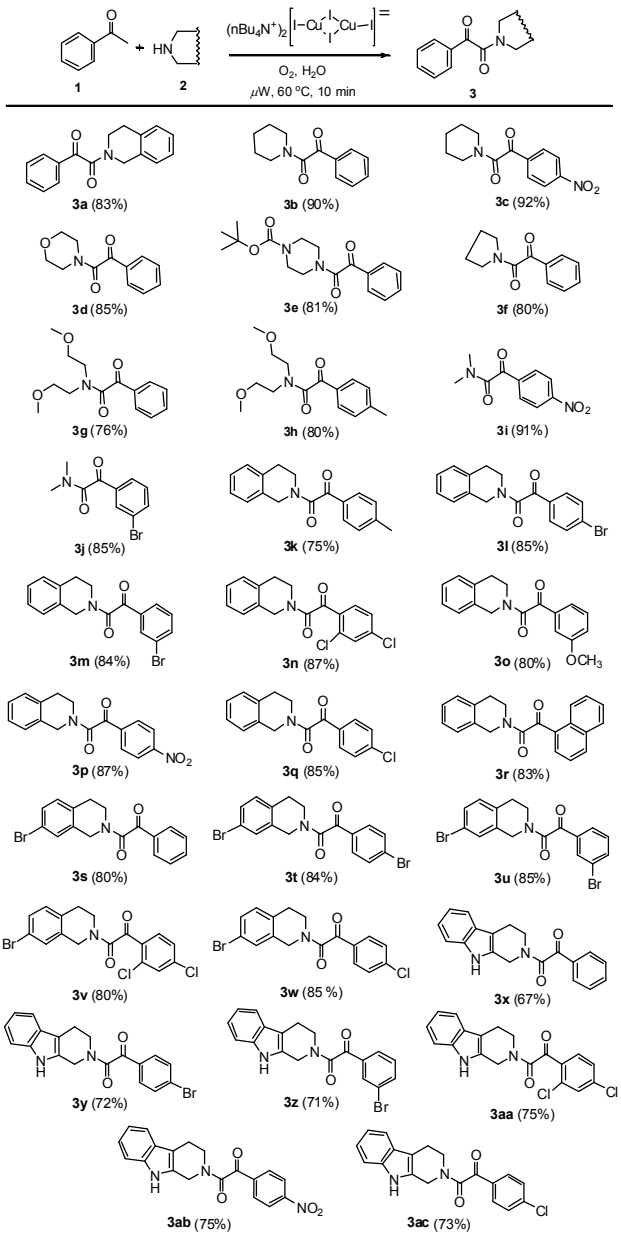
ketoamides. Similarly, the reaction of **2a** with 1-acetyl naphthalene proceeded efficiently to give product **3r** in 83% yield, which showed that steric hindrance had no impact on the outcome of the reaction. An alkyl-substituted aryl methyl ketone such as 4-methyl acetophenone could be transformed into the desired products **3h** and **3k** in 80% and 75% yields respectively.

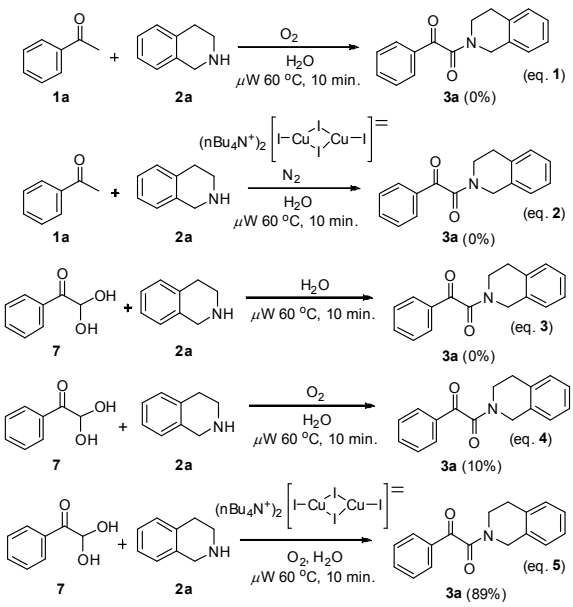
TABLE 2. Copper(I) catalyzed direct oxidative synthesis of α-ketoamides from aryl methyl ketones and secondary amines[a,b]



[a]Reaction conditions: **1a** (1 mmol), **2a** (2 mmol), catalyst (20 mol%) and water (2 mL) in a microwave vial purged with oxygen, [b]Isolated yields.

4-Chloroacetophenone, 4-bromoacetophenone, 3-bromoacetophenone and 2,4-dichloroacetophenone reacted well with **2a, 2h** and **2i** to form the corresponding α-ketoamides in good yields. Acetophenone derivatives that contain electron-withdrawing groups, such as a nitro group at the *para*-position, reacted satisfactorily with **2a**, **2b, 2g** and **2i** to provide the corresponding products **3c, 3i, 3p** and **3ab** in 92%, 91%, 87%, and 75% yields respectively.

With respect to amines, 1,2,3,4-tetrahydroisoquinolines (**2a)**, piperidine **(2b)**, morpholine **(2c)**, 1-boc-piperazine **(2d)**, pyrrolidine **(2e)**, bis(2-methoxyethyl)amine **(2f)**, dimethylamine **(2g)**, 7-substituted-1,2,3,4-tetrahydroisoquinolines (**2h)** and 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indoles (**2i)**, were all suitable substrates, and gave the corresponding α-ketoamides in moderate to good yields. However, no desired products were obtained from anilines, benzylamines or tertiary amines in the present reaction conditions, which indicated that the reaction might proceed via a pathway involving enamine intermediate **4** from ketone and secondary amine (**Scheme 2**). Moreover, when alkyl methyl ketones such as butanone, 2-pentanone and benzylacetone were used as substrates, no desired products were detected. It was interesting to note that, under these optimized microwave reaction conditions α-ketoamides were the exclusive products and devoid of any amide byproducts when compared with previous reports.[17a,18b]



Scheme 1. Control experiments.

To investigate the reaction mechanism, several control experiments were performed between **1a** and **2a** and the results were shown in **Scheme 1**. α-Ketoamide **3a** was not obtained when the copper catalyst was not used (Scheme 1, eq. 1) and the reaction was carried out under nitrogen atmosphere (Scheme 1, eq. 2). The reaction of the intermediate, phenylglyoxal monohydrate (**7**) with 1,2,3,4-

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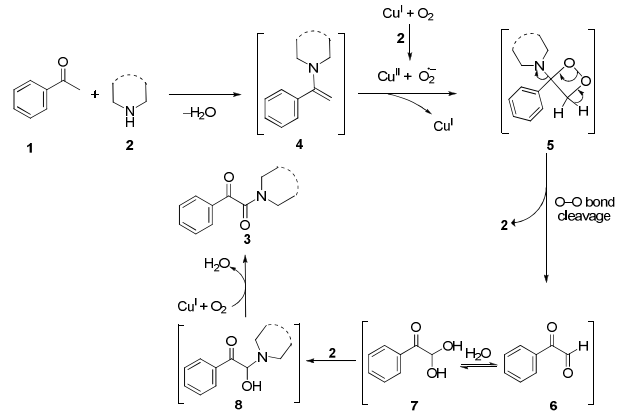
tetrahydroisoquinoline (**2a**) was also studied under different conditions. **3a** was not detected in the absence of Cu(I) catalyst and O_2 (Scheme 1, eq. 3) whereas, only 10% of **3a** was obtained when the reaction was conducted in the presence of O_2 (Scheme 1, eq. 4). Furthermore, **3a** was isolated in an enhanced yield of 89% when the reaction was performed in the presence of Cu(I) catalyst and with molecular oxygen (Scheme 1, eq. 5). The results clearly show that copper/oxygen system is responsible for the sp^3 C–H oxidation, oxidative amidation and hemiaminal oxidation. When 1 mmol of 2,2,6,6-tetramethyl piperidine-N-oxyl (TEMPO, a radical scavenger) was added to the reaction system, **3a** was not detected, which revealed that the reaction might involve a radical pathway.

Based on the above observations and supported by previous reports that the two oxygen atoms of α-ketoamide arise from O_2,[17a] we proposed the possible reaction pathway shown in **Scheme 2**. Initially, superoxide radical ($O_2^{\bullet-}$) is generated from O_2 during the oxidation of $(nBu_4N^+)_2(Cu_2I_4)^=$ to Cu(II) in the presence of amine **2**. Subsequently, Cu(II) and superoxide radical interacted with enamine **4** to produce aminodioxetane **5**, whose ring opening led to α-oxoaldehyde **6**. Finally, **6** is converted into hemiaminal **8** in the presence of the amine, which was readily oxidized by O_2 and the copper catalyst to produce α-ketoamide **3**.



Scheme 2. Possible reaction pathway.

The potential catalytic reusability was studied by performing the *in situ* recycling experiments for the synthesis of **3a** using 20 mol% catalyst. After each cycle, the aqueous reaction mixture was extracted by using ethyl acetate to quantitatively recover the products. For the next cycle, the resulting aqueous solution containing the catalyst was recharged with the same substrates in the same microwave vial. The catalytic solution could be reused for three cycles without any appreciable loss of reactivity, and by the fifth cycle, the yield of **3a** had dropped to 75% as shown in **Figure 2**.

Further, to explore the synthetic utility of the α-ketoamides, one of the representative derivatives **10** was synthesized by performing Pictet-Spengler reaction with α-ketoamide (**3p**) and tryptamine (**9**) by employing trimethylsilyl triflate as the catalyst. The reaction involves the condensation of **9** with **3p** in refluxing toluene with a Dean-Stark trap for 24 h followed by the addition of TMSOTf and continuous stirring at room temperature for another 48 h. However, the reaction was extremely sluggish and gave the derivative **10** in very low yield (25%, **Scheme 3**).

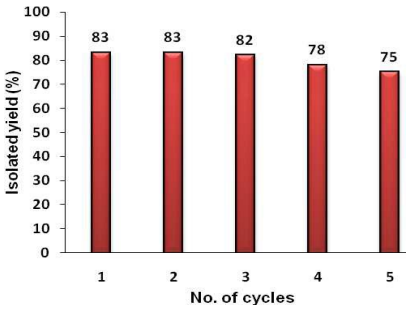
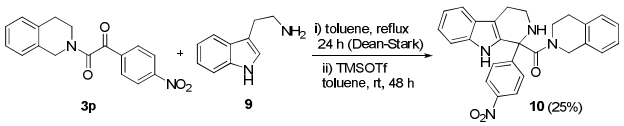


FIGURE 2. Recyclability chart of bis[(tetrabutylammonium) di-μ-iodo-diiododicuprate(I) complex in H_2O for the synthesis of compound **3a**.



Scheme 3. Pictet-Spengler reaction of **3p** with tryptamine (**9**).

Experimental

General methods.

All solvents were purified and dried using standard methods prior to use. Commercially available reagents were used without further purification. ^{1}H NMR spectra were recorded on an NMR instrument operated at 500 MHz. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: δ=7.26 ppm). ^{13}C NMR spectra were recorded on an NMR instrument operated at 125 MHz with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: δ=77.16 ppm). The following abbreviations were used for 1H NMR spectra to indicate the signal multiplicity: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). MS and HRMS were measured in EI or ESI mode and the mass analyzer of the HRMS was TOF. Thin layer chromatography was performed on pre-coated glass back plates and visualized with UV light at 254 nm.

Microwave Irradiation Experiments.

Microwave irradiation experiments were performed in a Monowave 300 single-mode microwave reactor from Anton Paar GmbH (Graz, Austria). The reaction temperature is monitored by an external infrared (IR) sensor housed in the side-walls of the microwave cavity measuring the surface temperature of the reaction vessel. Reaction times refer to the hold time at the desired set temperature and not to the total

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irradiation time. Pressure sensing is achieved by a hydraulic sensor integrated in the swiveling cover of the instrument. The reusable 10 mL G10 Pyrex vial is sealed with PEEK snap caps and standard PTFE coated silicone septa. Reaction cooling is performed by compressed air automatically after the heating period has elapsed. The required force of 6-8 bar is also used to pneumatically seal the vials tightly at the beginning to withstand 30 bar and to ensure smooth release of potentially remaining pressure before the cover is opened.

Bis[(tetrabutylammonium) di-μ-iodo-diiododicuprate(I) complex $(nBu_4N^+)_2(Cu_2I_4)^=$

A 3-neck round bottomed flask equipped with mechanical stirrer was charged with CuI (209.48 g, 1.10 mol), TBAI (410.01 g, 1.11 mol) and peroxide free anhydrous THF (500 mL) under nitrogen atmosphere. The mixture was warmed at 50 °C until a homogenous pale yellow solution was obtained. The mixture was cooled to room temperature and then to 6 °C over 60 min. Subsequently, degassed *t*BuOMe (750 mL) was added slowly and the mixture was stirred for 1h at 6 °C. The crystalline solid was filtered off and washed with *t*BuOMe (450 mL) 5 times. The solid was dried under a stream of nitrogen to provide $(nBu_4N^+)_2(Cu_2I_4)^=$ as an off white crystalline solid (600 g); mp 91–92 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=3.33–3.30 (m, 16H), 1.72–1.66 (m, 16H), 1.49 (apparent hextet, *J*=7.4, 16H), 1.01 (t, *J*=7.3, 24H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=59.22, 24.31, 19.82, 13.76.

General procedure for the preparation of compounds 3a–3ac. Aryl methyl ketones **1** (1 mmol), secondary amines **2** (2 mmol), catalyst (20 mol%) and water (2 mL) were added to a monowave vial G10 (10 mL) containing a Teflon coated stir bar. After the vial was sealed, the reaction mixture was purged with oxygen for 2 min. The vessel was subsequently placed in the microwave cavity and irradiated for 10 min at 60 °C (hold time). After cooling to room temperature, it was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic phase was washed with water (2 × 10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue after evaporation was purified by silica-gel column chromatography by using a mixture of petroleum ether and ethyl acetate as eluent solvent.

1-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2-phenylethane-1,2-dione (3a).[29] Yellow solid (219 mg, 83%); mp 106–107 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.94–7.99 (m, 2H), 7.61–7.66 (m, 1H), 7.48–7.53 (m, 2H), 6.92–7.25 (m, 4H), 4.54 and 4.91 (2s, 2H), 3.61 and 3.99 (2t, 3*J*H–H = 5.7 and 3*J*H–H = 5.9 Hz, 2H), 2.86 and 3.00 (2t, 3*J*H–H = 5.9 and 3*J*H–H = 6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=191.4, 191.3, 166.0, 165.7, 134.8, 134.7, 134.1, 133.3, 133.0, 132.9, 131.7, 131.4, 129.6, 129.0, 128.9, 128.9, 128.7, 127.1, 126.8, 126.7, 126.6, 126.5, 126.0, 47.2, 43.4, 43.3, 39.3, 29.1, 28.2; HRMS (ESI-TOF) *m/z* Calcd for $C_{17}H_{15}NO_2$ $[M+H]^+$ 266.1181, found 266.1179.

1-Phenyl-2-(piperidin-1-yl)ethane-1,2-dione (3b).[17a] Yellow solid (195 mg, 90%); mp 104–105 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.94 (d, *J* = 7.93 Hz, 2H), 7.63 (t, *J* = 7.32 Hz, 1H), 7.50 (t, *J* = 7.47 Hz, 2H), 3.70 (Brs, 2H), 3.28 (t, *J* = 5.49 Hz, 2H), 1.69 (Brs, 4H), 1.54 (Brs, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=191.9, 165.4, 134.6, 133.2, 129.5, 128.9, 47.0, 42.1, 26.1, 25.4. 24.3; HRMS (ESI-TOF) *m/z* Calcd for $C_{13}H_{15}NO_2$ $[M+H]^+$ 218.1181, found 218.1179.

1-(4-Nitrophenyl)-2-(piperidin-1-yl)ethane-1,2-dione (3c).[17a] Yellow solid (241 mg, 92%); mp 96–97 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.33 (d, *J* = 8.69 Hz, 2H), 8.13 (d, *J* = 8.69 Hz, 2H), 3.71 (Brs, 2H), 3.30 (t, *J* = 5.64 Hz, 2H), 1.71 (Brs, 4H), 1.57 (Brs, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=189.4, 164.0, 151.0, 137.6, 130.6, 124.0, 47.0, 42.4, 26.2, 25.4, 24.2; HRMS (ESI-TOF) *m/z* Calcd for $C_{13}H_{14}N_2O4$ $[M+H]^+$ 263.1032, found 263.1035.

1-Morpholino-2-phenylethane-1,2-dione (3d).[17a] Yellow oil (186 mg, 85%); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.96 (d, *J* = 7.62 Hz, 2H), 7.65 (t, *J* = 7.32 Hz, 1H), 7.51 (t, *J* = 7.47 Hz, 2H), 3.78 (Brs, 4H), 3.64 (t, *J* = 4.57 Hz, 2H), 3.37 (t, *J* = 4.73 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=191.0, 165.3, 134.9, 132.9, 129.6, 129.0, 66.7, 66.6, 46.2, 41.5; HRMS (ESI-TOF) *m/z* Calcd for $C_{12}H_{13}NO_3$ $[M+H]^+$ 220.0974, found 220.0973.

***tert*-Butyl 4-(2-oxo-2-phenylacetyl)piperazine-1-carboxylate (3e).**[17c] Pale yellow solid (257 mg, 81%); mp 121–122 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.95 (d, *J* = 7.62 Hz, 2H), 7.65 (t, *J* = 7.32 Hz, 1H), 7.51 (t, *J* = 7.62 Hz, 2H), 3.74 (t, *J* = 4.57 Hz, 2H), 3.54 (t, *J* = 5.18 Hz, 2H), 3.42 (t, *J* = 4.27 Hz, 2H), 3.32 (t, *J* = 5.18 Hz, 2H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=191.1, 165.5, 154.3, 134.9, 132.9, 129.6, 129.0, 80.5, 45.7, 41.1, 28.2; HRMS (ESI-TOF) *m/z* Calcd for $C_{17}H_{22}N_2O_4$ $[M+H]^+$ 319.1658, found 319.1659.

1-Phenyl-2-(pyrrolidin-1-yl)ethane-1,2-dione (3f).[17c] Yellow oil (162 mg, 80%); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.90 (d, *J* = 7.01 Hz, 2H), 7.55 (t, *J* = 7.47 Hz, 1H), 7.42 (t, *J* = 7.17 Hz, 2H), 3.57 (Brs, 2H), 3.33 (Brs, 2H), 1.86 (Brs, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=191.3, 164.7, 134.4, 132.6, 129.6, 128.7, 46.4, 45.0, 25.6, 23.7; HRMS (ESI-TOF) *m/z* Calcd for $C_{12}H_{13}NO_2$ $[M+H]^+$ 204.1025, found 204.1022.

***N,N*-Bis(2-methoxyethyl)-2-oxo-2-phenylacetamide (3g).**[17c] Yellow oil (201 mg, 76%); ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.97–7.95 (m, 2H), 7.62–7.59 (m, 1H), 7.50–7.46 (m, 2H), 3.78 (t, *J* = 5.34 Hz, 2H), 3.67 (t, *J* = 5.49 Hz, 2H), 3.54 (t, *J* = 5.49 Hz, 2H), 3.45 (t, *J* = 5.34 Hz, 2H), 3.40 (s, 3H), 3.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=190.9, 167.6, 134.2, 133.4, 129.8, 128.6, 128.5, 128.2, 70.5, 70.4, 58.8, 58.5, 48.2, 45.2; HRMS (ESI-TOF) *m/z* Calcd for $C_{14}H_{19}NO_4$ $[M+H]^+$ 266.1392, found 266.1392.

***N,N*-Bis(2-methoxyethyl)-2-oxo-2-p-tolylacetamide (3h).** Yellow oil (223 mg, 80%); ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.02 (d, *J* = 8.24 Hz, 2H), 7.46 (d, *J* = 8.08 Hz, 2H), 3.96 (t, *J* = 5.34 Hz, 2H), 3.85 (t, *J* = 5.34 Hz, 2H), 3.70 (t, *J* = 5.49 Hz, 2H), 3.63 (t, *J* = 5.18 Hz, 2H), 3.58 (s, 3H), 3.34 (s, 3H), 2.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=190.7, 167.8, 145.4, 130.9, 129.9, 129.3, 70.6, 70.3, 58.8, 58.5, 48.1, 45.1, 21.8; HRMS (ESI-TOF) *m/z* Calcd for $C_{15}H_{21}NO_4$ $[M+H]^+$ 280.1549, found 280.1549.

***N,N*-Dimethyl-2-(4-nitrophenyl)-2-oxoacetamide (3i).**[15c] Pale yellow solid (202 mg, 91%); mp 135–136 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.32 (d, *J* = 8.85 Hz, 2H), 8.12 (d, *J* = 8.85 Hz, 2H), 3.14 (s, 3H), 2.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=189.1,

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165.5, 151.0, 137.5, 130.7, 124.0, 37.0, 34.2; HRMS (ESI-TOF) *m/z* Calcd for $C_{10}H_{10}N_2O_4$ $[M+H]^+$ 223.0719, found 223.0721.

***N,N*-Dimethyl-2-(3-bromophenyl)-2-oxoacetamide (3j).**[15c] Yellow solid (215 mg, 85%); mp 126–127 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.03 (s, 1H), 7.83 (d, *J* = 7.78 Hz, 1H), 7.71 (d, *J* = 7.93 Hz, 1H), 7.36–7.32 (m, 1H), 3.07 (s, 3H), 2.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=189.8, 166.0, 137.3, 132.0, 130.4, 129.8, 128.2, 123.0, 36.8, 33.9; HRMS (ESI-TOF) *m/z* Calcd for $C_{10}H_{10}BrNO_2$ $[M+H]^+$ 255.9973, found 255.9976.

1-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2-(p-tolyl)ethane-1,2-dione (3k).[28] Yellow solid (209 mg, 75%); mp 116–117 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.83–7.88 (m, 2H), 7.27–7.32 (m, 2H), 6.92–7.24 (m, 4H), 4.53 and 4.90 (2s, 2H), 3.60 and 3.98 (2t, 3*J*H–H = 5.9 and 3*J*H–H = 6.1 Hz, 2H), 2.85 and 3.00 (2t, 3*J*H–H=5.7 and 3*J*H–H = 6.1 Hz, 2H), 2.41 and 2.44 (2s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=191.2, 191.0, 166.2, 165.9, 146.1, 146.0, 134.1, 133.4, 131.8, 131.5, 130.6, 130.6, 129.8, 129.7, 129.7, 128.9, 128.7, 127.1, 126.8, 126.7, 126.6, 126.5, 126.0, 47.3, 43.4, 43.3, 39.2, 29.2, 28.2, 21.8, 21.8; HRMS (ESI-TOF) *m/z* Calcd for $C_{18}H_{17}NO_2$ $[M+H]^+$ 280.1337, found 280.1336.

1-(4-Bromophenyl)-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)ethane-1,2-dione (3l). White solid (291 mg, 85%); mp 130–131 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.80–7.85 (m, 2H), 7.63–7.67 (m, 2H), 6.94–7.25 (m, 4H), 4.53 and 4.89 (2s, 2H), 3.61 and 3.98 (2t, 3*J*H–H = 5.7 and 3*J*H–H = 5.9 Hz, 2H), 2.87 and 3.00 (2t, 3*J*H–H=5.6 and 3*J*H–H = 5.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=190.2, 190.1, 165.4, 165.1, 134.0, 133.2, 132.4, 132.3, 131.8, 131.8, 131.6, 131.3, 131.0, 130.3, 130.3, 128.9, 128.7, 127.2, 126.9, 126.8, 126.6, 126.0, 47.3, 43.5, 43.5, 39.4, 29.2, 28.1; HRMS (ESI-TOF) *m/z* Calcd for $C_{17}H_{14}BrNO_2$ $[M+H]^+$ 344.0286, found 344.0282.

1-(3-Bromophenyl)-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)ethane-1,2-dione (3m). White solid (288 mg, 84%); mp 115–116 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.11–8.13 (m, 1H), 7.85–7.91 (m, 1H), 7.74–7.78 (m, 1H), 7.34–7.41 (m, 1H), 6.95–7.24 (m, 4H), 4.53 and 4.90 (2s, 2H), 3.61 and 3.99 (2t, 3*J*H–H = 5.7 and 3*J*H–H = 6.1 Hz, 2H), 2.88 and 3.01 (2t, 3*J*H–H = 5.7 and 3*J*H–H = 6.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=189.8, 189.6, 165.2, 164. 9, 137.6, 137.5, 134.8, 134.7, 134.0, 133.3, 132.3, 132.3, 131.6, 131.3, 130.5, 130.5, 128.9, 128.7, 128.4, 127.2, 126.9, 126.8, 126.6, 126.0, 123.3, 123.2, 47.3, 43.5, 39.5, 29.2, 28.1; HRMS (ESI-TOF) *m/z* Calcd for $C_{17}H_{14}BrNO_2$ $[M+H]^+$ 344.0286, found 344.0285.

1-(2,4-Dichlorophenyl)-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)ethane-1,2-dione (3n). Pale yellow solid (289 mg, 87%); mp 124–125 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.82–7.87 (m, 1H), 7.37–7.47 (m, 2H), 7.03–7.24 (m, 4H), 4.68 and 4.83 (2s, 2H), 3.73 and 3.93 (2t, 3*J*H–H = 5.9 and 3*J*H–H = 6.1 Hz, 2H), 2.96 and 2.98 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=188.9, 188.6, 165.5, 165.3, 140.3, 140.2, 134.7, 134.5, 134.1, 133.5, 133.2, 133.1, 132.0, 131.7, 131.5, 131.4, 130.6, 130.4, 128.8, 128.6, 127.8, 127.1, 126.8, 126.7, 126.6, 126.0, 47.3, 44.0, 43.5, 39.7, 28.8, 27.7; HRMS (ESI-TOF) *m/z* Calcd for $C_{17}H_{13}Cl_2NO_2$ $[M+H]^+$ 334.0401, found 334.0400.

1-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2-(3-methoxyphenyl)ethane-1,2-dione (3o). Pale yellow solid (236 mg, 80%); mp 103–104 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.47–7.52 (m, 2H), 7.35–7.42 (m, 1H), 6.92–7.24 (m, 5H), 4.52 and 4.90 (2s, 2H), 3.81 and 3.85 (2s, 3H), 3.60 and 3.99 (2t, 3*J*H–H = 5.7 and 3*J*H–H = 6.1 Hz, 2H), 2.86 and 3.00 (2t, 3*J*H–H=5.6 and 3*J*H–H = 5.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=191.3, 191.2, 166.0, 165.7, 160.0, 160.0, 134.3, 134.2, 134.1, 133.3, 131.7, 131.4, 130.0, 128.9, 128.7, 127.1, 126.8, 126.7, 126.6, 126.5, 126.0, 122.9, 122.8, 121.8, 121.7, 112.6, 55.5, 55.4, 47.3, 43.5, 43.4, 39.3, 29.1, 28.2; HRMS (ESI-TOF) *m/z* Calcd for $C_{18}H_{17}NO_3$ $[M+H]^+$ 296.1286, found 296.1283.

1-(3,4-Dihydroisoquinolin- 2(1*H*)-yl)-2-(4-nitrophenyl)ethane-1,2-dione (3p). Yellow solid (269 mg, 87%); mp 179–180 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.30–8.35 (m, 2H), 8.13–8.18 (m, 2H), 6.97–7.24 (m, 4H), 4.56 and 4.92 (2s, 2H), 3.65 and 4.00 (2t, 3*J*H–H=5.9 and 3*J*H–H=6.1 Hz, 2H), 2.90 and 3.02 (2t, 3*J*H–H=5.7 and 3*J*H–H=6.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=188.9, 188.9, 164.6, 164.3, 151.0, 151.0, 137.5, 137.4, 133.9, 133.1, 131.4, 131.1, 130.7, 129.0, 128.7, 127.4, 127.0, 126.9, 126.7, 126.6, 125.9, 124.0, 124.0, 47.3, 43.7, 43.6, 39.7, 29.2, 28.1; HRMS (ESI-TOF) *m/z* Calcd for $C_{17}H_{14}N_2O_4$ $[M+H]^+$ 311.1031, found 311.1033.

1-(4-Chlorophenyl)-2-(3,4-dihydroisoquinolin-2(1*H*)-yl)ethane-1,2-dione (3q). White solid (254 mg, 85%); mp 108–110 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.89–7.94 (m, 2H), 7.45–7.50 (m, 2H), 6.94–7.25 (m, 4H), 4.53 and 4.90 (2s, 2H), 3.61 and 3.98 (2t, 3*J*H–H=5.9 and 3*J*H–H=6.1 Hz, 2H), 2.87 and 3.00 (2t, 3*J*H–H=5.7 and 3*J*H–H=5.9 Hz, 2H)); ^{13}C NMR (125 MHz, $CDCl_3$): δ=190.0, 189.9, 165.5, 165.2, 141.4, 141.4, 134.0, 133.2, 131.6, 131.5, 131.4, 131.0, 129.4, 128.9, 128.7, 127.2, 126.9, 126.8, 126.6, 126.0, 47.3, 43.5, 43.5, 39.4, 29.2, 28.2; HRMS (ESI-TOF) *m/z* Calcd for $C_{17}H_{14}ClNO_2$ $[M+H]^+$ 300.0791, found 300.0788.

1-(3,4-Dihydroisoquinolin-2(1*H*)-yl)-2-(naphthalen-1-yl)ethane-1,2-dione (3r). White solid (261 mg, 83%); mp 131–132 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.30 (t, *J*=8.24, 1H), 8.14–7.91 (m, 3H), 7.72 (t, *J*=7.32, 1H), 7.61 (t, *J*=7.4, 1H), 7.46–7.56 (m, 1H), 6.89–7.24 (m, 4H), 4.61 and 4.95 (2s, 2H), 3.68 and 4.03 (2t, 3*J*H–H=5.7 and 3*J*H–H=6.1 Hz, 2H), 2.87 and 3.04 (2t, 3*J*H–H=5.4 and 3*J*H–H=5.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=193.9, 193.6, 166.6, 166.4, 136.0, 135.9, 134.6, 134.4, 134.2, 134.0, 134.0, 133.4, 131.9, 131.6, 131.0, 130.9, 129.4, 129.3, 128.9, 128.7, 128.7, 128.4, 128.3, 127.2, 127.0, 127.0, 126.8, 126.8, 126.6, 126.5, 126.0, 125.8, 124.5, 124.5, 47.5, 43.6, 43.5, 39.4, 29.1, 28.2; HRMS (ESI-TOF) *m/z* Calcd for $C_{21}H_{17}NO_2$ $[M+H]^+$ 316.1337, found 316.1342.

1-(7-Bromo-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-phenylethane-1,2-dione (3s). White solid (274 mg, 80%); mp 137–138 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.93–7.98 (m, 2H), 7.62–7.67 (m, 1H), 7.48–7.53 (m, 2H), 6.99–7.34 (m, 3H), 4.50 and 4.87 (2s, 2H), 3.59 and 3.97 (2t, 3*J*H–H=5.4 and 3*J*H–H=5.7 Hz, 2H), 2.80 and 2.94 (2t, 3*J*H–H=5.4 and 3*J*H–H=5.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=191.2, 191.1, 165.9, 165.6, 134.9, 133.9, 133.5, 133.0, 132.9, 132.8, 132.3, 130.6, 130.4, 130.3, 129.9, 129.6, 129.4, 129.0, 128.9, 120.3, 120.0, 46.8, 43.2, 42.9, 39.1, 28.7, 27.7; HRMS (ESI-TOF) *m/z* Calcd for $C_{17}H_{14}BrNO_2$ $[M+H]^+$ 344.0286, found 344.0283.

1-(7-Bromo-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-(4-bromophenyl)ethane-1,2-dione (3t). White solid (354 mg,

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84%); mp 164–165 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.80–7.84 (m, 2H), 7.63–7.67 (m, 2H), 6.99–7.34 (m, 3H), 4.49 and 4.85 (2s, 2H), 3.59 and 3.96 (2t, 3*J*H–H=5.7 and 3*J*H–H=6.1 Hz, 2H), 2.81 and 2.93 (2t, 3*J*H–H=5.6 and 3*J*H–H=5.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=189.9, 189.8, 165.4, 165.0, 133.7, 133.4, 132.9, 132.4, 132.2, 131.8, 131.7, 131.0, 130.6, 130.4, 130.4, 130.4, 130.0, 129.4, 128.9, 120.4, 120.1, 46.8, 43.3, 43.0, 39.2, 28.7, 27.7; HRMS (ESI-TOF) *m/z* Calcd for $C_{17}H_{13}Br_2NO_2$ $[M+H]^+$ 421.9391, found 421.9393.

1-(7-Bromo-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-(3-bromophenyl)ethane-1,2-dione (3u). Off-white solid (357 mg, 85%); mp 160–161 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.09–8.12 (m, 1H), 7.86–7.89 (m, 1H), 7.77 (s, 1H), 7.01–7.39 (m, 4H), 4.49 and 4.86 (2s, 2H), 3.59 and 3.96 (2s, 2H), 2.82 and 2.94 (2s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=189.5, 189.4, 165.1, 164.8, 137.7, 134.7, 134.6, 133.7, 133.4, 132.9, 132.4, 132.3, 132.2, 130.6, 130.5, 130.4, 130.4, 130.0, 129.4, 128.9, 128.3, 123.3, 123.3, 120.4, 120.1, 46.8, 43.3, 43.1, 39.3, 28.7, 27.7; HRMS (ESI-TOF) *m/z* Calcd for $C_{17}H_{13}Br_2NO_2$ $[M+H]^+$ 421.9391, found 421.9393.

1-(7-Bromo-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-(2,4-dichlorophenyl)ethane-1,2-dione (3v). White solid (328 mg, 80%); mp 129–130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.81–7.86 (m, 1H), 7.19–7.46 (m, 4H), 7.02–7.06 (m, 1H), 4.64 and 4.79 (2s, 2H), 3.71 and 3.91 (2t, 3*J*H–H=5.7 and 3*J*H–H=6.1 Hz, 2H), 2.91 (t, 3*J*H–H=5.7, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=188.8, 188.5, 165.4, 165.2, 140.4, 140.3, 134.6, 134.4, 133.7, 133.5, 133.2, 133.0, 132.5, 131.9, 131.7, 130.6, 130.5, 130.4, 130.3, 130.2, 130.0, 129.4, 128.9, 127.9, 120.3, 120.1, 46.9, 43.6, 43.2, 39.5, 28.4, 27.2; HRMS (ESI-TOF) *m/z* Calcd for $C_{17}H_{12}BrCl_2NO_2$ $[M+H]^+$ 411.9506, found 411.9503.

1-(7-Bromo-3,4-dihydroisoquinolin-2(1*H*)-yl)-2-(4-chlorophenyl)ethane-1,2-dione (3w). White solid (319 mg, 85%); mp 159–160 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ=7.88–7.92 (m, 2H), 7.46–7.50 (m, 2H), 6.99–7.34 (m, 3H), 4.49 and 4.86 (2s, 2H), 3.59 and 3.96 (2t, 3*J*H–H=5.7 and 3*J*H–H=6.1 Hz, 2H), 2.81 and 2.94 (2t, 3*J*H–H=5.7 and 3*J*H–H=5.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=189.7, 189.6, 165.4, 165.0, 141.5, 133.8, 133.4, 132.9, 132.2, 131.4, 131.3, 131.0, 130.6, 130.4, 130.3, 130.0, 129.4, 128.9, 120.3, 120.1, 46.8, 43.3, 43.0, 39.2, 28.7, 27.7; HRMS (ESI-TOF) *m/z* Calcd for $C_{17}H_{13}BrClNO_2$ $[M+H]^+$ 377.9896, found 377.9895.

1-Phenyl-2-(1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl)ethane-1,2-dione (3x). Red solid (203 mg, 67%); mp 127–128 °C; ^{1}H NMR (500 MHz, , DMSO-d_6): δ=10.62 and 11.00 (2s, 1H), 7.64–7.92 (m, 4H), 7.27–7.43 (m, 3H), 6.98–7.06 (m, 2H), 4.54 and 4.90 (2s, 2H), 3.63 and 4.03 (2t, 3*J*H–H=5.7 and 3*J*H–H=6.1 Hz, 2H), 2.67 and 2.87 (2t, 3*J*H–H=5.4 and 3*J*H–H=5.9 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ=191.6, 191.4, 165.8, 165.3, 135.9, 135.8, 135.1, 132.4, 132.3, 129.4, 129.3, 129.3, 129.1, 129.0, 126.2, 121.0, 120.9, 118.6, 118.5, 117.6, 117.4, 111.0, 111.0, 107.0, 106.0, 79.1, 78.8, 78.5, 43.6, 43.3, 21.2, 20.3; HRMS (ESI-TOF) *m/z* Calcd for $C_{19}H_{16}N_2O_2$ $[M+H]^+$ 305.1290, found 305.1289.

1-(4-Bromophenyl)-2-(1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl)ethane-1,2-dione (3y). White solid (275 mg, 72%); mp 240–241 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=10.61 and 10.97 (2s, 1H), 7.69–7.86 (m, 4H), 7.27–7.43 (m, 2H), 7.03–7.07 (m, 1H), 6.95–6.99 (m, 1H), 4.55 and 4.89 (2s, 2H), 3.63 and 4.02 (2t, 3*J*H–H=4.8 and 3*J*H–H=5.0 Hz, 2H), 2.68 and 2.87 (2t, 3*J*H–H=5.4 and 3*J*H–H=5.9 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ=190.4, 190.2, 165.3, 164.8, 135.8, 135.8, 132.4, 131.7, 131.4, 131.3, 130.9, 130.9, 129.5, 129.2, 128.9, 126.2, 126.1, 121.0, 120.9, 118.5, 118.5, 117.5, 117.4, 111.0, 110.9, 106.9, 105.9, 79.0, 78.8, 78.5, 43.6, 43.3, 21.3, 20.3; HRMS (ESI-TOF) *m/z* Calcd for $C_{19}H_{15}BrN_2O_2$ $[M+H]^+$ 383.0395, found 383.0401.

1-(3-Bromophenyl)-2-(1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl)ethane-1,2-dione (3z). Brick red solid (271 mg, 71%); mp 142–143 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=10.63 and 11.00 (2s, 1H), 7.86–8.06 (m, 3H), 7.53–7.61 (m, 1H), 7.28–7.44 (m, 2H), 7.04–7.08 (m, 1H), 6.96–7.00 (m, 1H), 4.58 and 4.90 (2s, 2H), 3.65 and 4.03 (2t, 3*J*H–H=5.1 and 3*J*H–H=5.4 Hz, 2H), 2.69 and 2.87 (2t, 3*J*H–H=5.4 and 3*J*H–H=5.9 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ=190.0, 189.8, 165.1, 164.6, 137.7, 135.9, 134.4, 134.3, 131.6, 131.1, 131.1, 129.3, 129.1, 128.5, 128.5, 126.2, 126.2, 122.5, 121.1, 120.9, 118.6, 117.6, 117.5, 111.1, 111.0, 106.9, 106.0, 79.0, 43.7, 43.4, 21.3, 20.3; HRMS (ESI-TOF) *m/z* Calcd for $C_{19}H_{15}BrN_2O_2$ $[M+H]^+$ 383.0395, found 383.0397.

1-(2,4-Dichlorophenyl)-2-(1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl)ethane-1,2-dione (3aa). Pale yellow solid (279 mg, 75%); mp 185–186 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=10.74 and 10.97 (2s, 1H), 7.79–7.92 (m, 2H), 7.62–7.67 (m, 1H), 7.31–7.43 (m, 2H), 6.97–7.08 (m, 2H), 4.71 and 4.82 (2s, 2H), 3.76 and 3.97 (2t, 3*J*H–H=4.8 and 3*J*H–H=5.0 Hz, 2H), 2.78 and 2.82 (2t, 3*J*H–H=5.4 and 3*J*H–H=5.9 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ=188.6, 188.5, 165.3, 164.9, 139.3, 139.3, 135.9, 134.1, 133.8, 133.6, 133.3, 131.2, 130.9, 130.6, 130.4, 129.2, 129.1, 128.2, 128.2, 126.2, 126.2, 121.0, 120.9, 118.5, 117.6, 117.5, 111.0, 111.0, 106.8, 106.1, 79.1, 78.8, 78.6, 43.7, 43.5, 21.0, 19.9; HRMS (ESI-TOF) *m/z* Calcd for $C_{19}H_{14}Cl_2N_2O_2$ $[M+H]^+$ 373.0510, found 373.0507.

1-(4-Nitrophenyl)-2-(1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl)ethane-1,2-dione (3ab). Red solid (261 mg, 75%); mp 195–196 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=10.65 and 11.00 (2s, 1H), 8.14–8.43 (m, 4H), 7.28–7.44 (m, 2H), 6.96–7.08 (m, 2H), 4.62 and 4.92 (2s, 2H), 3.69 and 4.05 (2t, 3*J*H–H=4.8 and 3*J*H–H=5.0 Hz, 2H), 2.70 and 2.88 (2t, 3*J*H–H=5.4 and 3*J*H–H=5.9 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ=189.9, 189.6, 164.8, 164.3, 150.9, 150.8, 136.8, 135.9, 131.0, 131.0, 130.7, 129.2, 129.0, 126.2, 126.2, 124.4, 124.3, 123.6, 121.1, 121.0, 118.5, 117.6, 117.5, 111.0, 106.9, 106.0, 79.1, 79.0, 78.8, 78.6, 43.7, 43.4, 21.3, 20.3; HRMS (ESI-TOF) *m/z* Calcd for $C_{19}H_{15}N_3O_4$ $[M+H]^+$ 350.1140, found 350.1142.

1-(4-Chlorophenyl)-2-(1,3,4,9-tetrahydro-2*H*-pyrido[3,4-*b*]indol-2-yl)ethane-1,2-dione (3ac). Red solid (246 mg, 73%); mp 108–109 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ=10.57 and 10.93 (2s, 1H), 7.65–7.82 (m, 4H), 7.23–7.39 (m, 2H), 6.99–7.03 (m, 1H), 6.91–6.95 (m, 1H), 4.51 and 4.85 (2s, 2H), 3.59 and 3.98 (2t, 3*J*H–H=4.8 and 3*J*H–H=5.0 Hz, 2H), 2.64 and 2.83 (2t, 3*J*H–H=5.4 and 3*J*H–H=5.9 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ=190.6, 190.4, 165.4, 165.0, 136.0, 136.0, 132.6, 131.8, 131.6, 131.5, 131.1, 131.0, 129.6, 129.4, 129.1, 126.3,

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126.3, 121.2, 121.0, 118.7, 118.6, 117.7, 117.6, 111.1, 111.1, 107.0, 106.1, 79.2, 78.9, 78.7, 43.8, 43.5, 21.4, 20.5; HRMS (ESI-TOF) *m/z* Calcd for $C_{19}H_{15}ClN_2O_2$ $[M+H]^+$ 339.0900, found 339.0899.

(3,4-Dihydroisoquinolin-2(1*H*)-yl)(1-(4-nitrophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)methanone (10). To a solution of tryptamine (**9**, 0.33 mmol, 1.05 equiv.) in 3.0 mL of toluene was added to the ketoamide **3p** (0.32 mmol, 1.0 equiv.), and the solution was heated at reflux using a Dean-Stark apparatus for 24 h. The solution was then cooled to -10 ^oC and the Dean-Stark apparatus was replaced with a septum. A solution of trimethylsilyl triflate (0.41 mmol, 1.3 equiv.) in toluene (3.0 mL) was added drop wise and the mixture was stirred at room temperature for 48 h. The reaction mixture was quenched by the addition of water (5 mL) and extracted with EtOAc (2 × 10 mL). The combined organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). It was dried over anhydrous Na_2SO_4, concentrated and the residue was purified by silica-gel column chromatography to yield **10**. Red solid (36 mg, 25%); ^1H NMR (500 MHz, $CDCl_3$): δ=8.25 (d, *J*H–H = 8.6 Hz, 1H), 8.19 (d, *J*H–H = 8.8 Hz, 1H), 8.02–7.86 (m, 3H), 7.65 and 7.59 (2d, 2*J*H–H = 7.9 Hz, 1H), 7.34–7.29 (m, 1H), 7.24–7.20 (m, 1H), 7.17–7.11 (m, 3H), 7.08–7.05 (m, 2H), 7.00–6.93 (m, 1H), 5.05 and 4.64 (2d, 2*J*H–H = 17.2 Hz, 1H), 4.02–3.90 (m, 2H), 3.85–3.74 (m, 2H), 3.36–3.14 (m, 2H), 3.11–2.87 (m, 2H), 2.41 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=165.1, 149.1, 140.1, 136.2, 136.1, 133.8, 132.9, 131.6, 128.9, 128.6, 128.0, 127.9, 126.8, 126.6, 125.7, 123.9, 123.8, 122.0, 119.3, 118.9, 111.0, 56.2, 56.1, 46.9, 43.1, 42.8, 39.2, 28.9, 28.2, 26.5, 26.4; HRMS (ESI-TOF) *m/z* Calcd for $C_{27}H_{24}N_4O_3$ $[M+H]^+$ 453.1927, found 453.1924.

Conclusions

In conclusion, we have developed a new microwave-assisted water soluble copper(I)-catalyzed direct oxidative synthesis of α-ketoamides with oxygen. The one-pot tandem protocol is highly versatile to rapidly access a variety of substituted α-ketoamides and biologically relevant libraries of substituted tetrahydroisoquinoline as well as tetrahydro-β-carboline derivatives. The recyclability and efficiency of the catalyst has also been studied under the optimized microwave reaction conditions. Next, we have also explored the synthetic utility of α-ketoamides by Pictet-Spengler condensation reaction. Further studies of the detailed reaction mechanism and the *in vitro* biological activity of these derivatives are under progress.

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A stable and isolable Cu(I) complex has been identified for the direct oxidative synthesis of α-ketoamides in water.