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Silver-catalyzed amidation of benzoylformic acids with tertiary amines *via* selective carbon–nitrogen bond cleavage†

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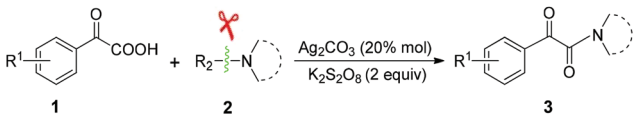
A novel approach towards the synthesis of α-ketoamides using tertiary amines as nitrogen group sources *via* C–N bond cleavage has been developed. In the presence of Ag_2CO_3 and $K_2S_2O_8$, α-keto acids reacted with tertiary amines to afford the corresponding α-ketoamides in good yields.

α-Ketoamides are important intermediates in organic synthesis that are widely found in natural products, biological compounds and pharmaceuticals.[1] Owing to their importance and broad applications, a variety of synthetic methodologies for their synthesis have been developed. Traditional synthetic routes to α-ketoamides usually require multiple steps, harsh reaction conditions, and toxic or expensive reagents.[2] For these reasons, considerable effort has been made on developing mild, efficient and environmentally friendly methods, which are still highly desirable. Recently, transition-metal-catalyzed and metal-free methodologies offer particularly appealing approaches to α-ketoamides.[3] In spite of the environmentally benign character and the high efficiency of these methods, the nitrogen group sources are only limited to primary and secondary amines, which narrowed the substrate scope of amines in the above processes. To our knowledge, the synthesis of α-ketoamides using tertiary amines as nitrogen group sources has not yet been reported.

The carbon–nitrogen bond (C–N) is difficult to cleave because it is stronger than the C–H bond in tertiary amines, and much work on α-H bond activation of tertiary amines has been reported.[4] Despite the big challenge in controlling C–H bond activation for further C–N cleavage, great progress has been made with transition-metal-catalyzed approaches recently.[5] For example, Zhang reported Pd-catalyzed allylic alkylation of carbonyl compounds through C–N bond cleavage of allylic amines.[5a] Takai reported Fe-catalyzed synthesis of glycine derivatives *via* C–N bond cleavage using diazoacetate.[5d]



1 2 3

Scheme 1 The amidation of α-keto acids with tertiary amines.

Then, Huang and coworkers reported a Cu-catalyzed oxidative amination of benzoxazoles using tertiary amines as nitrogen group sources.[5f] As part of our ongoing efforts on the synthesis of α-ketoamides,[6] we herein firstly report the Ag-catalyzed amidation reaction of α-keto acids with tertiary amines *via* C–N bond cleavage, which illustrates an alternative route to α-ketoamides (Scheme 1).

Results and discussion

Our initial investigation focused on the effect of transition-metal catalysts on the model reaction of 2-oxo-2-phenylacetic acid (**1a**) with Et_3N (**2a**), and the results are summarized in Table 1. Several Ag-, Cu- and Fe-salts were screened in the presence of $K_2S_2O_8$ as an oxidant in CCl_4, and the reactivity of Ag-salts (Ag_2CO_3, Ag_2O) is more than that of Cu-salts ($CuBr_2$, CuBr, $Cu(OTf)_2$, $Cu(OAc)_2$, CuI, $Cu(acac)_2$), while Fe-salts ($FeCl_3$, $Fe(acac)_3$, $FeCl_2$) did not exhibit catalytic activity (Table 1, entries 1–12).[5d,f] When 20 mol% of $Cu(OTf)_2$ was used, only 38% yield of **3a** was obtained (Table 1, entry 5). Among the tested transition-metal catalysts, Ag_2CO_3 showed the highest catalytic reactivity and the desired product **3a** was isolated in 46% yield when the model reaction was performed in CCl_4 at 120 °C for 12 h (Table 1, entry 12). Among additional oxidants, $K_2S_2O_8$ was the best one in air. Other oxidants, such as TBHP, $(NH_4)_2S_2O_8$, $PhI(OAc)_2$ and BQ, were ineffective for the generation of **3a** (Table 1, entries 13–16). However, only 8% yield of **3a** was obtained when the model reaction was performed under a nitrogen atmosphere (Table 1, entry 17). Next,

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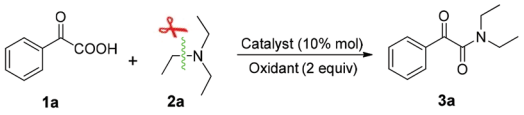
†Electronic supplementary information (ESI) available: Detailed procedures, analytical data, and ^1H, ^{13}C NMR and HRMS spectra of all intermediates and products. See DOI: 10.1039/c3ob40619a

Table 1 Optimization of the model reaction conditions[a]



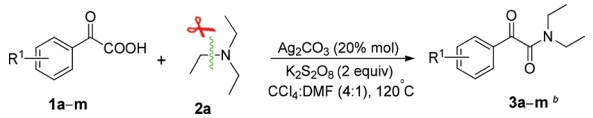
Entry	Catal.	Solvent	Oxidant	Yield[b] (%)
1	$CuBr_2$	CCl_4	$K_2S_2O_8$	26
2	CuBr	CCl_4	$K_2S_2O_8$	23
3	CuI	CCl_4	$K_2S_2O_8$	25
4	$Cu(OTf)_2$	CCl_4	$K_2S_2O_8$	30
5	$Cu(OAc)_2$	CCl_4	$K_2S_2O_8$	38[c]
6	$Cu(OAc)_2$	CCl_4	$K_2S_2O_8$	27
7	$Cu(acac)_2$	CCl_4	$K_2S_2O_8$	24
8	$FeCl_3$	CCl_4	$K_2S_2O_8$	Trace
9	$FeCl_2$	CCl_4	$K_2S_2O_8$	Trace
10	$Fe(acac)_3$	CCl_4	$K_2S_2O_8$	Trace
11	Ag_2O	CCl_4	$K_2S_2O_8$	38
12	Ag_2CO_3	CCl_4	$K_2S_2O_8$	46
13	Ag_2CO_3	CCl_4	$(NH_4)_2S_2O_8$	Trace
14	Ag_2CO_3	CCl_4	TBHP	35
15	Ag_2CO_3	CCl_4	$PhI(OAc)_2$	19
16	Ag_2CO_3	CCl_4	BQ	18
17	Ag_2CO_3	CCl_4	Ag_2CO_3	8[d]
18	AgOAc	CCl_4	$K_2S_2O_8$	21
19	$AgBF_4$	CCl_4	$K_2S_2O_8$	13
20	$AgNO_3$	CCl_4	$K_2S_2O_8$	9
21	Ag_2CO_3	Dioxane	$K_2S_2O_8$	NR
22	Ag_2CO_3	DMF	$K_2S_2O_8$	NR
23	Ag_2CO_3	DMSO	$K_2S_2O_8$	NR
24	Ag_2CO_3	CH_3CN	$K_2S_2O_8$	NR
25	Ag_2CO_3	Toluene	$K_2S_2O_8$	Trace
26	Ag_2CO_3	CCl_4–DMF (1 : 1, v/v)	$K_2S_2O_8$	48
27	Ag_2CO_3	CCl_4–DMF (2 : 1, v/v)	$K_2S_2O_8$	50
28	Ag_2CO_3	CCl_4–DMF (4 : 1, v/v)	$K_2S_2O_8$	54
29	Ag_2CO_3	CCl_4–DMF (8 : 1, v/v)	$K_2S_2O_8$	51
30	Ag_2CO_3	CCl_4–DMF (4 : 1, v/v)	$K_2S_2O_8$	68[e]
31	—	CCl_4–DMF (4 : 1, v/v)	$K_2S_2O_8$	NR

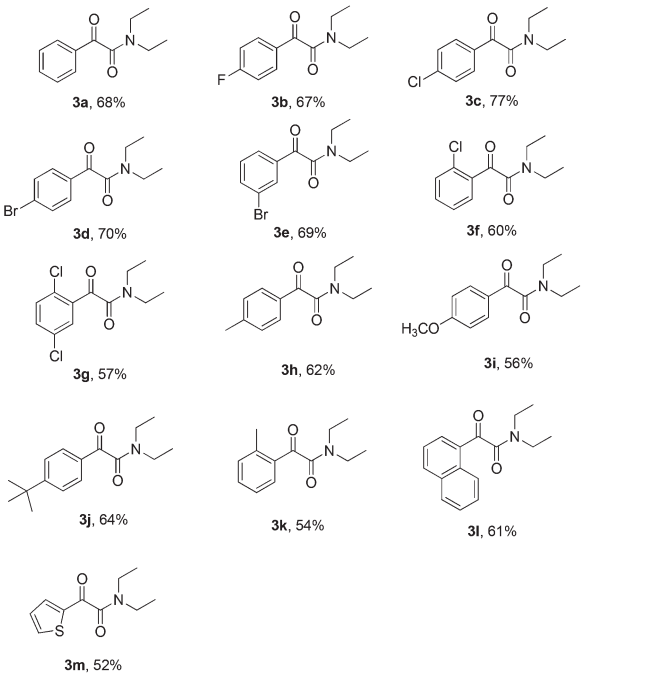
[a] Reaction conditions: **1a** (0.50 mmol), **2a** (1.50 mmol), catalyst (10 mol%), oxidant (1.0 mmol), solvent (3.0 mL), under air, 120 °C, 12 h. [b] Isolated yields. [c] $Cu(OTf)_2$ (20 mol%). [d] Under N_2 atmosphere. [e] Ag_2CO_3 (20 mol%).

some other silver salts were examined. The use of AgOAc, $AgBF_4$ and $AgNO_3$ showed relatively lower efficiency, and 9–21% yields of **3a** were obtained (Table 1, entries 18–20). The effect of solvent on the model reaction was also examined in the presence of Ag_2CO_3 and $K_2S_2O_8$, and the solvent plays an important role in the reaction. When the model reaction was carried out in dioxane, DMF, DMSO, CH_3CN and toluene, no desired product **3a** was detected by TLC (Table 1, entries 21–25). To our delight, when the model reaction was performed in a mixture of CCl_4 and DMF (4 : 1, v/v), **3a** was isolated in 54% yield (Table 1, entry 28). By changing the volume ratios of CCl_4 to DMF, the yields of **3a** were not increased (Table 1, entries 26–29). The ground-breaking result came with the use of 20% Ag_2CO_3, affording the desired product **3a** in 68% yield (Table 1, entry 30). It should be noted that no **3a** was observed when the model reaction was carried out in the absence of Ag_2CO_3 (Table 1, entry 31).

With the optimized reaction conditions in hand, we next investigated the scope of the reaction with a series of α-keto

Table 2 Substrate scope of α-keto acids[a]



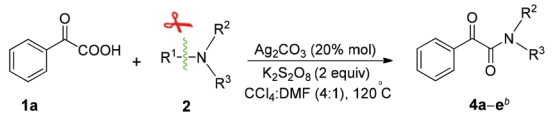


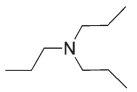
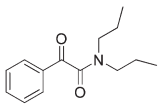
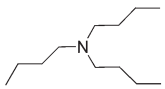
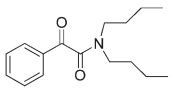
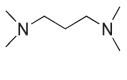
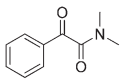
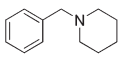
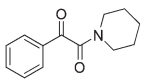
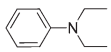
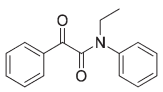
[a] Reaction conditions: **1** (0.50 mmol), **2a** (1.50 mmol), Ag_2CO_3 (0.10 mmol), $K_2S_2O_8$ (1.0 mmol), CCl_4–DMF (4 : 1, v/v, 3.0 mL), under air, 120 °C, 12 h. [b] Isolated yield.

acids and Et_3N (**2a**). The results are summarized in Table 2. The results indicated that 2-oxo-2-arylacetic acids with both electron-rich and electron-deficient groups on the benzene rings underwent the reaction smoothly with Et_3N to generate the corresponding products in good yields. For example, 2-oxo-2-arylacetic acids with F, Cl, Br, Me, MeO, and *tert*-C_4H_9 at the *para*-positions of benzene rings reacted with Et_3N efficiently, and the corresponding products (**3b–d**, **h–j**) were isolated in 56–77% yields. Meanwhile, 2-oxo-2-arylacetic acids, bearing a sterically hindered group, such as Cl or Br or Me at their *ortho*-/*meta*-positions, also underwent the reaction with Et_3N smoothly, providing the corresponding products (**3e**, **3f**, **3g** and **3k**) in slightly lower yields (54–69%) compared with their corresponding *para*-substituted ones. However, a weak *ortho*-position effect was observed in the reaction (**3f**, **3g** and **3l**). In addition, 2-(naphthalen-1-yl)-2-oxoacetic acid and 2-(furan-2-yl)-2-oxoacetic acid also underwent the reaction with Et_3N to generate **3l** and **3m** in 61% and 52% yields, respectively.

To expand the scope of amines, several tertiary amines were surveyed under the present reaction conditions, as shown in Table 3. When $(n\text{-}C_3H_7)_3N$ and $(n\text{-}C_4H_9)_3N$ reacted with 2-oxo-2-phenylacetic acid (**1a**), the desired α-ketoamides **4a** and **4b** were obtained in 55% and 43% yields respectively (Table 3,

Table 3 Substrate scope of tertiary amines[a]



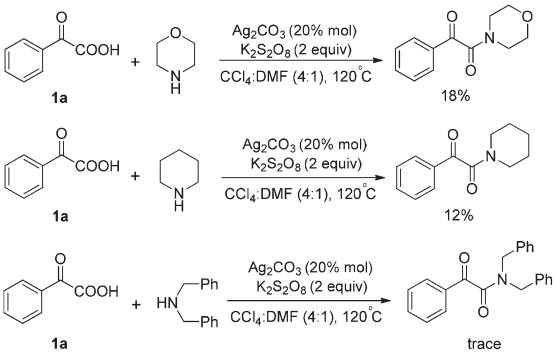
Entry	Tertiary amine	Product	4	Yield[b] (%)
1			**4a**	55
2			**4b**	43
3			**4c**	62
4			**4d**	46
5			**4e**	41

[a] Reaction conditions: **1a** (0.50 mmol), **2** (1.50 mmol), Ag_2CO_3 (0.10 mmol), $K_2S_2O_8$ (1.0 mmol), CCl_4–DMF (4 : 1, v/v, 3.0 mL), under air, 120 °C, 12 h. [b] Isolated yield.

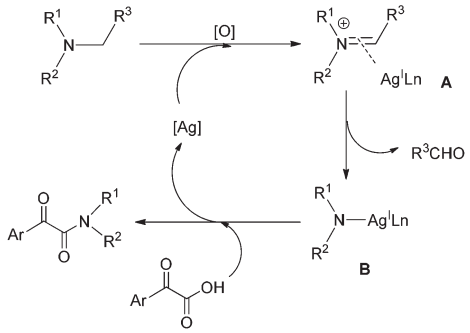
entries 1 and 2). It should be noted that the yield of α-keto-amides was decreased along with the carbon chain increasing of tertiary amines (**3a** *vs.* **4a** *vs.* **4b**). Furthermore, a selective C–N bond cleavage of aliphatic tertiary amines, including tetramethylethylenediamine (TMEDA) and 1-benzylpiperidine, was observed in the reaction with 2-oxo-2-phenylacetic acid under current reaction conditions, providing the sole product **4c** and **4d** in 62% and 46% yields respectively (Table 3, entries 3 and 4). It is important to note that the α-H of the tertiary amine plays a key role in C–N cleavage under current conditions.[5f] When *N*,*N*-diethylaniline as one of the substrates reacted with 2-oxo-2-phenylacetic acid, the corresponding product α-ketoamide **4e** was isolated in 41% yield (Table 3, entry 5), indicating that C–N bond cleavage took place at the carbon containing α-H.

When the reactions of **1a** with secondary amines, such as morpholine, piperidine and dibenzylamine, were performed under the present reaction conditions, only 18% yield, 12% yield, and trace amounts of the corresponding products were obtained. These results show the lower reactivity of secondary amines in this reaction system (Scheme 2).

Although the exact mechanism of this reaction is not clear till now, a possible amination pathway was proposed on the basis of the above experimental results and the literature,[5b,e,f,7] as shown in Scheme 3. Firstly, iminium ion **A** is generated in this reaction system *via* one-electron oxidation of nitrogen, deprotonation of C–H adjacent to a nitrogen atom, and further one-electron oxidation.[8] Then hydrolysis of **A** leads to the key intermediate **B** by elimination of aldehyde. The origination of



Scheme 2 The reactions of **1a** with secondary amines.



Scheme 3 Possible reaction mechanism.

the oxygen atom in the aldehyde byproduct was possibly from H_2O in the system.[9] The obtained **B** further undergoes reaction with α-keto acid to afford the final product α-ketoamide and regenerates Ag catalyst.[10]

Conclusion

In conclusion, we have demonstrated a novel protocol for the direct synthesis of α-ketoamides through an Ag-catalyzed amidation of benzoylformic acids with tertiary amines *via* selective C–N bond cleavage. Compared with other reported α-keto-amides preparation, the current approach shows that inactivated tertiary amines can be used as available nitrogen group sources, which make it more attractive for organic synthesis. Further investigation on the reaction is ongoing in our laboratory.

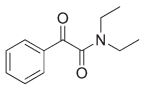
Experimental section

All ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 MHz Bruker FT-NMR spectrometers (400 MHz or 100 MHz, respectively). All chemical shifts are given as δ values (ppm) with reference to tetramethylsilane (TMS) as an internal standard. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, *J*, are reported in Hertz (Hz). High resolution mass spectroscopy data of the product were collected on a Waters

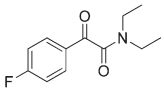
Micromass GCT instrument. Products were purified by flash chromatography on 100–200 mesh silica gels, SiO_2. α-Keto acids were prepared from the oxidation of corresponding aryl methyl ketones with SeO_2 and pyridine according to the reported procedure (K. Wadhwa, C.-X. Yang, P. R. West, K. C. Deming, S. R. Chemburkar and R. E. Reddy, *Synth. Commun.*, 2008, **38**, 4434). Unless otherwise noted, the chemicals and solvents were purchased from commercial suppliers either from Aldrich, USA or Shanghai Chemical Company, China and were used without purification prior to use.

General procedure for the synthesis of α-ketoamides

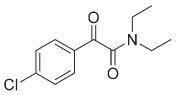
A sealable reaction tube equipped with a magnetic stirrer bar was charged with α-keto acid (0.50 mmol), tertiary amine (1.50 mmol, 3.0 equiv.), Ag_2CO_3 (0.10 mmol, 20%), and $K_2S_2O_8$ (1.0 mmol, 2 equiv.) in a mixture of CCl_4–DMF (4 : 1, v/v, 3.0 mL). The reaction was carried out at 120 °C for 12 h. Then the mixture was cooled and diluted with ethyl acetate. The resulting solution was washed with brine (3 × 5.0 mL). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluant: hexane–ethyl acetate 5 : 1) to afford the corresponding product.



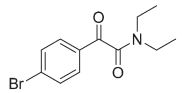
***N*,*N*-Diethyl-2-oxo-2-phenylacetamide (3a): yellow oil.**[3a] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 7.2 Hz, 2H), 7.63 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 8.0 Hz, 2H), 3.56 (q, J = 7.2 Hz, 2H), 3.24 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.55, 166.76, 134.55, 133.25, 129.59, 128.95, 42.12, 38.82, 14.07, 12.80.



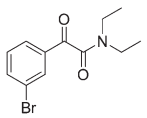
***N*,*N*-Diethyl-2-(4-fluorophenyl)-2-oxoacetamide (3b): yellow oil.** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98–7.95 (m, 2H), 7.17 (t, J = 8.4 Hz, 2H), 3.55 (q, J = 7.2 Hz, 2H), 3.24 (q, J = 7.2 Hz, 2H), 1.27 (t, J = 7.2 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.81, 166.56 (d, J_{CF} = 256.0 Hz), 166.42, 132.40 (d, J_{CF} = 9.6 Hz), 129.80 (d, J_{CF} = 2.6 Hz), 116.25 (d, J_{CF} = 22.1 Hz), 42.16, 38.92, 14.12, 12.79. HRMS (ESI) ([M] + H) Calcd for $C_{12}H_{15}FNO_2$: 224.1087, Found: 240.1084.



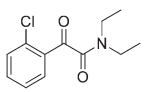
2-(4-Chlorophenyl)-*N*,*N*-diethyl-2-oxoacetamide (3c): yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 3.55 (q, J = 7.2 Hz, 2H), 3.23 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.10, 166.24, 141.15, 131.69, 130.95, 129.35, 42.16, 38.96, 14.15, 12.80. HRMS (ESI) ([M] + H) Calcd for $C_{12}H_{15}ClNO_2$: 240.0791, Found: 240.0788.



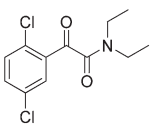
2-(4-Bromophenyl)-*N*,*N*-diethyl-2-oxoacetamide (3d): yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 3.56 (q, J = 7.2 Hz, 2H), 3.24 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.33, 166.17, 132.34, 132.10, 131.01, 130.00, 42.14, 38.94, 14.18, 12.82. HRMS (ESI) ([M] + H) Calcd for $C_{12}H_{15}BrNO_2$: 284.0286, Found: 283.0283.



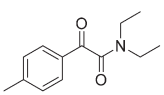
2-(3-Bromophenyl)-*N*,*N*-diethyl-2-oxoacetamide (3e): yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (s, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 3.55 (q, J = 7.2 Hz, 2H), 3.23 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.89, 165.95, 137.34, 135.08, 132.24, 130.51, 128.29, 123.22, 42.18, 39.01, 14.15, 12.80. HRMS (ESI) ([M] + H) Calcd for $C_{12}H_{15}BrNO_2$: 284.0286, Found: 283.0283.



2-(2-Chlorophenyl)-*N*,*N*-diethyl-2-oxoacetamide (3f): yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, J = 7.6 Hz, 1H), 7.51–7.48 (m, 1H), 7.44–7.38 (m, 2H), 3.52 (q, J = 7.2 Hz, 2H), 3.35 (q, J = 7.2 Hz, 2H), 1.28–1.23 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.14, 166.49, 134.14, 133.82, 133.44, 132.32, 130.84, 127.18, 42.18, 39.09, 13.61, 11.89. HRMS (ESI) ([M] + H) Calcd for $C_{12}H_{15}ClNO_2$: 240.0791, Found: 240.0788.

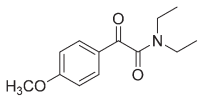


2-(2,5-Dichlorophenyl)-*N*,*N*-diethyl-2-oxoacetamide (3g): yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, J = 2.0 Hz, 1H), 7.47–7.45 (m, 1H), 7.37 (d, J = 8.4 Hz, 1H), 3.52 (q, J = 7.2 Hz, 2H), 3.36 (q, J = 7.2 Hz, 2H), 1.28–1.23 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.66, 165.79, 134.95, 133.89, 133.60, 131.89, 131.87, 131.80, 42.23, 39.26, 13.65, 11.85. HRMS (ESI) ([M] + H) Calcd for $C_{12}H_{12}Cl_2NO_2$: 274.0402, Found: 274.0405.

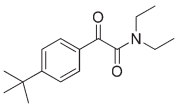


***N*,*N*-Diethyl-2-oxo-2-(*p*-tolyl)acetamide (3h): yellow oil.**[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 3.55 (q, J = 7.2 Hz, 2H), 3.23 (q, J = 7.2 Hz, 2H), 2.42 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.14 (t, J = 7.2 Hz, 3H);

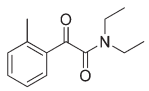
^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.33, 166.95, 145.74, 130.87, 129.71, 129.65, 42.08, 38.74, 21.83, 14.07, 12.80.



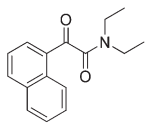
***N*,*N*-Diethyl-2-(4-methoxyphenyl)-2-oxoacetamide (3i): yellow oil.**[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H), 3.53 (q, J = 7.2 Hz, 2H), 3.22 (q, J = 7.2 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.34, 167.06, 164.70, 132.00, 126.34, 114.25, 55.58, 42.10, 38.70, 14.09, 12.81.



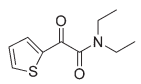
2-(4-(*tert*-Butyl)phenyl)-*N*,*N*-diethyl-2-oxoacetamide (3j): yellow oil.[12] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 3.56 (q, J = 7.2 Hz, 2H), 3.24 (q, J = 7.2 Hz, 2H), 1.34 (br, s, 9H), 1.28 (t, J = 7.2 Hz, 3H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.29, 166.98, 158.59, 130.75, 129.57, 125.94, 42.12, 38.75, 35.31, 30.98, 14.09, 12.80.



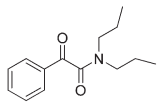
***N*,*N*-Diethyl-2-oxo-2-(*o*-tolyl)acetamide (3k): yellow oil.** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, J = 7.6 Hz, 1H), 7.46 (t, J = 7.2 Hz, 1H), 7.30 (t, J = 7.2 Hz, 2H), 3.54 (q, J = 7.2 Hz, 2H), 3.25 (q, J = 7.2 Hz, 2H), 2.65 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.57, 167.43, 141.37, 133.48, 132.58, 132.53, 131.74, 126.08, 42.10, 38.74, 21.73, 13.88, 12.65. HRMS (ESI) ([M] + H) Calcd for $C_{13}H_{18}NO_2$: 220.1338, Found: 220.1335.



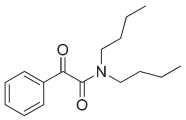
***N*,*N*-Diethyl-2-(naphthalen-1-yl)-2-oxoacetamide (3l): yellow oil.** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.27 (d, J = 8.8 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 7.2 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.72–7.68 (m, 1H), 7.61–7.52 (m, 2H), 3.60 (q, J = 7.2 Hz, 2H), 3.31 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.06, 167.27, 135.70, 134.23, 134.08, 131.03, 129.21, 128.71, 128.65, 126.91, 125.85, 124.51, 42.26, 38.86, 13.93, 12.76. HRMS (ESI) ([M] + H) Calcd for $C_{16}H_{18}NO_2$: 256.1338, Found: 240.1343.



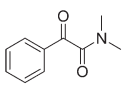
***N*,*N*-Diethyl-2-oxo-2-(thiophen-2-yl)acetamide (3m): yellow oil.**[13] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.77 (m, 2H), 7.18 (t, J = 4.4 Hz, 1H), 3.54 (q, J = 7.2 Hz, 2H), 3.33 (q, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.62, 165.68, 140.60, 136.03, 135.84, 128.52, 42.38, 39.28, 14.25, 12.72.



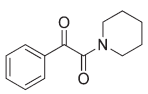
2-Oxo-2-phenyl-*N*,*N*-dipropylacetamide (4a): yellow oil.[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, J = 7.6 Hz, 2H), 7.64 (t, J = 7.2 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 3.48 (t, J = 7.6 Hz, 2H), 3.14 (t, J = 7.6 Hz, 2H), 1.78–1.69 (m, 2H), 1.65–1.55 (m, 2H), 1.02 (t, J = 7.6 Hz, 3H), 0.80 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.52, 167.18, 134.46, 133.39, 129.63, 128.91, 49.32, 45.86, 21.81, 20.62, 11.40, 10.99.



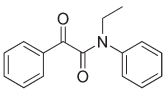
***N*,*N*-Dibutyl-2-oxo-2-phenylacetamide (4b): yellow oil.**[3e] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 7.2 Hz, 2H), 7.62 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 3.49 (t, J = 7.6 Hz, 2H), 3.14 (t, J = 7.6 Hz, 2H), 1.71–1.63 (m, 2H), 1.57–1.49 (m, 2H), 1.44–1.39 (m, 2H), 1.21–1.15 (m, 2H), 0.99 (t, J = 7.6 Hz, 3H), 0.81 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.56, 167.06, 134.44, 133.39, 129.56, 128.89, 47.41, 44.01, 30.61, 29.43, 20.22, 19.73, 13.80, 13.50.



***N*,*N*-Dimethyl-2-oxo-2-phenylacetamide (4c): yellow oil.**[11] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, J = 7.6 Hz, 2H), 7.65 (t, J = 7.6 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 3.13 (s, 3H), 2.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.78, 167.04, 134.72, 133.06, 129.66, 129.01, 37.06, 34.01.



1-Phenyl-2-(piperidin-1-yl)ethane-1,2-dione (4d): yellow oil.[3e] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, J = 7.2 Hz, 2H), 7.65 (t, J = 7.6 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 3.72 (br s, 2H), 3.30 (t, J = 5.6 Hz, 2H), 1.71–1.70 (m, 4H), 1.56 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.94, 165.47, 134.67, 133.25, 129.59, 129.01, 47.06, 42.18, 26.20, 25.45, 24.38.



***N*-Ethyl-2-oxo-*N*,2-diphenylacetamide (4e): yellow oil.**[3d] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, J = 7.2 Hz, 2H), 7.56 (t, J = 7.6 Hz, 1H), 7.43 (t, J = 8.0 Hz, 2H), 7.27–7.23 (m, 3H), 7.14–7.12 (m, 2H), 3.98 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.79, 166.59, 139.31,

134.15, 133.59, 129.41, 129.31, 128.71, 128.32, 128.27, 43.55, 12.91.

Acknowledgements

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Notes and references

1 (*a*) Y.-H. Chen, Y.-H. Zhang, H.-J. Zhang, D.-Z. Liu, M. Gu, J.-Y. Li, F. Wu, X.-Z. Zhu, J. Li and F.-J. Nan, *J. Med. Chem.*, 2006, **49**, 1613; (*b*) J. Holenz, R. Mercè, J. L. Díaz, X. Guitart, X. Codony, A. Dordal, G. Romero, A. Torrens, J. Mas, B. Andaluz, S. Hernández, X. Monroy, E. Sánchez, E. Hernández, R. Pérez, R. Cubí, O. Sanfeliu and H. Buschmann, *J. Med. Chem.*, 2005, **48**, 1781; (*c*) A. Natarajan, K. Wang, V. Ramamurthy, J. Scheffer and B. Patrick, *Org. Lett.*, 2002, **4**, 1443; (*d*) M. M. Sheha, N. M. Mahfouz, H. Y. Hassan, A. F. Youssef, T. Mimoto and Y. Kiso, *Eur. J. Med. Chem.*, 2000, **35**, 887; (*e*) S. Chatterjee, D. Dunn, M. Tao, G. Wells, Z.-Q. Gu, R. Bihovsky, M. A. Ator, R. Siman and J. P. Mallamo, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2371; (*f*) Z. Li, A.-C. Ortega-Vilain, G. S. Patil, D.-L. Chu, J. E. Foreman, D. D. Eveleth and J. C. Powers, *J. Med. Chem.*, 1996, **39**, 4089; (*g*) D. H. Slee, K. L. Laslo, J. H. Elder, I. R. Ollmann, A. Gustchina, J. Kervinen, A. Zdanov, A. Wlodawer and C.-H. Wong, *J. Am. Chem. Soc.*, 1995, **117**, 11867; (*h*) B. E. Maryanoff, M. N. Greco, H.-C. Zhang, P. Andrade-Gordon, J. A. Kauffman, K. C. Nicolaou, A. Liu and P. H. Brungs, *J. Am. Chem. Soc.*, 1995, **117**, 1225; (*i*) M. Hagihara and S. L. Schreiber, *J. Am. Chem. Soc.*, 1992, **114**, 6570; (*j*) B. Munoz, C.-Z. Giam and C.-H. Wong, *Bioorg. Med. Chem.*, 1994, **2**, 1085.

2 (*a*) I. Ojima, N. Yoda, M. Yatabe, T. Tanaka and T. Kogure, *Tetrahedron*, 1984, **40**, 1255; (*b*) A. Chiou, T. Markidis, V. Constantinou-Kokotou, R. Verger and G. Kokotos, *Org. Lett.*, 2000, **2**, 347; (*c*) G. M. Dubowchik, J. L. Ditta, M. V. Vrudhula, B. DasGupta, J. Ditta, T. Chen, S. Sheriff, K. Sipman, M. Witmer, J. Tredup, D. M. Vyas, T. A. Verdoorn, S. Bollini and A. Vinitsky, *Org. Lett.*, 2001, **3**, 3987.

3 For the synthesis of α-ketoamides by transition-metal-catalyzed approaches, see: (*a*) J. Liu, R. Zhang, S. Wang, W. Sun and C. Xia, *Org. Lett.*, 2009, **11**, 1321; (*b*) C. Zhang and N. Jiao, *J. Am. Chem. Soc.*, 2010, **132**, 28; (*c*) C. Zhang, Z. Xu, L. Zhang and N. Jiao, *Angew. Chem., Int. Ed.*, 2011, **50**, 11088; (*d*) C. Zhang, X. Zong, L. Zhang and N. Jiao, *Org. Lett.*, 2012, **14**, 3280; (*e*) F.-T. Du and J.-X. Ji, *Chem. Sci.*, 2012, **3**, 460. For the synthesis of α-ketoamides by metal-free approaches, see: (*f*) W. Wei, Y. Shao, H. Hu, F. Zhang, C. Zhang, Y. Xu and X. Wan, *J. Org. Chem.*, 2012, **77**, 7157; (*g*) W.-P. Mai, H.-H. Wang, Z.-C. Li, J.-W. Yuan, Y.-M. Xiao, L.-R. Yang, P. Mao and L.-B. Qu, *Chem. Commun.*, 2012, **48**, 10117; (*h*) M. Lamani and K. R. Prabhu, *Chem.–Eur. J.*, 2012, **18**, 14638.

4 For examples of α-H bond action of tertiary amines: (*a*) X. Xu and X. Li, *Org. Lett.*, 2009, **11**, 1027; (*b*) T. Yoshimitsu, K. Matsuda, H. Nagaoka, K. Tsukamoto and T. Tanaka, *Org. Lett.*, 2007, **9**, 5115; (*c*) M. Niu, Z. Yin, H. Fu, Y. Jiang and Y. Zhao, *J. Org. Chem.*, 2008, **73**, 3961; (*d*) S.-I. Murahashi, T. Nakae, H. Terai and N. Komiya, *J. Am. Chem. Soc.*, 2008, **130**, 11005; (*e*) T. Sugiishi and H. Nakamura, *J. Am. Chem. Soc.*, 2012, **134**, 2504; (*f*) L. Chu, X. Zhang and F. Qing, *Org. Lett.*, 2009, **11**, 2197; (*g*) F. Yang, J. Li, J. Xie and Z.-Z. Huang, *Org. Lett.*, 2010, **12**, 5214; (*h*) X. Ye, C. Xie, Y. Pan, L. Han and T. Xie, *Org. Lett.*, 2010, **12**, 4240; (*i*) Y. Zhang, H. Peng, M. Zhang, Y. Cheng and C. Zhu, *Chem. Commun.*, 2011, **47**, 2354; (*j*) L. Liu, Z. Wang, X. Fu and C.-H. Yan, *Org. Lett.*, 2012, **14**, 5692.

5 (*a*) X. Zhao, D. Liu, H. Guo, Y. Liu and W. Zhang, *J. Am. Chem. Soc.*, 2011, **133**, 19354; (*b*) Y. Liu, B. Yao, C.-L. Deng, R.-Y. Tang, X.-G. Zhang and J.-H. Li, *Org. Lett.*, 2011, **13**, 2184; (*c*) S. Li and J. Wu, *Org. Lett.*, 2011, **13**, 712; (*d*) Y. Kuninobu, M. Nishi and K. Takai, *Chem. Commun.*, 2010, **46**, 1350; (*e*) W. Liu, J. Liu, D. Ogawa, Y. Nishihara, X. Guo and Z. Li, *Org. Lett.*, 2011, **13**, 6272; (*f*) S. Guo, B. Qian, Y. Xie, C. Xia and H. Huang, *Org. Lett.*, 2011, **13**, 522.

6 X. Zhang and L. Wang, *Green Chem.*, 2012, **14**, 2141.

7 For recent examples on silver-mediated reactions, see: (*a*) J. M. Weibel, A. Blanc and P. Pale, *Chem. Rev.*, 2008, **108**, 3149; (*b*) M. Alvarez-Corral, M. Munoz-Dorado and I. Rodriguez-Garcoa, *Chem. Rev.*, 2008, **108**, 3174; (*c*) K. Chen, J. M. Richter and P. S. Baran, *J. Am. Chem. Soc.*, 2008, **130**, 7247; (*d*) T. Furuya, A. E. Strom and T. Ritter, *J. Am. Chem. Soc.*, 2009, **131**, 1662.

8 (*a*) K. McCamley, J. A. Ripper, R. D. Singer and P. J. Scammells, *J. Org. Chem.*, 2003, **68**, 9847; (*b*) F. Minisci, F. Fontana, S. Araneo, F. Recupero and L. Zhao, *Synlett*, 1996, 119; (*c*) S. H. Cho, J. Y. Kim, S. Y. Lee and S. Chang, *Angew. Chem., Int. Ed.*, 2009, **48**, 9127.

9 (*a*) Y. Liu, B. Yao, C.-L. Deng, R.-Y. Tang, X.-G. Zhang and J.-H. Li, *Org. Lett.*, 2011, **13**, 2184; (*b*) G.-W. Wang, X.-P. Chen and X. Cheng, *Chem.–Eur. J.*, 2006, **12**, 7246.

10 J. Li, K. Subramaniam, D. Smith, J. X. Qiao, J. J. Li, J. Qian-Cutrone, J. F. Kadow, G. D. Vite and B.-C. Chen, *Org. Lett.*, 2012, **14**, 214.

11 F. Ozawa, H. Soyama, H. Yanagihara, I. Aoyama, H. Takino, K. Izawa, T. Yamamoto and A. Yamamoto, *J. Am. Chem. Soc.*, 1985, **107**, 3235.

12 Z. Yang, Z. Zhang, N. A. Meanwell, J. F. Kadow and T. Wang, *Org. Lett.*, 2002, **4**, 1103.

13 R. P. Singh and J. M. Shreeve, *J. Org. Chem.*, 2003, **68**, 6063.

