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One Pot Synthesis of α-Ketoamides from Ethylarenes and Amines: A Metal Free Difunctionalization Strategy†

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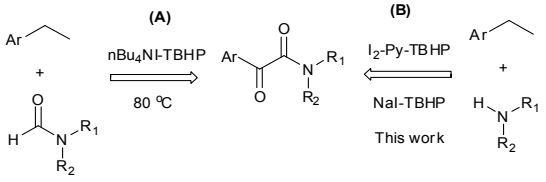
One-pot and metal free synthesis of α-ketoamides has been described through *in situ* generation of aryl ketones from easily available ethylarenes followed by amidation with various amines. This multiple oxidation protocol involves catalytic I_2-pyridine-TBHP (*t*-butyl hydroperoxide) mediated oxidative benzylic carbonylation and sequential NaI-TBHP mediated oxidative amidation without using any solvent.

Introduction

α-Ketoamides, a structurally privileged core found in array of biological compounds,[1] pharmaceuticals,[2] and natural products,[3] have received much attention due to the inherent pharmacological and biological applications. Furthermore, they also serve as versatile synthetic intermediates in functional group transformation and synthesis. Thus, various appealing synthetic approaches have been reported for this motif in recent years. Even though, few review articles summarize these synthetic methodologies,[4-7] there is still a growing interest in the development of one-pot preparation of α-ketoamides from commercial chemicals. A variety of precursors such as acetophenone,[8] styrene,[9] phenylacetylene,[10] 1-arylethanol,[11] phenylacetaldehyde,[12] phenyl glyoxal,[13] and 2-hydroxy-1-phenyl-ethanone,[14] have been achieved. Despite the aforementioned works, chemists are interested in the development of efficient methods from unfunctionalized molecules such as ethylbenzenes[15] or toluenes.[16]

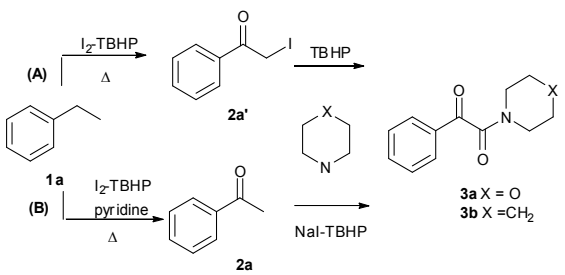
Ethylbenzene is a commercially available substrate and has been studied for the preparation of α-ketoamides. A pioneered work by Sun and co-workers showed that a range of α-ketoamides can be prepared from ethylarenes and *N,N*-dialkylformamides under n-Bu_4NI/TBHP mediated oxidative conditions (Scheme 1A).[15] However, requirement of formamide and limitation to *N,N*-dialkyl subsitutents with this process drove us to improve the preparation of α-ketoamides from ethylarenes and amines (Scheme 1B). Our approach negates the requirement of *N*-formylated amine precursors and exploits the greater number of commercially available amines, thus expanding the diversity of α-ketoamide libraries.



Scheme 1 α-Ketoamides from ethylbenzenes

Results and discussion

Guided by the literature, we envisaged that the ethylbenzenes could be transformed into corresponding phenacyl iodides **2a'** under catalytic I_2-TBHP system,[17] which might undergo oxidative amidation leading to the desired α-ketoamides in a one-pot fashion (Scheme 2A). Optimization studies with ethylbenzene in the presence of 20 mol% of I_2 and *t*-butyl hydroperoxide (TBHP) at 120 °C followed by the treatment of morpholine/TBHP led to the formation of **3a** in trace yields (Table 1, entry 1). Replacement of morpholine by piperidine gave the desired product in trace amount. Upon extending the reaction time to 12 h at 100 °C, we observed a slight increment to 30% (Table 1, entry 3). These results prompted us to explore this protocol with different solvents, time, and amount of TBHP (Table 1, entries 4-10). Though, we performed the above reactions carefully with the confirmation of the formation of intermediate **2a'**, yield of **3a** could only be improved up to 55%.



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†Electronic Supplementary Information (ESI) available: ^1H, ^{13}C NMR spectra for all synthesized compounds. See DOI: 10.1039/x0xx00000x

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Scheme 2 Synthetic approaches leading to α-ketoamides from ethylbenzene

<<Table 1>>

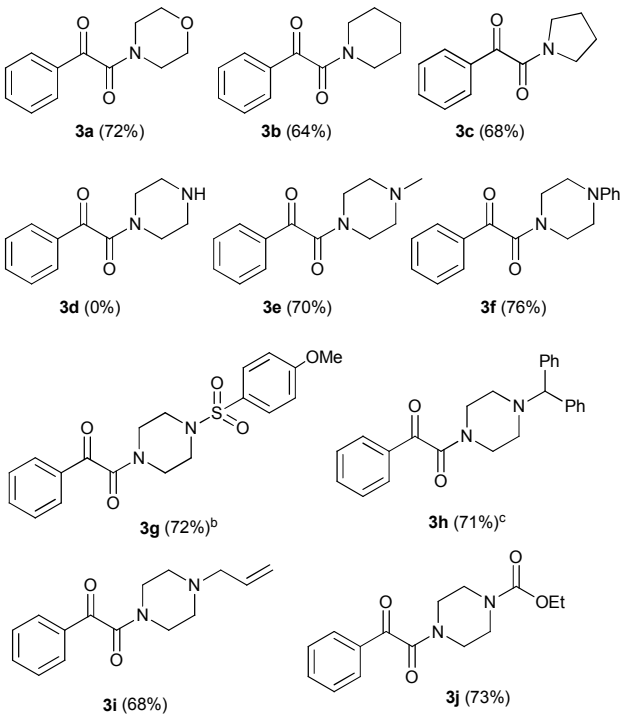
It is known that the α-ketoamide **3a** can be prepared from acetophenone and morpholine.[8] We then resumed our approach by conversion of ethylbenzene into acetophenone followed by the oxidative amidation in a one-pot fashion (scheme 2B). By modification of Wang and co-workers' procedure,[18] we observed that ethylbenzene was transferred into acetophenone with the treatment of a combination of I_2-pyridine-TBHP in a high conversion as monitored by the NMR determination. Then, morpholine, NaI (20 mol%) and an extra amount of TBHP were added to the above mixture for the further reaction at the ambient temperature. To our delight, this approach furnished **3a** in good yield (table 2, entry 1). By increasing the amount of NaI or with the use of I_2, the yields of **3a** were improved (table 2, entries 2-3). However, it reached to the maximum when 60 mol% of NaI used (table 2, entry 4). It was noticed that the yield was decreased significantly when we use diaklylamine under this conditions. By monitoring the reaction under various temperature, we found that lowering the reaction temperature down to 0 ^{o}C is the best choice (table 2, entry 7).

<<Table 2>>

With the optimized conditions, we contemplated the scope of the reaction with various commercially and readily available amines. Common cyclic secondary amines such as morpholine, piperidine and pyrrolidine reacted well with ethylbenzene to furnish the corresponding α-ketoamides in synthetically useful yields (Table 3, entries **3a**-**3c**). Though piperazine was an unsuccessful partner in this oxidative transformation (Table 3, entry **3d**), mono N-methylated piperazines smoothly converted to α-ketoamides (Table 3, entry **3e**). Utilization of mono-*N*-functionalized piperazines with divergent functional groups such as *N*-ethoxycarbonyl, *N*-allyl, and *N*-(4-methoxy)phenyl sulfonyl groups were well tolerated under the reaction conditions and afforded the corresponding α-ketoamides in good yields (Table 3, entries **3f**-**3j**). Synthetically distinct α-ketoamides of these types are previously not reported by any other known methods.

The applicability of this method was further extended to acyclic primary and secondary amines with the amidation at 0 ^{o}C. Linear and heterocycle bound primary amines participated well in this reaction to give the corresponding α-ketoamides in appreciable yields (Table 4). In the case of n-hexylamine as the reacting partner, not only the desired product **4a** was obtained, also trace amount of decarbonylated product was isolated (Table 4, entry **4a'**). Other classes of primary amines such as isopropyl, t-butylamine were also participated to afford the α-ketoamides in moderate yields (Table 4, entries **4b** ~ **4d**). Acyclic secondary amines reacted equally well as their cyclic counterparts albeit in slightly lower yields (Table 4, entries **4e**-**4f**). Notably, dibenzylamine delivered the corresponding α-ketoamide in minor amount together with complicated entities (Table 4, entry **4g**). This might be attributed to the presence of multiple benzylic protons present in the amino precursor. On the other hand, benzylamine furnished the corresponding product under our optimized conditions without any complications in 61% isolated yield (Table 4, entry **4h**). Although, the generality of this presented method is applicable to variety of primary, secondary and benzylic amines, despite our best efforts, no desired products were obtained with 2,6-dimethyl piperidine, diisopropyl amine, 2-hydroxy ethylamine and aniline. In the case of aniline, we obtained a black unidentified solid, which was presumably to be the polyanilines.

Table 3 α-Ketoamides prepared from ethylbenzene and various cyclic amines



[a] Reaction Conditions: **1a** (1.88 mmol), I_2 (0.09 mmol), pyridine (0.09 mmol), TBHP (5.65 mmol), 80 ^{o}C for 10 h, then TBHP (5.65 mmol), NaI (1.13 mmol), cyclic amine (2.5 eq), rt, 6h; isolated yields. [b] amine dissolved in MeCN (1 mL). [c] amine dissolved in 1 mL MeCN/0.5 mL MeOH.

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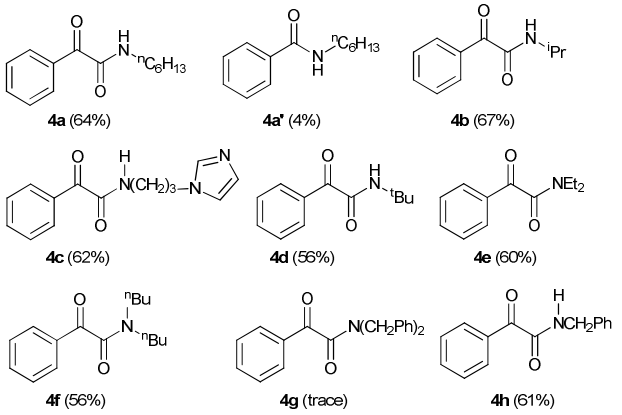
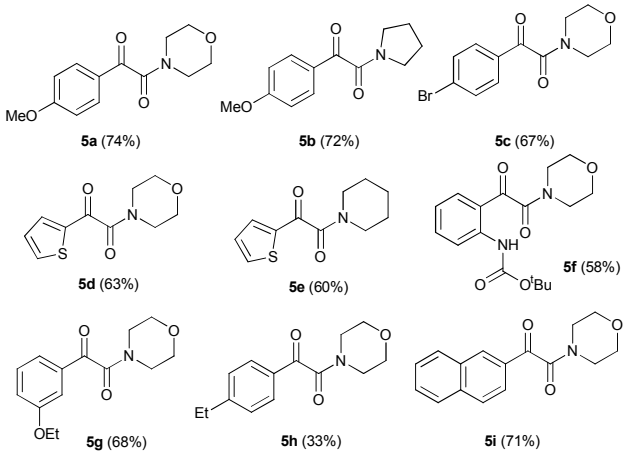
Table 4 α-Ketoamides prepared from ethylbenzene and various aliphatic amines



[a] Reaction Conditions: ethylarene (1.88 mmol), I_2 (0.09 mmol), pyridine (0.09 mmol), TBHP (5.65 mmol), 80 °C for 10 h, then TBHP (7.52 mmol), NaI (1.13 mmol), cyclic amine (2.5 eq), 0 °C, 12h; isolated yields.

To extend the synthetic utility of this method, we examined various ethyl substituted arenes and heteroarenes to this methodology (Table 5). It was found that ethylarenes with methoxy groups and bromo substituents were tolerated under the reaction conditions to afford the corresponding α-ketoamides (Table 5, entries **5a-5c**). Oxidative amidation of ethylthiophene proceeded as well to give the desired product (Table 5, entry **5d-5e)**, but not 2-ethylpyridine and 2-ethylimidazole. Oxidation of 2-ethylpyridine gave 2-pyridinecarboxylic acid as the only product.

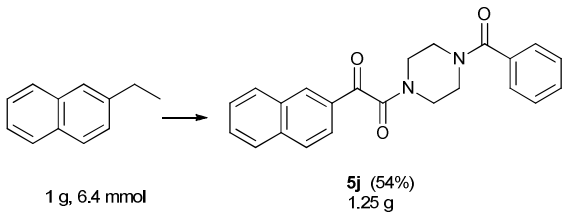
Table 5 α-Ketoamides prepared from ethylarenes[a]



[a] Reaction Conditions: ethylarene (1.88 mmol), I_2 (0.09 mmol), pyridine (0.09 mmol), TBHP (5.65 mmol), 80 °C for 10 h, then TBHP (5.65 mmol), NaI (1.13 mmol), cyclic amine (2.5 eq), r, 6 h; isolated yields.

It is notable that *o*-*N*-Boc substituted ethylbenzene provided the corresponding α-ketoamide in 58% yield (Table 5, entry **5f**), thus illustrating the scope and compatibility of the presented reaction. Presence of free phenolic hydroxyl group led to complicated results, on the other hand, 3-alkoxy ethylbenzene afforded the desired product in good yield (Table 5, entry **5g**). We found that 3-acetoxy-1-ethylbenzene led to 3-hydroxyacetophenone as sole product. Attempts to prepare bis-α-ketoamide from *p*-diethylbenzene resulted a mixture of oxidation products in various ratios. However, 1-(4-ethylphenyl)-2-morpholinoethane-1,2-dione (Table 5, entry **5h**) was isolated in 33% yield. 2-Ethylnaphthalene also participated in the reaction very well and furnished **5i** in good yield (Table 5, entry **5i**). However, 4-nitro-1-ethylbenzene does not undergo such an oxidative amidation. Instead, *p*-nitrobenzoic acid was obtained as the major product with trace amount of *p*-nitroacetophenone.[19]

To further extend this practical application, we focused our efforts to synthesize anti-HIV compound **5j**, which was previously prepared from Au/Pd catalysed double carbonylation of aryl halides with carbon monoxide.[20] We carried out a gram scale synthesis of **5j** from 2-ethylnaphthalene and *N*-benzoyl-piperazine under the optimized conditions. To our delight this transformation proceeded smoothly to furnish the desired product in moderate yield (Scheme 3), thus demonstating the applicability of this method for larger scales via a metal free approach.



Scheme 3 Gram scale synthesis of anti-HIV agent **5j**

Conclusions

In summary, we have developed a convenient method for the synthesis of a variety of α-ketoamides from available ethylarenes and amines. This reaction proceeds in one-pot fashion under metal-free conditions *via* sequential dehydrogenation of five sp^3 C-H bonds.[21] A comprehensive scope and the tolerance of various functional groups were demonstrated successfully. In addition, a gram scale synthesis of anti-HIV agent is achieved in good yield, illustrating the possibility for the industrial application.

Experimental

General information.

^1H and ^{13}C NMR were recorded in a 400 MH_z spectrometer in $CDCl_3$ or DMSO-d_6 solvents referenced to TMS. Ethylarenes were commercially purchased and used without further purification. Column Chromatography was performed using silica gel 230-400 mesh. Analytical thin layer chromatography (TLC) was performed using Merck-60 F-254 plates and visualized using UV lamp (254-365 nm). In cases of known compounds, their ^1H and ^{13}C values were compared with the literature reports. FT-IR were recorded on Thermo Scientific-Nicolet iS5 spectrometer and reported in frequency of

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absorption (cm^{-1}). Melting points were determined on a Fargo MP-1D instrument.

<<**Caution**: TBHP is a dangerous and toxic chemical. It should be handled carefully!>>

General procedure for the preparation of α-Ketoamides.

Ethylarene (1 eq.), I_2 (5 mol%), pyridine (5 mol%) andTBHP (3 eq., 70% aqueous solution) were added in a 20 mL sealed tube with a Teflon lined screw cap. The reaction mixture was stirred in an oil bath at 80 °C for 10h (stage 1). Then TBHP (3 eq. 70% aqueous solution), NaI (0.6 eq.) and the corresponding cyclic secondary amine (2.5 eq.) were added sequentially and stirred at room temperature for 6h. The reaction mixture was directly purified by a silica gel column chromatography hexane/ethyl acetate as eluent to give the corresponding α-ketoamides. In cases of acyclic primary, secondary and benzylic amines, reaction mixture was cooled down to 0 °C after the stage 1. Then TBHP (4 eq., 70% aqueous solution), NaI (0.6 eq) and the corresponding amine (2.5 eq.) were added sequentially and stirred at 0 °C for 10h. The purification step is similar to the above.

1-morpholino-2-phenylethane-1,2-dione (3a).[22]

Pale Yellow Viscous Oil (72%); Purified by chromatography (EtOAc/Hexane 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.92 (m, 2H), 7.60-7.61 (m, 1H), 7.52-7.48 (m, 2H), 3.17 (brs, H), 3.64-3.62 (m, 2H), 3.37-3.34 (m, 2H); ^{13}C NMR (100 MHz): δ 191.1, 165.4, 134.9, 133.0, 129.6, 129.0, 66.7, 66.6, 46.2, 41.6; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1683, 1652; HRMS (ESI) calcd. for $C_{12}H_{14}NO_3$ $(M+H)^+$: 220.0974; found 220.0984.

1-phenyl-2-(piperidin-1-yl)ethane-1,2-dione (3b).[23]

White solid (64%); mp 94-95°C; Purified by flash column chromatography (EtOAc/Hexane 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 7.6 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2 H), 3.64 (brs, 2H), 3.22 (t, *J* = 5.6 Hz, 2H), 1.63 (t, *J* = 2.8 Hz, 4H), 1.49 (d, *J* = 5.2 Hz, 2H); ^{13}C NMR (100 MHz): δ 191.8, 165.3, 134.5, 133.1, 129.4, 128.8, 46.9, 42.0, 26.0, 25.3, 24.2; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1680, 1640; HRMS (ESI) calcd. for $C_{13}H_{16}NO_2$ $(M+H)^+$: 218.1181; found 218.1187.

1-phenyl-2-(pyrrolidin-1-yl)ethane-1,2-dione (3c).[22]

Pale Yellow Viscous Oil (68%); Purified by flash column chromatography (EtOAc/Hexane 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95-7.93 (m, 2H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 2H), 3.60 (t, *J* = 6.4 Hz, 2H), 3.37 (t, *J* = 6.4 Hz, 2H), 1.93-1.87 (m, 4H); ^{13}C NMR (100 MHz): δ 191.4, 164.8, 134.5, 132.8, 129.7, 128.8, 46.5, 45.1, 25.8, 23.9; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1685, 1651; HRMS (ESI) calcd. for $C_{12}H_{14}NO_2$ $(M+H)^+$: 204.1025; found 204.1034.

1-(4-methylpiperazin-1-yl)-2-phenylethane-1,2-dione (3e).[24]

Pale yellow gummy solid (70%); Purified by chromatography (EtOAc/Hexane 35%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87-7.85 (m, 2H), 7.59-7.54 (m, 1H), 7.45-7.31 (m, 2H), 3.70 (t, *J* = 5.2 Hz, 2H), 3.29 (t, *J* = 5.2 Hz, 2H), 2.42 (t, *J* = 5.2 Hz, 2H), 2.28 (t, *J* = 5.2 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz): δ 191.5, 165.4, 134.8, 133.0, 129.6, 129.0, 54.8, 54.4, 45.9, 45.7, 41.1; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1681, 1643; HRMS (ESI) calcd. for $C_{13}H_{17}N_2O_2$ $(M+H)^+$: 233.1290; found 233.1310.

1-phenyl-2-(4-phenylpiperazin-1-yl)ethane-1,2-dione (3f).[25]

Brown viscous oil (76%); Purified by chromatography (EtOAc/Hexane 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89-7.87 (m, 2H), 7.57-7.54 (m, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 8.0 Hz, 2H), 6.83-6.80 (m, 3H), 3.83 (t, *J* = 5.2 Hz, 2H), 3.42 (t, *J* = 5.2 Hz, 2H), 3.19 (t, *J* = 5.2Hz, 2H), 3.04 (t, *J* = 5.2 Hz, 2H); ^{13}C NMR (100 MHz): δ 191.2, 165.3, 150.6, 134.8, 133.0, 129.6, 129.2, 129.0, 120.8, 116.9, 49.8, 49.5, 45.7, 41.2; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1682, 1644; HRMS (ESI) calcd. for $C_{18}H_{19}N_2O_2$ $(M+H)^+$:295.1447; found 295.1451.

1-(4-((4-methoxyphenyl)sulfonyl)piperazin-1-yl)-2-phenylethane-1,2-dione (3g).

Yellow solid (72%); mp 154-155°C; Purified by chromatography (EtOAc/Hexane 50%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85-7.83 (m, 2H), 7.65-7.62 (m, 2H), 7.60-7.58 (m, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 6.99-6.95 (m, 2H), 3.84 (s, 3H), 3.82-3.80 (m, 2H), 3.40 (t, *J* = 5.2 Hz, 2H), 3.08 (t, *J* = 5.2 Hz, 2H), 2.98 (t, *J* = 4.8 Hz, 2H); ^{13}C NMR (100 MHz): δ 190.8, 165.2, 163.3, 135.0, 132.7, 129.7, 129.6, 129.0, 126.6, 114.5, 55.6, 55.5, 46.0, 45.6, 45.2, 40.6; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1680, 1651; HRMS (ESI) calcd. for $C_{19}H_{21}N_2O_5S$ $(M+H)^+$:389.1171; found 389.1198.

1-(4-diphenylmethylpiperazin-1-yl)-2-phenylethane-1,2-dione (3h).

Brown viscous oil (71%); Purified by chromatography (EtOAc/Hexane 35%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86-7.84 (m, 2H), 7.56-7.52 (m, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.31 (d, *J* = 7.2 Hz, 4H), 7.21-7.17 (m, 4H), 7.12-7.08 (m, 2H), 4.20 (s, 1H), 3.70 (t, *J* = 5.2 Hz, 2H), 3.28 (t, *J* = 5.2 Hz, 2H), 2.44 (t, *J* = 5.2 Hz, 2H), 2.28 (t, *J* = 4.8 Hz, 2H); ^{13}C NMR (100 MHz): δ , 191.5, 165.3, 141.8(2C), 134.7, 133.1, 129.5 (2C), 128.9, 128.6 (2C), 127.7(2C), 127.2, 75.8, 51.8, 51.4, 46.0, 41.4. IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1681, 1643; HRMS (ESI) calcd. for $C_{25}H_{25}N_2O_2$ $(M+H)^+$:385.1916; found 385.1919.

1-(4-allylpiperazin-1-yl)-2-phenylethane-1,2-dione (3i).

Brown viscous oil (68%); Purified by chromatography (EtOAc/Hexane 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93-7.91 (m, 2H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 5.85-5.75 (m, 1H), 5.19-5.13 (m, 2H), 3.76 (t, *J* = 5.2 Hz, 2H), 3.35 (t, *J* = 5.2 Hz, 2H), 3.0 (d, *J* = 6.8 Hz, 2H), 2.53 (t, *J* = 5.2 Hz, 2H), 2.38 (t, *J* = 4.8 Hz, 2H); ^{13}C NMR (100 MHz): δ 191.4, 165.3, 134.7, 134.2, 133.1, 129.6, 129.0, 118.6, 61.4, 52.8, 52.4, 45.8, 41.2; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1682, 1643; HRMS (ESI) calcd. for $C_{15}H_{19}N_2O_2$ $(M+H)^+$:259.1447; found 259.1445.

Ethyl 4-(2-oxo-2-phenylacetyl)piperazine-1-carboxylate (3j).

Brown viscous oil (73%); Purified by chromatography (EtOAc/Hexane 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94-7.90 (m, 2H), 7.64-7.60 (m, 1H), 7.48 (t, *J* = 7.6 Hz, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.72 (t, *J* = 5.6 Hz, 2H), 3.58-3.56 (m, 2H), 3.46-3.43 (m, 2H), 3.32-3.29 (m, 2H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 191.0, 165.5, 155.1, 134.9, 132.9, 129.6, 129.0, 61.8, 45.6 (2C), 41.0 (2C), 14.5; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1732, 1697, 1645; HRMS (ESI) calcd. for $C_{15}H_{19}N_2O_4$ $(M+H)^+$:291.1345; found 291.1350.

***N*-Hexyl-2-oxo-2-phenylacetamide (4a)**.[8d]

Pale yellow viscous oil (64%); Purified by chromatography (EtOAc/Hexane 35%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8.0

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Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.12 (brs, 1H), 3.34 (q, *J* = 7.2 Hz, 2H), 1.59-1.52 (m, 2H), 1.36-1.22 (m, 6H), 0.85 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz): δ 187.9, 161.7, 134.2, 133.3, 131.1, 128.3, 39.4, 31.3, 29.2, 26.5, 22.4, 13.9; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1686, 1670, 1521; HRMS (ESI) calcd. for $C_{14}H_{20}NO_2$ (M+H)$^+$:234.1494; found 234.1508.

***N*-Hexylbenzamide (4a')**.[26]

Off-white solid (4%); Purified by chromatography (EtOAc/Hexane 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 7.2 Hz, 2H), 7.46-7.42 (m, 2H), 7.37 (t, *J* = 7.2 Hz, 2H), 6.23 (brs, 1H), 3.40 (q, *J* = 6.4 Hz, 2H), 1.60-1.37 (m, 2H), 1.36-1.22 (m, 6H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz): δ 167.5, 134.8, 131.1, 128.4, 126.8, 40.0, 31.4, 29.6, 22.5, 13.9.

***N*-Isopropyl-2-oxo-2-phenylacetamide (4b)**.[15]

Off-white solid (67%); mp 77-78^{o}C; Purified by chromatography (EtOAc/Hexane 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, *J* = 7.6 Hz, 2H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 6.90 (brs, 1H), 4.19-4.07 (m, 1H), 1.23 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz): δ 188.0, 160.9, 134.2, 133.4, 131.1, 128.4, 41.7, 22.4; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1682, 1597; HRMS (ESI) calcd. for $C_{11}H_{14}NO_2$ (M+H)$^+$:192.1025; found 192.1030.

***N*-(3-(1H-Imidazol-1-yl)propyl)-2-oxo-2-phenylacetamide (4c).**

Brown viscous oil (62%); Purified by chromatography (EtOAc/Hexane 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28-8.26 (m, 2H), 7.62-7.57 (m, 2H), 7.49 (brs, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.03 (s, 1H), 6.94 (s, 1H), 4.02 (t, *J* = 6.8 Hz, 2H), 3.39 (q, *J* = 6.8 Hz, 2H), 2.12-2.06 (m, 2H); ^{13}C NMR (100 MHz): δ 187.5, 162.3, 137.1, 134.5, 133.1, 131.1, 129.3, 128.5, 118.8, 44.5, 36.5, 30.8; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1688, 1671; HRMS (ESI) calcd. for $C_{14}H_{16}N_3O_2$ (M+H)$^+$:258.1243; found 258.1258.

***N*-(tert-Butyl)-2-oxo-2-phenylacetamide (4d)**.[27]

Pale yellow viscous oil (56%); Purified by chromatography (EtOAc/Hexane 20%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.0 Hz, 2H), 7.58 (t, *J* = 7.2 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 2H), 6.90 (brs, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz): δ 188.6, 161.1, 134.1, 133.4, 131.2, 128.3, 51.6, 28.4; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1670, 1516; HRMS (ESI) calcd. for $C_{12}H_{16}NO_2$ (M+H)$^+$:206.1181; found 206.1198.

***N,N*-Diethyl-2-oxo-2-phenylacetamide (4e)**.[22]

Pale yellow viscous oil (60%); Purified by chromatography (EtOAc/Hexane 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 7.2 Hz, 2H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 3.53 (q, *J* = 7.2 Hz, 2H), 3.21 (q, *J* = 7.2 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 191.5, 166.7, 134.5, 133.3, 129.5, 128.9, 42.0, 38.8, 14.0, 12.8; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1681, 1637; HRMS (ESI) calcd. for $C_{12}H_{16}NO_2$ (M+H)$^+$:206.1181; found 206.1191.

***N,N*-Dibutyl-2-oxo-2-phenylacetamide (4f)**.[22]

Pale yellow viscous oil; (56%); Purified by chromatography (EtOAc/Hexane 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-7.89 (m, 2H), 7.62-7.58 (m, 1H), 7.49-7.45 (m, 2H), 3.46 (t, *J* = 7.6 Hz, 2H), 3.11 (t, *J* = 7.6 Hz, 2 H), 1.67-1.60 (m, 2H), 1.54-1.47 (m, 3H), 1.41-1.34 (m, 2H), 1.20 (t, *J* = 7.6 Hz, 2H), 1.18-1.12 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H), 0.78(t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz): δ 191.6, 167.0, 134.4, 133.3, 129.6, 128.9, 47.4, 44.0, 30.6, 29.4, 20.2, 19.7, 13.8, 13.5; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1680, 1637; HRMS (ESI) calcd. for $C_{16}H_{24}NO_2$ (M+H)$^+$:262.1807; found 262.1811.

***N*-Benzyl-2-oxo-2-phenylacetamide (4h)**.[8h]

Orange solid (61%); mp 91-92^{o}C; Purified by chromatography (EtOAc/Hexane 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63-7.59 (m, 1H), 7.48-7.44 (m, 2H), 7.40 (brs, 1H), 7.39-7.28 (m, 5H), 8.35-8.33 (m, 2H), 4.55 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (100 MHz): δ 187.5, 161.5, 137.1, 134.4, 133.3, 131.2, 128.8, 128.5, 127.9, 127.8, 43.5; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1678; HRMS (ESI) calcd. for $C_{15}H_{14}NO_2$ (M+H)$^+$:240.1025; found 240.1029.

1-(4-Methoxyphenyl)-2-morpholinoethane-1,2-dione (5a).[28]

Brown solid (74%); mp 112-113^{o}C; Purified by chromatography (EtOAc/Hexane 35%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88(d, *J* = 9.2 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H), 3.73 (brs, 4H), 3.60 (t, *J* = 4.8 Hz, 2H), 3.33 (t, *J* = 4.8 Hz, 2H); ^{13}C NMR (100 MHz): δ 189.7, 165.7, 164.9, 132.0, 126.0, 114.3, 66.7, 66.6, 55.6, 55.5, 46.2, 41.4; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1688, 1644; HRMS (ESI) calcd. for $C_{13}H_{16}NO_4$ (M+H)$^+$:250.1079; found 250.1091.

1-(4-Methoxyphenyl)-2-(pyrrolidin-1-yl)ethane-1,2-dione (5b).[29]

Pale yellow viscous oil (72%); Purified by chromatography (EtOAc/Hexane 35%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.85 (s, 3H), 3.60 (t, *J* = 6.8 Hz, 2H), 3.38 (t, *J* = 6.4 Hz, 2H), 1.93-1.87 (m, 4H); ^{13}C NMR (100 MHz): δ 190.2, 165.2, 164.7, 132.3, 125.9, 114.2, 55.6, 46.7, 45.1, 25.8, 24.0; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1672, 1636; HRMS (ESI) calcd. for $C_{13}H_{16}NO_3$ (M+H)$^+$:234.1130; found 234.1149.

1-(4-Bromophenyl)-2-morpholinoethane-1,2-dione (5c).[13c]

Off white solid; (67%); mp 135-136^{o}C; Purified by chromatography (EtOAc/Hexane 35%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 3.75 (s, 3H), 3.62 (t, *J* = 4.4 Hz, 2H), 3.34 (t, *J* = 4.4 Hz, 2H); ^{13}C NMR (100 MHz): δ 189.8, 164.8, 132.4, 131.8, 131.0, 130.4, 66.7, 66.6, 46.2, 41.6; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1683, 1648; HRMS (ESI) calcd. for $C_{12}H_{13}BrNO_3$ (M+H)$^+$: 298.0079; found 298.0067.

1-Morpholino-2-(thiophen-2-yl)ethane-1,2-dione (5d).[28]

Brown viscous oil (63%); Purified by chromatography (EtOAc/Hexane 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77-7.75 (m, 2H), 7.13 (t, *J* = 4.0 Hz, 1H), 3.70-3.69 (m, 4H), 3.60 (t, *J* = 4.8 Hz, 2H), 3.42 (t, *J* = 4.8 Hz, 2H); ^{13}C NMR (100 MHz): δ 182.7, 164.2, 140.1, 136.7, 136.2, 128.6, 66.6, 66.5, 46.3, 41.8; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1729, 1656; HRMS (ESI) calcd. for $C_{10}H_{12}NO_3S$ (M+H)$^+$:226.0538; found 226.0550.

1-(Piperidin-1-yl)-2-(thiophen-2-yl)ethane-1,2-dione (5e).[8h]

Brown solid (60%); mp 115-116^{o}C; Purified by chromatography (EtOAc/Hexane 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.64 (t, *J* = 5.2 Hz, 2H), 3.34 (t, *J* = 5.2Hz, 2H), 1.69-1.65 (m, 5H), 1.56-1.53 (m, 2H); ^{13}C NMR (100 MHz): δ 184.1, 164.7, 140.8, 136.4, 136.0, 128.8, 47.4, 42.7, 26.4, 25.6, 24.5; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1643; HRMS (ESI) calcd. for $C_{11}H_{14}NO_2S$ (M+H)$^+$:224.0745; found 224.0740.

***tert*-Butyl (2-(2-morpholino-2-oxoacetyl)phenyl)carbamate (5f)**.

Brown viscous Oil (58%); Purified by chromatography (EtOAc/Hexane 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.5 (brs, 1H),

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8.50 (dd, *J* = 8.6, 1.2 Hz, 1H), 7.61-7.53 (m, 2H), 7.04-6.99 (m, 1H), 3.74 (t, *J* = 1.9 Hz, 4H), 3.62-3.60 (m, 2H), 3.33-3.30 (m, 2H), 1.50 (d, *J* = 2.6 Hz, 9 H); ^{13}C NMR (100 MHz): δ 194.7, 164.7, 152.6, 143.4, 136.8, 133.4, 121.4, 119.1, 117.3, 81.1, 66.6, 46.3, 41.6, 28.2; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1731, 1651, 1607; HRMS (ESI) calcd. for $C_{17}H_{23}N_2O_5$ $(M+H)^+$:335.1607; found 335.1639.

1-(3-ethoxyphenyl)-2-morpholinoethane-1,2-dione (5g).

Pale yellow viscous Oil (68%); Purified by chromatography (EtOAc/Hexane 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46-7.43 (m, 2H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.16-7.13 (m, 1H), 4.05 (q, *J* = 6.8 Hz, 2H), 3.756 (brs, 4H), 3.61 (t, *J* = 5.2 Hz, 2H), 3.33 (t, *J* = 4.8 Hz, 2H), 1.40 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz): δ 191.1, 165.4, 159.5, 134.3, 130.0, 122.5, 122.1, 113.5, 66.7, 66.6, 63.8, 46.2, 41.6, 14.6; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1682, 1646; HRMS (ESI) calcd. for $C_{14}H_{18}NO_4$ $(M+H)^+$:264.1236; found 264.1259.

1-(4-ethylphenyl)-2-morpholinoethane-1,2-dione (5h).[30]

Pale yellow viscous Oil (33%); Purified by chromatography (EtOAc/Hexane 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.75 (brs, H), 3.61 (t, *J* = 4.8 Hz, 2H), 3.34 (t, *J* = 4.8 Hz, 2H), 2.70 (q, *J* = 7.6 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz): δ 190.8, 165.6, 152.3, 130.8, 129.8, 128.6, 66.7, 66.6, 46.2, 41.5, 29.1, 14.9; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1677, 1646; HRMS (ESI) calcd. for $C_{14}H_{18}NO_3$ $(M+H)^+$:248.1287; found 248.1290.

1-Morpholino-2-(naphthalen-2-yl)ethane-1,2-dione (5i).[8c]

Brown viscous Oil (71%); Purified by chromatography (EtOAc/Hexane 30%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (s, 1H), 8.01-7.91 (m, 3H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.65-7.61 (m, 1H), 7.58-7.54 (m, 1H), 3.82 (brs, 4H), 3.64 (t, *J* = 4.4 Hz, 2H), 3.39 (t, *J* = 4.4 Hz, 2H): ^{13}C NMR (100 MHz): δ 191.2, 165.5, 136.4, 133.0, 132.4, 130.4, 129.8, 129.5, 129.1, 127.9, 127.2, 123.5, 66.7, 66.6, 46.3, 41.7; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1674, 1645; HRMS (ESI) calcd. for $C_{16}H_{16}NO_3$ $(M+H)^+$:270.1130; found 270.1151.

1-(4-Benzoylpiperazin-1-yl)-2-(naphthalen-2-yl)ethane-1,2-dione (5j).[20]

2-Ethylnaphthalene (1 g, 6.40 mmol),I_2 (81 mg, 0.03 mmol), pyridine (26 mg, 0.03 mmol), TBHP (2.5 mL, 19.20 mmol, 70% aqueous solution) were mixed in a 20 mL sealed tube. The reaction mixture was stirred in an oil bath at 80 ^{o}C for 10 h. After confirming the reaction progress by TLC, the reaction mixture was transferred to a 25 mL round bottomed flask. Then TBHP (2.5 mL, 19.20 mmol, 70% aqueous solution), NaI (288 mg, 1.92 mmol) and a solution of phenyl(piperazin-1-yl)methanone (3 g, 16.00 mmol) in acetonitrile (2.5 mL) were added sequentially and stirred at room temperature for 6 h. The volume of the reaction mixture reduced to half by vacuum and purified by a silica gel column chromatography using hexane/ethyl acetate as eluent (30% to 35%) to give 5j as a pale brown solid. (1.25 g, 54%); mp 140-141^{o}C; Purified by chromatography (EtOAc/Hexane 35%); ^{1}HNMR (400 MHz, $CDCl_3$): δ 8.43 (s, 1H), 8.00-7.91 (m, 3H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 7.2 Hz, 1H), 7.39 (brs, 5H), 3.83-3.69 (m, 4H), 3.42 (brs, 4H); ^{13}C NMR (100 MHz): δ 191.0, 170.7, 165.7, 136.4, 134.8, 133.0, 132.4, 130.3, 130.2, 129.9, 129.6, 129.2, 128.7, 127.9, 127.2, 127.0, 123.5, 46.0, 41.5; IR (KBr, cm^{-1}) $\upsilon_{C=O}$ 1674, 1641; HRMS (ESI) calcd. for $C_{23}H_{21}N_2O_3$ $(M+H)^+$:373.1552; found 373.1558.

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Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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Table 1 Optimization of the one pot oxidative amidation of ethylbenzene *via* phenacyl iodide **2a'**

entry	Conditions for step 1	Conditions for step 2	yields
1	I_2(20 mol%)/TBHP(3eq)/120 °C/1 h	morpholine(2.5 eq)/TBHP(3eq)/rt/12 h	14%
2	I_2(20 mol%)/TBHP(3eq)/120 °C/1 h	piperidine(2.5 eq)/TBHP(3eq)/rt/12 h	trace
3	I_2(20 mol%)/TBHP(3eq)/100 °C/12 h	piperidine(2.5 eq)/TBHP(3eq)/rt/12 h	32%
4	I_2(20 mol%)/TBHP(3eq)/100 °C/12 h/CH_3CN	piperidine(2.5 eq)/TBHP(3eq)/rt/12 h	47%
5	I_2(20 mol%)/TBHP(3eq)/100 °C/12 h/dioxane	piperidine(2.5 eq)/TBHP(3eq)/rt/12 h	40%
6	benzoyl peroxide (20 mol%)/I_2(20 mol%)/TBHP(3eq)/100 °C/12 h/EtOAc	morpholine(2.5 eq)/TBHP(3eq)/rt/12 h	47%
7	AIBN(20 mol%)/ I_2(20 mol%)/TBHP(3eq)/100 °C/12 h/EtOAc	morpholine(2.5 eq)/TBHP(3eq)/rt/12 h	36%
8	I_2(20 mol%)/TBHP(3eq)/70 °C/12 h/250W *hv*	morpholine(2.5 eq)/TBHP(3eq)/rt/12 h	49%
9	I_2(20 mol%)/TBHP(10eq)/120 °C/1 h	morpholine(2.5 eq)/TBHP(3eq)/rt/12 h	45%
10	I_2(20 mol%)/TBHP(3eq)/65 °C/50 h	morpholine(2.5 eq)/TBHP(3eq)/rt/12 h	55%

[a] Reaction conditions: **1a** (1.88 mmol) no solvent used, unless noted; Isolated yields.

Table 2 Optimization of the one pot oxidative amidation of ethylbenzene *via* **2a**

entry	Conditions for step 1	Conditions for step 2	yields
1	I_2(5 mol%)/pyridine (5 mol%)/TBHP(3eq)/80 °C/10 h	morpholine(2.5 eq)/NaI (20 mol%)/TBHP(3eq)/rt/12 h	56%
2	I_2(5 mol%)/pyridine (5 mol%)/TBHP(3eq)/80 °C/10 h	morpholine(2.5 eq)/NaI (30 mol%)/TBHP(3eq)/rt/12 h	72%
3	I_2(5 mol%)/pyridine (5 mol%)/TBHP(3eq)/80 °C/10 h	morpholine(2.5 eq)/I_2 (30 mol%)/TBHP(3eq)/rt/12 h	68%
4	I_2(5 mol%)/pyridine (5 mol%)/TBHP(3eq)/80 °C/10 h	morpholine(2.5 eq)/NaI (60 mol%)/TBHP(3eq)/rt/12 h	75%
5	I_2(5 mol%)/pyridine (5 mol%)/TBHP(3eq)/80 °C/10 h	Et_2NH(2.5 eq)/NaI (40 mol%)/TBHP(3eq)/rt/12 h	31%
6	I_2(5 mol%)/pyridine (5 mol%)/TBHP(3eq)/80 °C/10 h	Et_2NH(2.5 eq)/NaI (40 mol%)/TBHP(3eq)/10 °C/12 h	57%
7	I_2(5 mol%)/pyridine (5 mol%)/TBHP(3eq)/80 °C/10 h	Et_2NH(2.5 eq)/NaI (40 mol%)/TBHP(3eq)/0 °C /12 h	65%
8	I_2(5 mol%)/pyridine (5 mol%)/TBHP(3eq)/80 °C/10 h	Et_2NH(2.5 eq)/NaI (40 mol%)/TBHP(3eq)/- 5 °C/12 h	42%
9	I_2(5 mol%)/pyridine (5 mol%)/TBHP(3eq)/80 °C/10 h	morpholine(2.5 eq)/TBHP(3eq)/rt/12 h	51%

[a] Reaction conditions: **1a** (1.88 mmol) no solvent was used; Isolated yields.