Unveiling the reaction process of the amine in direct amidation of aromatic ketones in H$_2$O

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Supporting information

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1. **Experiments**

1.1 **General methods**

All chemicals were economically available and purchased from Aladdin (Shanghai, China), and were used without any further purifications. All chemicals were of analytical grade. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on a Bruker Avance 400 spectrometer in DMSO or CDCl$_3$ depending on their dissolution. All chemical shifts (δ) were quoted in parts per million (ppm) and reported relative to an internal tetramethylsilane (TMS, δ 0.00) standard. The yield of products was measured with a SHIMADZU HPLC instrument equipped with a Wonda Sil C18-WR 5µm column. HPLC-MS spectra were recorded on a Shimadzu liquid chromatography/mass spectrometry ion-trap time-of-flight (LCMS-IT-TOF) instrument.

X-ray diffraction (XRD) patterns was collected from 5° to 80° with a step of 0.02 on a Bruker D 8 Advance diffractometer with Cu Kα radiation ($\lambda = 1.5418$ Å) and a Lynxeye one-dimensional detector. Photos were shoot by smart phone.

1.2 **General procedures for the synthesis of α-ketoamides.**

A mixture of Aryl methyl ketone 0.1mmol, amine or aqueous ammonia 0.2mmol, iodine 0.1mmol 25mg was charged in a 25ml double mouth round-bottom flask filled with 1 ml water, air was flushed into a balloon and sealed along with the flask, stirred at room temperature for 24 hours. Then, the reaction mixture was extracted with ethyl acetate 3 times, each time with 50ml. The organic layers were separated and combined together, and washed with brine solution, dried over anhydrous MgSO$_4$ and filtrated with a pad of cotton. Ethyl acetate was removed under vacuum, the residues were collected and purified by chromatography to afford pure products.

1.3 **Optimization of reaction conditions**

Initial evaluations for suitable reaction conditions were performed at millilitre scale employing acetophenone (1a) and morpholine (1b) as the model substrates. Reaction parameters, such as solvent (H$_2$O, MeOH, MeCN, Hexane,), catalyst ((Diacetoxyiodo)benzene, HI, I$_2$, NIS, NaI and NaIO$_3$), balloon filling (air, and O$_2$, N$_2$) and temperatures (rt., 35°C, and 50°C, 75°C), reaction time, the amount of iodine used in the reaction, all of this were investigated and the results were summarized in Table S1.
**Table S1.** Optimization of reaction conditions:

| Entry | Catalysts | Solvent | pH | Temperature (°C) | Time (hour) | I₂ (equiv.) | Gas | Yield (%) |
|-------|------------|---------|----|-----------------|-------------|-------------|-----|-----------|
| 1     | I₂         | MeCN    | -- | rt.             | 24          | 1.0         | Air | 17        |
| 2     | I₂         | MeOH    | -- | rt.             | 24          | 1.0         | Air | 61        |
| 3     | I₂         | n-Hexane| -- | rt.             | 24          | 1.0         | Air | 7         |
| 4     | HI         | H₂O     | 7.0| rt.             | 24          | 1.0         | Air | n.d.      |
| 5     | NaI        | H₂O     | 7.0| rt.             | 24          | 1.0         | Air | n.d.      |
| 6     | NaIO       | H₂O     | 7.0| rt.             | 24          | 1.0         | Air | n.d.      |
| 7     | NaIO₃      | H₂O     | 7.0| rt.             | 24          | 1.0         | Air | n.d.      |
| 8     | NIS        | H₂O     | 7.0| rt.             | 24          | 1.0         | Air | 17        |
| 9     | (Diacetoxyiido)benzene | H₂O | 7.0| rt.             | 24          | 1.0         | Air | n.d.      |
| 10    | CuI        | H₂O     | 7.0| rt.             | 24          | 1.0         | Air | n.d.      |
| 11    | I₂         | H₂O     | 3.0| rt.             | 24          | 1.0         | Air | 71        |
| 12    | I₂         | H₂O     | 5.0| rt.             | 30          | 1.0         | Air | 91        |
| 13    | I₂         | H₂O     | 5.0| rt.             | 24          | 0.5         | Air | 57        |
| 14    | I₂         | H₂O     | 5.0| rt.             | 24          | 0.8         | Air | 86        |
| 15    | I₂         | H₂O     | 5.0| rt.             | 24          | 1.0         | Air | 91        |
| 16    | I₂         | H₂O     | 5.0| rt.             | 24          | 1.2         | Air | 91        |
| 17    | I₂         | H₂O     | 5.0| rt.             | 24          | 1.5         | Air | 89        |
| 18    | I₂         | H₂O     | 5.0| rt.             | 18          | 1.0         | Air | 87        |
| 19    | I₂         | H₂O     | 5.0| rt.             | 12          | 1.0         | Air | 79        |
| 20    | I₂         | H₂O     | 5.0| rt.             | 6           | 1.0         | Air | 61        |
| 21    | I₂         | H₂O     | 5.0| 35              | 24          | 1.0         | Air | 75        |
| 22    | I₂         | H₂O     | 5.0| 50              | 24          | 1.0         | Air | 44        |
| 23    | I₂         | H₂O     | 5.0| 75              | 24          | 1.0         | Air | 15        |
| 24    | I₂         | H₂O     | 7.0| rt.             | 24          | 1.0         | Air | 81        |
| 25    | I₂         | H₂O     | 9.0| rt.             | 24          | 1.0         | Air | 87        |
| 26    | I₂         | H₂O     | 5.0| rt.             | 24          | 1.0         | O₂  | 91        |
| 27    | I₂         | H₂O     | 5.0| rt.             | 24          | 1.0         | N₂  | n.d.      |

*Conditions: 1a (0.1 mmol), 1b (0.2 mmol), I₂ (100 mol%) and water (1 ml), air balloon (1 atm), reaction time 24h, rt., room temperature, n.d., not found. Yields was determined by HPLC analysis, and the yields in brackets were isolated ones.*
2. I₂ and I⁻ Detection

The reaction solution was carried out for 24h, then separate with ethyl acetate by separating funnel. We detected I₂ by added murexide indicator liquid to the upper layer solution. Added silver nitrate to download water phase, we gain some sediment, and the color of solution changed, it's XRD peak matching well with standard sample silver iodide and standard pdf card-PDF#09-0374.

![Figure S1. I₂ detection with murexide indicator liquid](image1)

![Figure S2. I₂ detection with Silver nitrate](image2)
3. Profiles of pH Variation with Time and Yield Variation with Substrates Ratio and pH

We would get the best product yield at pH = 5.0 solvent before added substrates (we thought the solvent pH would be at 5 all times during the reaction before we made the test). We investigated the reaction to explore the reason, after we added all substrate to reaction system, we tested the reaction solvent pH, we found solvent pH raised to 9.5. When the reaction for 24 hours, the solvent pH come down to 4.5. Then we investigated 3 controls experiment for exploring the reason, we find when we use NaOH solvent to adjust reaction solvent pH floating above 7, using lower amine would get the same product yield. The result showed us the reaction system would release H\(^+\) to solvent, then H\(^+\) influenced the amine for continuing reaction.

In the influence of the amount of NaOH added on the reaction yield, we tested more NaOH, and the junction yield decreased. When using the 0.2M Phosphate buffer solution, we also found that the buffer solution with pH = 7 was good As a result yield 95%, when a buffer solution with a higher pH value was selected, the yield also decreases. This result match well with pH value test of Optimization of reaction condition. We believed that there was a reaction equilibrium between OH\(^-\) and iodine molecules. Too much OH\(^-\) would reduce the concentration of iodine in the reaction system, making the reaction equilibrium unfavorable the amidation reaction proceeds.
Figure S4. Profiles of pH with reaction time (h) and reaction yields with substrate ratio 1b/1a (mmol/mmol)
4. mechanism of I₂ promoted amidation of aromatic ketones

[Diagram showing the mechanism of iodine-promoted amidation of aromatic ketones, including structures for 1a, 1b, P, A1, A2, A3, A4, and the reaction with water and I₇H⁺.]
Scheme 2. Insights of the mechanism of I$_2$ promoted amidation of aromatic ketones (take acetophenone and morpholine for the example).

**Step A1-A2:** I$_2$ act as coupling agent$^{5,6}$

**Step I2-I3:** I$_2$ act as oxidation agent$^7$

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**A1**

**A2**
In our control experiments, MS Scan 100-600 m/z. The intermediate species (A1, A2, A3, A4 (A1 calculated m/z for [M+H]+, C12H15NO, 188.1081, observed, 188.0906); A2 calculated m/z for [M-H]-, C16H22N2O2, 273.1609, observed, 273.1500; and A4 calculated m/z for [M+H]+, C16H22N2O4, 307.1731, observed, 307.1795)). Substrates (a, I2 calculated m/z for [M+H]+, C8H8O, 121.0648, observed 121.0597; I2 calculated m/z for [M+H]+, C12H13NO3, 254.8162, observed 254.8098)). And product (p (p calculated m/z for [M+H]+, C12H13NO3, 220.0969, observed 220.0971)).
[MS Spectrum]
# of Peaks 42
Raw Spectrum [0.940], (scan: [283])
Background Spectrum No Background Spectrum
Base Peak m/z 371.2238 (inten: 183,996)

[MS Spectrum]
# of Peaks 114
Raw Spectrum [7.460→7.853], (scan: [2239→2357])
Background Spectrum No Background Spectrum
Base Peak m/z 220.0971 (inten: 1,631,455)
[MS Spectrum]
# of Peaks  3
Raw Spectrum  [3.767],(scan:[1132])
Background Spectrum  No Background Spectrum
Base Peak  m/z 341.8743 (Inten : 195,416)

[\text{[M+H]}^+]
[MS Spectrum]
# of Peaks  95
Raw Spectrum  [0.787->1.027],(scan:[238->310])
Background Spectrum  No Background Spectrum
Base Peak  m/z 341.8761 (Inten : 1,003,314)
[MS Spectrum]
# of Peaks  98
Raw Spectrum [0.787->1.027].(scan:[237->309])
Background Spectrum  No Background Spectrum
Base Peak   m/z 212.1175 (Inten : 593,876)

[MS Spectrum]
# of Peaks  1
Raw Spectrum [2.493].(scan:[749])
Background Spectrum  No Background Spectrum
Base Peak   m/z 273.1500 (Inten : 19,584)
6. $^1$H NMR and $^{13}$C NMR

6.1 Spectrum Data

1-morpholino-2-phenylethane-1,2-dione (2a).

Yellow oil $^1$H NMR (400 MHz, CDCl$_3$): $\delta=7.90$ (d, $J=7.2$Hz, 2H), $\delta=7.60$ (t, $J=7.5$, 1H), $\delta=7.49$ (t, $J=8.1$Hz, 2H), $\delta=3.75$ (s, 4H), $\delta=3.61$ (t, $J=5.3$Hz, 2H), $\delta=3.34$ (t, $J=5.4$Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta=191.19$, $\delta=165.46$, $\delta=134.95$, $\delta=133.03$, $\delta=129.62$, $\delta=129.11$, $\delta=66.67$, $\delta=66.59$, $\delta=46.23$, $\delta=41.59$.

1-morpholino-2-(4-nitrophenyl)ethane-1,2-dione (2b).

Yellow solid 1H NMR (400 MHz, CDCl$_3$): $\delta=8.37$ (d, $J=8.9$Hz, 2H), $\delta=8.19$-8.16 (m, 2H), $\delta=3.83$ (s, 4H), $\delta=3.72$-3.70 (m, 2H), $\delta=3.44$ (t, $J=5.0$Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta=188.70$, $\delta=164.04$, $\delta=151.19$, $\delta=137.49$, $\delta=130.83$, $\delta=124.16$, $\delta=66.73$, $\delta=66.61$, $\delta=46.35$, $\delta=41.95$. 
**morpholino-2-(p-tolyl)ethane-1,2-dione (2c).**

Yellow solid $^1$H NMR (400 MHz, CDCl$_3$): $\delta=7.90$-$7.88$(m, 2H), $\delta=7.35$(t, $J=7.8$Hz, 2H), $\delta=3.84$-$3.83$(m, 4H), $\delta=3.69$(t, $J=4.8$Hz, 2H), $\delta=3.41$(t, $J=4.6$Hz, 2H), $\delta=2.45$(s, 3H); $^{13}$C NMR(100 MHz, CDCl$_3$): $\delta=190.96$, $\delta=165.74$, $\delta=146.38$, $\delta=130.65$, $\delta=129.89$, $\delta=129.84$, $\delta=66.78$, $\delta=66.72$, $\delta=46.31$, $\delta=41.62$, $\delta=21.98$.

**1-(4-fluorophenyl)-2-morpholinoethane-1,2-dione (2d).**

Yellow solid $^1$H NMR (400 MHz, CDCl$_3$): $\delta=8.06$-$8.02$(m, 2H), $\delta=7.24$(t, $J=7.8$Hz, 2H), $\delta=3.84$-$3.82$(m, 4H), $\delta=3.70$(t, $J=4.6$Hz, 2H), $\delta=3.43$(t, $J=4.6$Hz, 2H); $^{13}$C NMR(100 MHz, CDCl$_3$): $\delta=189.44$, $\delta=168.12$, $\delta=165.55$, $\delta=165.13$, $\delta=132.64$, $\delta=132.55$, $\delta=129.63$, $\delta=129.60$, $\delta=116.62$, $\delta=116.40$, $\delta=66.78$, $\delta=66.68$, $\delta=46.34$, $\delta=41.73$.

**1-(4-chlorophenyl)-2-morpholinoethane-1,2-dione (2e).**

Yellow solid $^1$H NMR(400 MHz, CDCl$_3$): $\delta=7.95$-$7.93$(m, 2H), $\delta=7.54$(t, $J=6.6$Hz, 2H), $\delta=3.84$-$3.82$(m, 4H), $\delta=3.70$(t, $J=4.8$Hz, 2H), $\delta=3.42$(t, $J=4.8$Hz, 2H); $^{13}$C NMR(100 MHz, CDCl$_3$): $\delta=189.75$, $\delta=164.94$, $\delta=141.65$, $\delta=131.48$, $\delta=131.08$, $\delta=129.55$, $\delta=66.77$, $\delta=66.67$, $\delta=46.32$, $\delta=41.74$.

**1-(4-bromophenyl)-2-morpholinoethane-1,2-dione (2f).**

Yellow solid $^1$H NMR(400 MHz, CDCl$_3$): $\delta=7.83$(d, $J=8.8$Hz, 2H), $\delta=7.66$(d, $J=8.6$Hz, 2H), $\delta=3.78$(s, 4H), $\delta=3.65$(t, $J=5.0$Hz, 2H), $\delta=3.38$(t, $J=5.0$Hz, 2H); $^{13}$C NMR(100 MHz, CDCl$_3$): $\delta=189.91$, $\delta=164.86$, $\delta=132.50$, $\delta=131.90$, $\delta=131.06$, $\delta=130.45$, $\delta=66.72$, $\delta=66.62$, $\delta=46.28$, $\delta=41.72$.

**1-(3-methoxyphenyl)-2-morpholinoethane-1,2-dione (2g).**
1-(3-bromophenyl)-2-morpholinoethane-1,2-dione (2h).

Yellow oil ¹H NMR(400 MHz, CDCl₃): δ=8.08(s, 1H), δ=7.84(d, J=8.0Hz, 1H), δ=7.39(t, J=8.0Hz, 1H), δ=3.84-3.80(m, 4H), δ=3.55-3.50(t, J=4.2Hz, 2H), δ=2.51(s, 3H); ¹³C NMR(100 MHz, CDCl₃): δ=190.44, δ=164.86, δ=135.50, δ=134.30, δ=134.06, δ=127.89, δ=121.50, δ=126.32, δ=126.26, δ=46.13, δ=42.07.

1-morpholino-2-(o-tolyl)ethane-1,2-dione (2j).

Yellow oil ¹H NMR(400 MHz, CDCl₃): δ=7.81(d, J=7.0Hz, 1H), δ=7.67(d, J=7.0Hz, 1H), δ=7.51-7.43(m, 2H), δ=3.61(s, 4H), δ=3.50(t, J=4.2Hz, 2H), δ=2.51(s, 3H); ¹³C NMR(100 MHz, CDCl₃): δ=193.13, δ=166.04, δ=141.29, δ=133.82, δ=132.59, δ=131.44, δ=126.21, δ=66.48, δ=66.43, δ=46.13, δ=41.47, δ=21.67.

1-morpholino-2-(thiophen-2-yl)ethane-1,2-dione (2k).

Yellow oil ¹H NMR(400 MHz, CDCl₃): δ=7.83-7.76(m, 2H), δ=7.24-7.16(m, 1H), δ=3.82-3.79(m, 4H),
δ=3.71(t, J=5.0Hz, 2H), δ=3.52(t, J=5.0Hz, 2H); $^{13}$C NMR(100 MHz, CDCl₃): δ=182.88, δ=164.40, δ=140.28, δ=136.92, δ=128.83, δ=66.85, δ=66.67, δ=46.50, δ=42.01, δ=27.76.

1-(furan-2-yl)-2-morphinoethane-1,2-dione (2l).

![Image](image1)

Yellow oil $^1$H NMR(400 MHz, CDCl₃): δ=7.74(s, 1H), δ=7.42-7.39(m, 1H), δ=6.65-6.62(m, 1H), δ=3.78(d, J=3.0Hz, 2H), δ=3.75(d, J=3.6Hz, 2H), δ=3.68(t, J=4.2Hz, 2H), δ=3.48(t, J=4.2Hz, 2H); $^{13}$C NMR(100 MHz, CDCl₃): δ=177.81, δ=163.89, δ=150.14, δ=149.00, δ=122.64, δ=113.01, δ=66.75, δ=66.55, δ=46.34, δ=41.92.

1-phenyl-2-(piperidin-1-yl)ethane-1,2-dione (2m).

![Image](image2)

Yellow oil $^1$H NMR(400 MHz, CDCl₃): δ=7.95(d, J=8.6Hz, 2H), δ=7.66-7.62(m, 1H), δ=7.52(t, J=7.8Hz, 2H), δ=3.71(s, 2H), δ=3.29(t, J=5.4Hz, 2H), δ=1.70(t, J=3.0Hz, 4H), δ=1.55(d, J=5.0Hz, 2H); $^{13}$C NMR(100 MHz, CDCl₃): δ=191.97, δ=165.47, δ=134.66, δ=133.29, δ=129.55, δ=129.01, δ=47.03, δ=42.15, δ=26.19, δ=25.45, δ=24.36.

1-phenyl-2-(pyrrolidin-1-yl)ethane-1,2-dione (2n).

Yellow oil $^1$H NMR(400 MHz, CDCl₃): δ=8.00(d, J=7.8Hz, 2H), δ=7.65(t, J=7.8Hz, 1H), δ=7.52(t, J=7.8Hz, 2H), δ=3.67(t, J=6.2Hz, 2H), δ=3.43(t, J=6.2Hz, 2H), δ=1.99-1.94(m, 4H); $^{13}$C NMR(100 MHz, CDCl₃): δ=191.59, δ=164.96, δ=134.62, δ=132.93, δ=129.87, δ=128.94, δ=46.69, δ=45.26, δ=25.91, δ=24.02.

$N,N$-dimethyl-2-oxo-2-phenylacetamide (2o).

Yellow oil $^1$H NMR(400 MHz, CDCl₃): δ=8.00(d, J=7.8Hz, 2H), δ=7.65(t, J=7.8Hz, 1H), δ=7.52(t, J=7.8Hz, 2H), δ=3.67(t, J=6.2Hz, 2H), δ=3.43(t, J=6.2Hz, 2H), δ=1.99-1.94(m, 4H); $^{13}$C NMR(100 MHz, CDCl₃): δ=191.87, δ=167.09, δ=134.78, δ=133.05, δ=129.67, δ=129.06, δ=37.08, δ=34.01.
**N,N-diethyl-2-oxo-2-phenylacetamide (2p).**

![Chemical structure of N,N-diethyl-2-oxo-2-phenylacetamide](image)

Yellow oil $^1$H NMR(400 MHz, CDCl$_3$): $\delta=7.97$ (d, $J=7.6$Hz, 2H), $\delta=7.67$ (t, $J=7.6$Hz, 1H), $\delta=7.54$ (t, $J=7.4$Hz, 2H), $\delta=3.60$ (q, $J=7.4$Hz, 2H), $\delta=3.28$ (t, $J=7.6$Hz, 2H); $^1$C NMR(100 MHz, CDCl$_3$): $\delta=191.61$, $\delta=166.76$, $\delta=134.58$, $\delta=133.28$, $\delta=129.63$, $\delta=128.97$, $\delta=42.13$, $\delta=38.82$, $\delta=14.12$, $\delta=12.86$.

**1-oxo-2-phenyl-N,N-dipropylacetamide (2q).**

Yellow oil $^1$H NMR(400 MHz, CDCl$_3$): $\delta=7.91$ (d, $J=8.4$Hz, 2H), $\delta=7.60$ (t, $J=7.4$Hz, 1H), $\delta=7.47$ (t, $J=7.4$Hz, 2H), $\delta=3.47-3.43$ (m, 2H), $\delta=3.10$ (t, $J=7.4$Hz, 2H), $\delta=1.73-1.67$ (m, 2H), $\delta=0.97$ (t, $J=7.4$Hz, 3H), $\delta=0.75$ (t, $J=7.4$Hz, 3H); $^1$C NMR(100 MHz, CDCl$_3$): $\delta=191.59$, $\delta=167.21$, $\delta=134.56$, $\delta=133.29$, $\delta=129.55$, $\delta=128.95$, $\delta=49.28$, $\delta=45.81$, $\delta=21.77$, $\delta=20.60$, $\delta=11.39$, $\delta=10.96$.

**1-(4-methylpiperidin-1-yl)-2-phenylethane-1,2-dione (2r).**

Yellow oil $^1$H NMR(400 MHz, CDCl$_3$): $\delta=7.95$ (d, $J=7.4$Hz, 2H), $\delta=7.64$ (t, $J=7.4$Hz, 1H), $\delta=7.52$ (t, $J=7.4$Hz, 2H), $\delta=4.64$ (d, $J=8.4$Hz, 1H), $\delta=3.53$ (d, $J=8.6$Hz, 1H), $\delta=3.07$ (t, $J=9.0$Hz, 1H), $\delta=2.81-2.78$ (m, 1H), $\delta=1.82-1.62$ (m, 3H), $\delta=1.27-1.13$ (m, 2H), $\delta=0.97$ (d, $J=6.0$Hz, 3H); $^1$C NMR(100 MHz, CDCl$_3$): $\delta=191.98$, $\delta=165.46$, $\delta=134.70$, $\delta=133.25$, $\delta=129.58$, $\delta=129.04$, $\delta=46.36$, $\delta=41.55$, $\delta=34.30$, $\delta=33.61$, $\delta=31.06$, $\delta=21.65$.

**1-(piperidin-1-yl)-2-(p-tolyl)ethane-1,2-dione (2s).**

Yellow oil $^1$H NMR(400 MHz, CDCl$_3$): $\delta=7.82$ (d, $J=7.8$Hz, 2H), $\delta=7.29$ (d, $J=7.8$Hz, 2H), $\delta=3.68$ (s, 2H), $\delta=3.26$ (t, $J=5.4$Hz, 2H), $\delta=2.41$ (s, 3H), $\delta=1.67$ (s, 4H), $\delta=1.53$ (d, $J=5.4$Hz, 2H); $^1$C NMR(100 MHz, CDCl$_3$): $\delta=191.74$, $\delta=165.66$, $\delta=145.92$, $\delta=129.74$, $\delta=129.65$, $\delta=47.03$, $\delta=42.08$, $\delta=26.20$, $\delta=25.46$, $\delta=24.37$, $\delta=21.89$. 
1-(pyrrolidin-1-yl)-2-(p-tolyl)ethane-1,2-dione (2t).

Yellow solid ¹H NMR(400 MHz, CDCl₃): δ=7.82(d, J=7.4Hz, 2H), δ=7.24(d, J=8.0Hz, 2H), δ=3.58(t, J=6.6Hz, 2H), δ=3.34(t, J=6.6Hz, 2H), δ=2.36(s, 3H), δ=1.88-1.85(m, 4H); ³¹C NMR(100 MHz, CDCl₃): δ=191.36, δ=165.19, δ=145.82, δ=130.43, δ=129.91, δ=129.65, δ=46.62, δ=45.14, δ=26.85, δ=21.84.

1-(4-nitrophenyl)-2-(piperidin-1-yl)ethane-1,2-dione (2u).

Yellow solid ¹H NMR(400 MHz, CDCl₃): δ=8.37(d, J=8.6Hz, 2H), δ=8.16(d, J=8.6Hz, 2H), δ=3.75(s, 2H), δ=3.34(t, J=5.4Hz, 2H), δ=1.75(d, J=2.6Hz, 4H), δ=1.61(6s, 2H); ³¹C NMR(100 MHz, CDCl₃): δ=189.52, δ=164.14, δ=151.11, δ=137.76, δ=130.66, δ=124.13, δ=47.13, δ=42.52, δ=26.33, δ=25.46, δ=24.32.

1-(4-nitrophenyl)-2-(pyrrolidin-1-yl)ethane-1,2-dione (2v).

Yellow solid ¹H NMR(400 MHz, CDCl₃): δ=8.35(d, J=8.6Hz, 2H), δ=8.23(d, J=8.6Hz, 2H), δ=3.85(d, J=8.6Hz, 2H), δ=3.52(t, J=5.4Hz, 2H), δ=2.01(s, 4H); ³¹C NMR(100 MHz, CDCl₃): δ=189.04, δ=163.19, δ=151.00, δ=137.67, δ=131.12, δ=123.96, δ=46.97, δ=45.73, δ=26.02, δ=23.96.

1-(4-bromophenyl)-2-(piperidin-1-yl)ethane-1,2-dione (2w).

Yellow oil ¹H NMR(400 MHz, CDCl₃): δ=7.80(d, J=8.6Hz, 2H), δ=7.65(d, J=8.6Hz, 2H), δ=3.70-3.68(m, 2H), δ=3.27(t, J=5.6Hz, 2H), δ=1.69(t, J=3.0Hz, 4H), δ=1.55-1.54(m, 2H); ³¹C NMR(100 MHz, CDCl₃): δ=190.72, δ=164.90, δ=132.40, δ=131.40, δ=130.95, δ=130.11, δ=47.06, δ=42.27, δ=26.26, δ=25.45, δ=24.34.

1-(4-bromophenyl)-2-(pyrrolidin-1-yl)ethane-1,2-dione (2x).
Yellow oil $^1$H NMR(400 MHz, CDCl$_3$): $\delta=7.85$ (d, $J=8.6$ Hz, 2H), $\delta=7.62$ (d, $J=8.6$ Hz, 2H), $\delta=3.62$ (t, $J=6.6$ Hz, 2H), $\delta=3.40$ (t, $J=6.6$ Hz, 2H), $\delta=1.93$ (m, 4H); $^{13}$C NMR(100 MHz, CDCl$_3$): $\delta=190.29$, $\delta=164.21$, $\delta=132.28$, $\delta=131.79$, $\delta=131.33$, $\delta=130.04$, $\delta=46.75$, $\delta=45.38$, $\delta=25.92$, $\delta=23.97$.

1-(piperidin-1-yl)-2-(m-tolyl)ethane-1,2-dione (2y).

![](image)

Yellow solid $^1$H NMR(400 MHz, CDCl$_3$): $\delta=7.52$ (d, $J=8.8$ Hz, 2H), $\delta=7.22$ (d, $J=7.4$ Hz, 1H), $\delta=7.17$ (t, $J=7.6$ Hz, 1H), $\delta=3.46$ (s, 2H), $\delta=3.04$ (t, $J=5.6$ Hz, 2H), $\delta=2.17$ (s, 3H), $\delta=1.43$ (s, 4H), $\delta=1.29$ (s, 2H); $^{13}$C NMR(100 MHz, CDCl$_3$): $\delta=191.99$, $\delta=165.32$, $\delta=138.74$, $\delta=135.37$, $\delta=133.102$, $\delta=129.49$, $\delta=128.79$, $\delta=126.61$, $\delta=46.74$, $\delta=41.79$, $\delta=25.99$, $\delta=25.30$, $\delta=24.12$, $\delta=21.00$.

1-(3-bromophenyl)-2-(piperidin-1-yl)ethane-1,2-dione (2z).

![](image)

Yellow oil $^1$H NMR(400 MHz, CDCl$_3$): $\delta=8.10$ (s, 1H), $\delta=7.88$ (d, $J=8.0$ Hz, 1H), $\delta=7.77$ (d, $J=8.0$ Hz, 1H), $\delta=7.41$ (t, $J=7.6$ Hz, 1H), $\delta=3.71$ (s, 2H), $\delta=3.30$ (t, $J=5.8$ Hz, 2H), $\delta=1.71$ (d, $J=2.6$ Hz, 4H), $\delta=1.57$ (s, 2H); $^{13}$C NMR(100 MHz, CDCl$_3$): $\delta=190.33$, $\delta=164.67$, $\delta=137.48$, $\delta=135.09$, $\delta=132.24$, $\delta=130.61$, $\delta=128.25$, $\delta=126.30$, $\delta=47.10$, $\delta=42.33$, $\delta=26.26$, $\delta=25.47$, $\delta=24.37$.

1-(piperidin-1-yl)-2-(o-tolyl)ethane-1,2-dione (2ab).

![](image)

Yellowish solid $^1$H NMR(400 MHz, CDCl$_3$): $\delta=7.63$ (d, $J=7.8$ Hz, 1H), $\delta=7.36$ (t, $J=7.8$ Hz, 1H), $\delta=7.23$-7.18 (m, 2H), $\delta=3.58$ (s, 2H), $\delta=3.19$ (t, $J=5.6$ Hz, 2H), $\delta=2.56$ (s, 3H), $\delta=1.57$ (s, 4H), $\delta=1.44$ (s, 2H); $^{13}$C NMR(100 MHz, CDCl$_3$): $\delta=193.86$, $\delta=166.03$, $\delta=141.18$, $\delta=133.59$, $\delta=132.59$, $\delta=132.53$, $\delta=131.55$, $\delta=126.12$, $\delta=46.89$, $\delta=41.98$, $\delta=25.99$, $\delta=25.33$, $\delta=24.27$, $\delta=21.71$.

N-methyl-2-oxo-2-phenylacetamide (3a).

![](image)

Yellow oil $^1$H NMR(400 MHz, CDCl$_3$): $\delta=8.27$ (d, $J=4.2$ Hz, 2H), $\delta=7.57$ (d, $J=4.2$ Hz, 1H), $\delta=7.43$ (t, $J=4.2$ Hz, 3H), $\delta=2.91$ (d, $J=8.4$ Hz, 3H); $^{13}$C NMR(100 MHz, CDCl$_3$): $\delta=188.02$, $\delta=162.92$, $\delta=134.36$, $\delta=133.27$, $\delta=131.03$, $\delta=128.47$, $\delta=26.00$. 
**N-ethyl-2-oxo-2-phenylacetamide (3b).**

Yellow oil $^1H$ NMR(400 MHz, CDCl$_3$): $\delta=8.22$ (d, $J=4.2$Hz, 2H), $\delta=7.52$ (d, $J=4.2$Hz, 1H), $\delta=7.38$ (t, $J=4.2$Hz, 2H), $\delta=3.36-3.31$ (m, 2H), $\delta=1.15$ (t, $J=4.2$Hz, 3H); $^{13}$C NMR(100 MHz, CDCl$_3$): $\delta=188.31$, $\delta=162.25$, $\delta=134.26$, $\delta=133.33$, $\delta=130.96$, $\delta=128.41$, $\delta=34.31$, $\delta=14.36$.

**2-oxo-2-phenyl-N-propylacetamide (3c).**

Colorless liquid $^1H$ NMR(400 MHz, CDCl$_3$): $\delta=8.26$ (d, $J=3.8$Hz, 2H), $\delta=7.57$ (t, $J=7.0$Hz, 1H), $\delta=7.40-7.48$ (m, 2H), $\delta=3.29-3.34$ (m, 2H), $\delta=1.54-1.63$ (m, 2H), $\delta=0.92$ (t, $J=7.8$Hz, 3H); $^{13}$C NMR(100 MHz, CDCl$_3$): $\delta=188.30$, $\delta=162.36$, $\delta=134.25$, $\delta=133.30$, $\delta=130.95$, $\delta=128.40$, $\delta=41.05$, $\delta=22.49$, $\delta=11.33$.

**N-cyclohexyl-2-oxo-2-phenylacetamide (3d).**

Light yellow solid $^1H$ NMR(400 MHz, DMSO-d$_6$): $\delta=8.85$ (d, $J=3.8$Hz, 1H), $\delta=7.97$ (d, $J=3.4$Hz, 2H), $\delta=7.74-7.70$ (m, 1H), $\delta=7.59$ (t, $J=8.4$Hz, 2H), $\delta=3.77$ (s, 1H), $\delta=1.87-1.13$ (m, 10H); $^{13}$C NMR(100 MHz, DMSO-d$_6$): $\delta=191.18$, $\delta=164.93$, $\delta=134.90$, $\delta=133.47$, $\delta=130.07$, $\delta=129.40$, $\delta=48.20$, $\delta=32.53$, $\delta=25.54$, $\delta=25.00$.

**N-ethyl-2-oxo-2-(p-tolyl)acetamide (3e).**

Yellow solid $^1H$ NMR(400 MHz, CDCl$_3$): $\delta=8.24$ (d, $J=8.4$Hz, 2H), $\delta=7.26$ (d, $J=8.4$Hz, 2H), $\delta=3.46-3.39$ (m, 2H), $\delta=2.41$ (s, 3H), $\delta=1.23$ (t, $J=4.2$Hz, 3H); $^{13}$C NMR(100 MHz, CDCl$_3$): $\delta=187.57$, $\delta=162.14$, $\delta=145.52$, $\delta=131.31$, $\delta=130.89$, $\delta=129.21$, $\delta=34.32$, $\delta=21.32$, $\delta=14.47$.

**3-oxo-N-propyl-2-(p-tolyl)acetamide (3f).**

Yellow solid $^1H$ NMR(400 MHz, CDCl$_3$): $\delta=7.98$ (d, $J=4.2$Hz, 2H), $\delta=7.62$ (s, 1H), $\delta=7.02$ (d, $J=4.2$Hz, 2H),...
δ=3.13(t, J=3.4Hz, 2H), δ=2.17(s, 3H), δ=1.41(d, J=4.2Hz, 2H), δ=0.77-0.74(m, 3H); 13C NMR(100 MHz, CDCl₃): δ=187.84, δ=162.86, δ=145.14, δ=130.91, δ=130.80, δ=128.98, δ=40.89, δ=22.40, δ=21.53, δ=11.19. HRMS m/z(ESI) Calcd for C₁₂H₁₅NO₂ (M+Na)⁺ 228.0995, found 228.0997.

2-(4-fluorophenyl)-2-oxo-N-propylacetamide (3g).

Yellow solid ¹H NMR(400 MHz, CDCl₃): δ=8.37-8.34(m, 2H), δ=7.33(s, 1H), δ=7.10-7.05(m, 2H), δ=3.32-3.27(m, 2H), δ=1.60-1.55(m, 2H), δ=0.92(t, J=5.2Hz, 3H); ¹³C NMR(100 MHz, CDCl₃): δ=186.14, δ=167.76, δ=161.81, δ=134.16, δ=129.85, δ=115.73, δ=41.09, δ=22.50, δ=11.28. HRMS m/z(ESI) Calcd for C₁₁H₁₂NO₂F (M-H)- 208.0779, found 208.0780.

N-benzyl-2-(4-fluorophenyl)-2-oxoacetamide (3h).

Yellow solid ¹H NMR(400 MHz, DMSO-d₆): δ=9.55(t, J=5.4Hz, 1H), δ=8.18-8.14(m, 2H), δ=7.44-7.41(m, 2H), δ=7.38-7.28(m, 5H), δ=4.51(d, J=3.2Hz, 2H); ¹³C NMR(100 MHz, DMSO-d₆): δ=188.89, δ=167.51, δ=164.99, δ=164.90, δ=138.94, δ=133.56, δ=133.46, δ=127.90, δ=127.56, δ=116.70, δ=116.48, δ=42.51. HRMS m/z(ESI) Calcd for C₁₅H₁₂NO₂F(M-H)- 256.0779, found 256.0786.

3-oxo-2-phenylacetamide (3i).

Yellow solid ¹H NMR(400 MHz, CDCl₃): δ=8.24(d, J=3.6Hz, 2H), δ=7.61(t, J=5.4Hz, 1H), δ=7.46(t, J=7.8Hz, 2H), δ=7.21(s, 1H), δ=6.91(s, 1H); ¹³C NMR(100 MHz, CDCl₃): δ=187.92, δ=164.80, δ=134.57, δ=132.96, δ=131.03, δ=128.60.

2-(4-fluorophenyl)-2-oxoacetamide (3j).

Yellow solid ¹H NMR(400 MHz, DMSO-d₆): δ=8.37(s, 1H), δ=8.06-8.12(m, 3H), δ=7.40(t, J=9.2Hz, 2H); ¹³C NMR(100 MHz, DMSO-d₆): δ=189.48, δ=167.41, δ=167.16, δ=164.89, δ=133.39, δ=133.29, δ=130.04, δ=130.02, δ=116.69, δ=116.47.
2-(3-methoxyphenyl)-2-oxoacetamide (3k).

Yellow solid $^1$H NMR(400 MHz, CDCl$_3$): $\delta=7.90$(d, $J=3.6$Hz, 1H), $\delta=7.88$(s, 1H), $\delta=7.74$(t, $J=2.2$Hz, 1H), $\delta=7.18$-$7.16$(m, 2H), $\delta=6.81$(s, 1H), $\delta=3.83$(s, 3H); $^{13}$C NMR(100 MHz, CDCl$_3$): $\delta=187.58$, $\delta=164.73$, $\delta=149.56$, $\delta=134.12$, $\delta=129.62$, $\delta=121.40$, $\delta=114.61$, $\delta=55.45$.

2-oxo-2-(p-tolyl)acetamide (3l).

White solid $^1$H NMR(400 MHz, CDCl$_3$): $\delta=8.21$(d, $J=3.6$Hz, 2H), $\delta=7.28$(d, $J=4.2$Hz, 2H), $\delta=7.09$(s, 1H), $\delta=6.53$(s, 1H), $\delta=2.42$(s, 3H); $^{13}$C NMR(100 MHz, CDCl$_3$): $\delta=187.01$, $\delta=164.68$, $\delta=145.87$, $\delta=131.29$, $\delta=130.49$, $\delta=129.36$, $\delta=21.92$.

2-oxo-2-(m-tolyl)acetamide (3m).

Yellow solid $^1$H NMR(400 MHz, DMSO-d$_6$): $\delta=8.35$(s, 1H), $\delta=8.00$(s, 1H), $\delta=7.80$(d, $J=7.56$(d, $J=8.2$Hz, 1H), $\delta=7.49$(t, $J=8.2$Hz, 1H), $\delta=2.96$(s, 3H); $^{13}$C NMR(100 MHz, DMSO-d$_6$): $\delta=191.48$, $\delta=167.80$, $\delta=135.60$, $\delta=133.30$, $\delta=130.30$, $\delta=129.33$, $\delta=21.28$.

2-oxo-2-(o-tolyl)acetamide (3n).

White solid $^1$H NMR(400 MHz, CDCl$_3$): $\delta=7.87$(d, $J=3.6$Hz, 1H), $\delta=7.45$(t, $J=6.2$Hz, 1H), $\delta=7.28$(t, $J=8.6$Hz, 2H), $\delta=7.08$(s, 1H), $\delta=6.85$(s, 1H), $\delta=2.50$(s, 3H); $^{13}$C NMR(100 MHz, CDCl$_3$): $\delta=191.06$, $\delta=164.96$, $\delta=140.23$, $\delta=132.96$, $\delta=132.43$, $\delta=131.87$, $\delta=131.81$, $\delta=125.49$, $\delta=20.91$.

2-oxo-2-(thiophen-2-yl)acetamide (3o).

Brown solid $^1$H NMR(400 MHz, CDCl$_3$): $\delta=8.36$(d, $J=1.6$Hz, 1H), $\delta=7.82$(d, $J=2.2$Hz, 1H), $\delta=7.46$(s, 1H), $\delta=7.17$(t, $J=3.2$Hz, 1H), $\delta=7.04$(s, 1H); $^{13}$C NMR(100 MHz, CDCl$_3$): $\delta=178.38$, $\delta=163.50$, $\delta=138.68$, $\delta=138.23$, $\delta=136.75$, $\delta=128.40$. 

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2-(furan-2-yl)-2-oxoacetamide (3p).

Yellow solid $^1$H NMR(400 MHz, DMSO-d$_6$): $\delta$=8.25(s, 1H), $\delta$=8.14(d, $J$=2.8Hz, 1H), $\delta$=7.93(s, 1H), $\delta$=7.82(d, $J$=2.8Hz, 1H), $\delta$=6.78-6.77(m, 1H); $^{13}$C NMR(100 MHz, DMSO-d$_6$): $\delta$=176.36, $\delta$=164.42, $\delta$=150.45, $\delta$=149.64, $\delta$=125.30, $\delta$=113.61.

6.2 $^1$H NMR and $^{13}$C NMR Spectrum

1-morpholino-2-phenylethane-1,2-dione (2a)
1-morpholino-2-(4-nitrophenyl)ethane-1,2-dione (2b)
morpholino-2-(p-tolyl)ethane-1,2-dione (2c)
1-(4-fluorophenyl)-2-morpholinoethane-1,2-dione (2d)
1-(4-chlorophenyl)-2-morpholinoethane-1, 2-dione (2e)
1-(4-bromophenyl)-2-morpholinoethane-1,2-dione (2f).
1-(3-methoxyphenyl)-2-morpholinoethane-1,2-dione (2g)
30

1-(3-bromophenyl)-2-morpholinoethane-1,2-dione (2h)
31

1-(2-bromophenyl)-2-morpholinoethane-1,2-dione (2i)

137.72
130.89
123.33
171.52
177.20
77.52
70.88
66.60
46.27
47.74

7.85
7.83
7.66
7.51
7.47
7.43
7.30
3.84
3.81
3.77
3.76
3.76
3.60
3.59

1.68
2.06
2.20
2.14
1-morpholino-2-(o-toly)ethane-1,2-dione (2j)
1-morpholino-2-(thiophen-2-yl)ethane-1,2-dione (2k)
1-(furan-2-yl)-2-morpholinoethane-1,2-dione (2l)
1-phenyl-2-(piperidin-1-yl)ethane-1,2-dione (2m)
1-phenyl-2-(pyrrolidin-1-yl)ethane-1,2-dione (2n)
N,N-dimethyl-2-oxo-2-phenylacetamide (2o)
N,N-diethyl-2-oxo-2-phenylacetamide (2p)
2-oxo-2-phenyl-N,N-dipropylacetamide (2q)
1-(4-methylpiperidin-1-yl)-2-phenylethane-1,2-dione (2r)
1-(piperidin-1-yl)-2-(p-tolyl)ethane-1,2-dione (2s)
1-(pyrrolidin-1-yl)-2-(p-tolyl)ethane-1,2-dione (2t)
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1-(4-nitrophenyl)-2-(piperidin-1-yl)ethane-1,2-dione (2u)
1-(4-nitrophenyl)-2-(pyrrolidin-1-yl)ethane-1,2-dione (2v)
1-(4-bromophenyl)-2-(piperidin-1-yl)ethane-1,2-dione (2w)
1-(4-bromophenyl)-2-(pyrrolidin-1-yl)ethane-1,2-dione (2x)
1-(piperidin-1-yl)-2-(m-tolyl)ethane-1,2-dione (2y)
1-(3-bromophenyl)-2-(piperidin-1-yl)ethane-1,2-dione (2z)
1-(piperidin-1-yl)-2-(o-tolyl)ethane-1,2-dione (2ab)
$N$-methyl-$2$-oxo-$2$-phenylacetamide (3a)
N-ethyl-2-oxo-2-phenylacetamide (3b)
2-oxo-2-phenyl-N-propylacetamide (3c)
N-cyclohexyl-2-oxo-2-phenylacetamide (3d)

\[
\begin{align*}
\text{f1 (ppm)} & \quad 210 & 190 & 170 & 150 & 130 & 110 & 90 & 70 & 50 & 30 & 20 & 10 & 0
\end{align*}
\]
$N$-ethyl-2-oxo-2-(p-toly)acetamide (3e)
2-oxo-N-propyl-2-(p-tolyl)acetamide (3f)
2-(4-fluorophenyl)-2-oxo-N-propylacetamide (3g)
N-benzyl-2-(4-fluorophenyl)-2-oxoacetamide (3h)
2-oxo-2-phenylacetamide (3i)
2-(4-fluorophenyl)-2-oxoacetamide (3j)
2-(3-methoxyphenyl)-2-oxoacetamide (3k)
2-oxo-2-(p-tolyl)acetamide (3l)
2-oxo-2-(m-tolyl)acetamide (3m)
2-oxo-2-(o-tolyl)acetamide (3n)
2-oxo-2-(thiophen-2-yl)acetamide (3o)
2-(furan-2-yl)-2-oxoacetamide (3p)
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