JOC The Journal of Organic Chemistry

Note

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b01555 • Publication Date (Web): 19 Sep 2018

ACS Publications

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Copper-Catalyzed *N*-Formylation of Amines through Tandem Amination/Hydrolysis/Decarboxylation Reaction of Ethyl Bromodifluoroacetate

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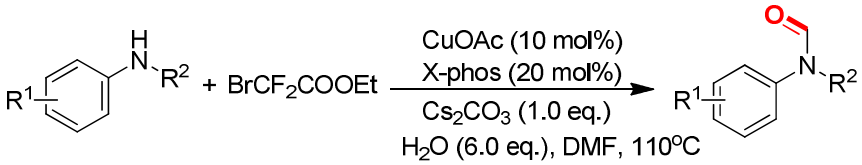
Abstract



Ethyl bromodifluoroacetate ($BrCF_2COOEt$) was firstly used as the *N*-formylating reagent in the copper-catalyzed *N*-formylation of amines. A range of primary, secondary, cyclic arylamines and aliphatic amines underwent the *N*-formylation smoothly to furnish the *N*-formamides in moderate to excellent yields.

N-Formylation of amines is an important and useful reaction in synthetic chemistry because this transformation provides direct access for the synthesis of structurally diverse formamides, which are widely featured in natural products or pharmaceuticals. [1] For example, leucovorin, [2] formoterol [3] and orlistat [4] contain the formamide moiety. In addition, *N*-formyl derivatives are very useful reagents in Vilsmeier formylation reactions [5] and often used as the precursor to provide isocyanide, [6] formamidines, [7] aryl amides, [8] isocyanates, [9] and nitriles. [10] Generally, *N*-formylation

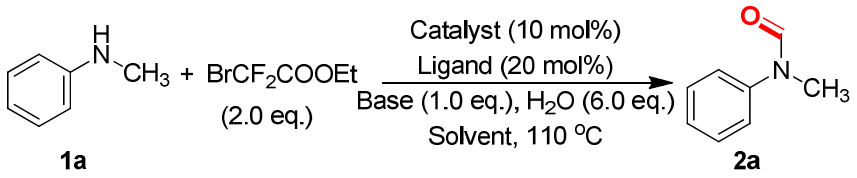
reaction of amines were commonly realized using formylating reagents such as formic acid or formate, [11] *N, N*-dimethylformamide, [12] acetic formic anhydride, [13] ammonium formate, [14] and some special reagents. [15-18] In addition, in the presence of metal catalyst, paraformaldehyde [19] and methanol [20] can also serve as the formylating reagents to provide *N*-formamides. However, many *N*-formylation reactions suffered from long reaction time, high temperature and poor functional group tolerance. Therefore, the development of new *N*-formylating reagent for the formylation is still desirable.

As a cheap, stable and readily available chemical, ethyl bromodifluoroacetate ($BrCF_2COOEt$) was often used to construct various difluoroacetylated molecules *via* radical process, [21] metal-catalyzed coupling reactions [22] or Reformatsky reactions. [23] Recently, Song's group developed a radical-involved method for the synthesis of 3,3-difluoro-2-oxindole derivatives using copper-catalyzed difluoroacetylation of aniline with $BrCF_2COOEt$ *via* C–H activation followed by intramolecular amidation. [24] However, we accidentally found that ethyl bromodifluoroacetate could act as *N*-formylating reagent during our preparation of fluorinated compound. Herein, we wished to report a copper-catalyzed *N*-formylation of arylamines using ethyl bromodifluoroacetate as formyl source.

The reaction of *N*-methylaniline **1a** with 2.0 equiv of ethyl bromodifluoroacetate was chosen as the model reaction to optimize the reaction conditions (Table 1). Initially, the reaction was conducted in the presence of 10 mol % Cu_2O, H_2O (6.0 eq.) and 1.0 equiv of K_2CO_3 in dry MeCN at 110 ^oC for 12h, product **2a** was isolated in 32% yield (entry 1). Encouraged by these results, different solvents (entries 2-4), copper (I) catalysts (entries 5-8), base (entries 9-11), some ligands (entries 12-15) were investigated, respectively. The results showed that CuOAc, Cs_2CO_3 and X-phos were the most suitable reagents for the *N*-Formylation, giving the target product **2a** in 82% (entry 15). When the loading of $BrCF_2COOEt$ was decreased to 1.5 equiv, the yield of the formylating product **2a** was reduced seriously (entry 16). It is well known that the solvent *N, N*-dimethylformamide (DMF) can also serve as a precursor to generate formamides. [12] Therefore, the reaction of **1a** was conducted in the absence of $BrCF_2COOEt$, but the reaction was totally kept intact, which suggested $BrCF_2COOEt$

really acted as the *N*-formylating reagent (entry 17).

Table 1. Screening Conditions [a]



1a **2a**

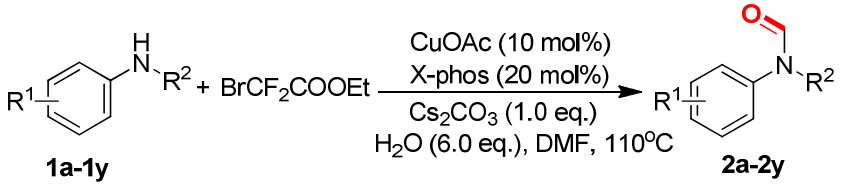
Entry	Catalyst	Ligand	Base	Solvent	Yield (%)
1	Cu_2O	-	K_2CO_3	MeCN	32
2	Cu_2O	-	K_2CO_3	DMF	38
3	Cu_2O	-	K_2CO_3	1,4-dioxane	25
4	Cu_2O	-	K_2CO_3	DCE	ND
5	CuCl	-	K_2CO_3	DMF	35
6	CuI	-	K_2CO_3	DMF	29
7	CuOTf	-	K_2CO_3	DMF	20
8	CuOAc	-	K_2CO_3	DMF	53
9	CuOAc	-	Na_2CO_3	DMF	32
10	CuOAc	-	K_3PO_4	DMF	48
11	CuOAc	-	Cs_2CO_3	DMF	61
12	CuOAc	Bpy	Cs_2CO_3	DMF	65
13	CuOAc	1,10-phen	Cs_2CO_3	DMF	44
14	CuOAc	PPh_3	Cs_2CO_3	DMF	72
15	CuOAc	X-phos	Cs_2CO_3	DMF	82
16	CuOAc	X-phos	Cs_2CO_3	DMF	51[b]
17	CuOAc	X-phos	Cs_2CO_3	DMF	ND[c]

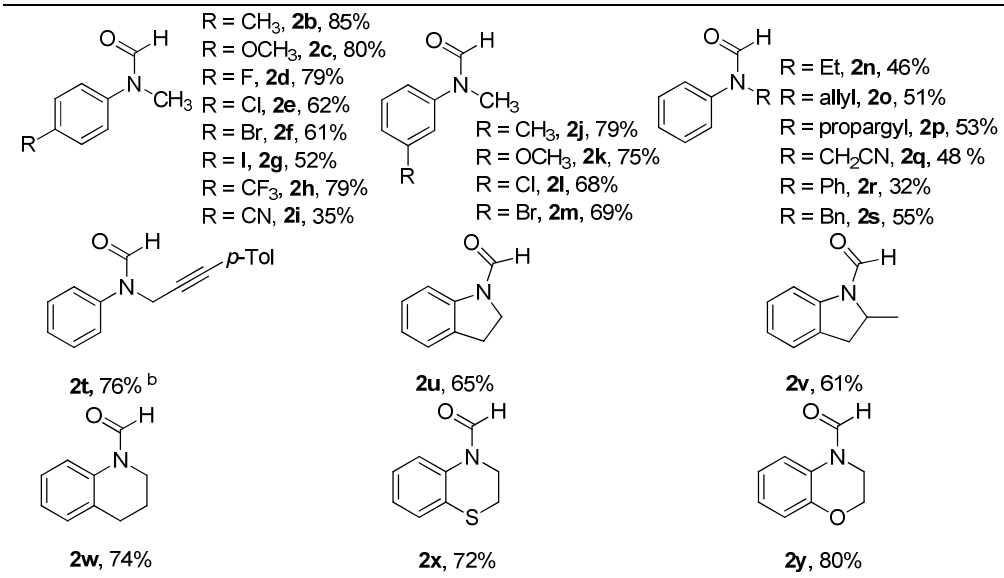
[a] Reaction conditions: **1a** (0.2 mmol), $BrCF_2COOEt$ (0.4 mmol), catalyst (0.02 mmol), ligand (0.04 mmol), base (0.2 mmol), H_2O (1.2 mmol), dry solvent (2 mL), 110 °C, 12 h. isolated yield; [b.] $BrCF_2COOEt$ (0.3 mmol); [c] Without $BrCF_2COOEt$.

With the optimal reaction conditions in hand, the substrate scope of a variety of aromatic amines was next investigated (Table 2). *N*-methylanilines with both electron-donating and electron-withdrawing groups underwent the *N*-formylation smoothly, affording the products **2b - 2m** in moderate to good yields. *N*-(4-iodophenyl)-*N*-methylformamide **2g** was also obtained in a moderate yield (52%), which could provide potential handles for further modification. For *meta*-substituted *N*-methylanilines, such as 3-methyl, 3-methoxy, 3-chloro and 3-bromo amine, the *N*-formylation occurred smoothly, giving the corresponding formamides **2j - 2m** in good yields. Unfortunately, the *N*-formylation of *N*-methylanilines bearing *ortho*-group did not work owing to the steric hindrance.

Subsequently, various *N*-substituted anilines were evaluated and the results demonstrated that steric effects had obvious influence on the formylating reaction yields. For example, formamides **2n** - **2s** were isolated in lower yields (32-55%). Nevertheless, ligand Bpy was more suitable for the formylation of *N*-(3-(p-tolyl)prop-2-yn-1-yl)aniline **1t**. Notably, cyclic arylamines **1u** - **1y** also participated in the reaction well to give the desired formamides **2u** - **2y** in 61-80% yields.

Table 2. Scope with respect to the amine [a]

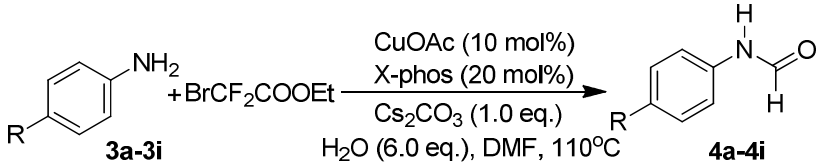


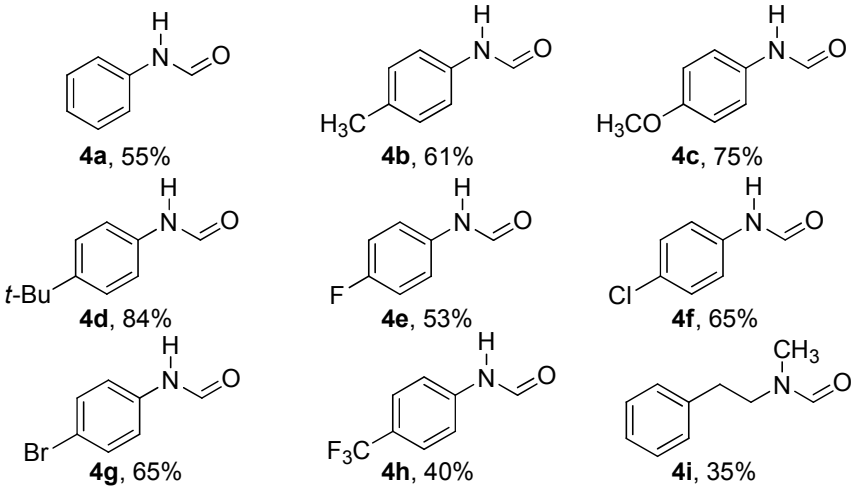


[a] Reaction conditions: **1** (0.2 mmol), $BrCF_2COOEt$ (0.4 mmol, 2.0 eq.), CuOAc (10 mol %), X-phos (20 mol%), Cs_2CO_3 (1.0 eq.), H_2O (6.0 eq.), dry DMF (2 mL), 110 °C, 12h; isolated yield; [b] Bpy instead of X-phos.

As for aromatic primary amines, methyl, methoxyl, *tert*-butyl, fluoride, chloride, bromide and trifluoromethyl substituted anilines **3a** - **3h** underwent the *N*-formylation successfully to furnish *N*-phenylformamides **4a** - **4h** in 40-84% yields (Table 3). Significantly, when the *N*-formylation of aliphatic amine such as *N*-methyl-2-phenylethanamine **3i** was carried out under the optimal conditions, the formamide **4i** was also obtained in 35% yield.

Table 3. Scope with respect to the aromatic primary and aliphatic amines [a]

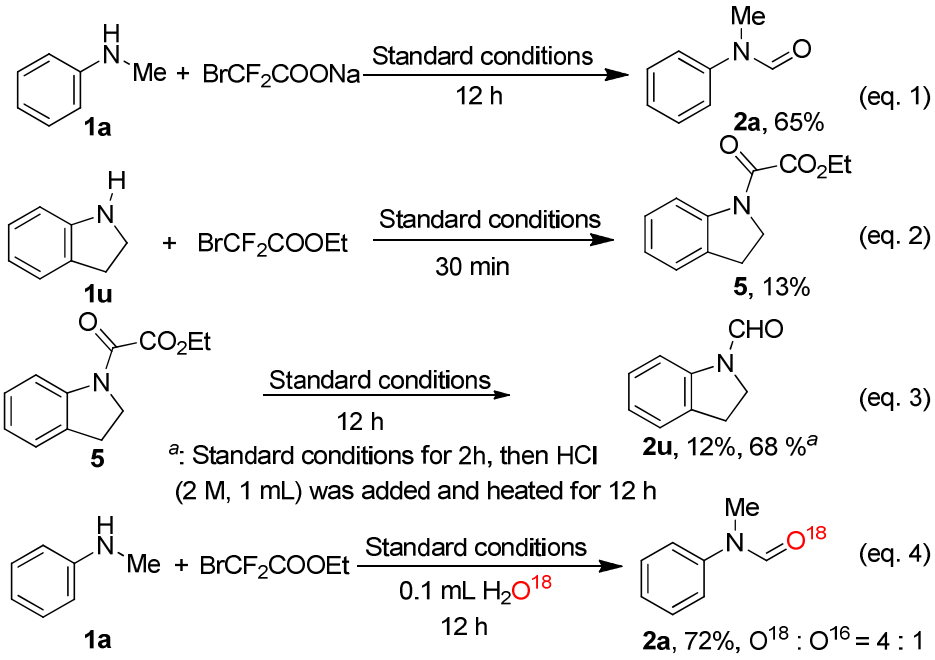




[a] Reaction conditions: **3** (0.2 mmol), $BrCF_2COOEt$ (0.4 mmol, 2.0 eq.), CuOAc (10 mol %), X-phos (20 mol%), Cs_2CO_3 (1.0 eq.), H_2O (6.0 eq.), dry DMF (2 mL), 110 °C, 12h; isolated yield.

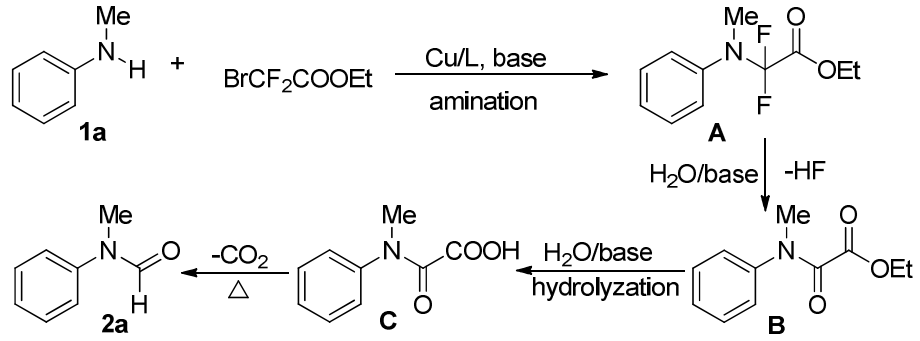
To prove the reaction mechanism, some control experiments were conducted as shown in Scheme 1. Another reagent, sodium bromodifluoroacetate ($BrCF_2COONa$) [25] was used as formyl source in the reaction with *N*-methyl aniline, the formamide **2a** was isolated in 65% yield (eq. 1, Scheme 1). In addition, amine **1u** was conducted with $BrCF_2COOEt$ for 30 min, an aminated product **5** was obtained and identified (eq. 2). The formylated product **2u** could be obtained when the isolated compound **5** was conducted under the standard reaction conditions (eq. 3). These results suggested that the *N*-formylation reaction might proceed *via* a tandem amination/hydrolysis/decarboxylation process. Furthermore, 0.1 mL H_2O^{18} was added into the reaction using the anhydrous DMF as solvent, the product **2a** was isolated in 72 % yield with the ratio of O^{18}-**2a**: O^{16}-**2a** in 4:1 according to the GC results and HRMS (eq. 4). These results suggested that the oxygen atom of *N*-formylating group might derive from the water.

Scheme 1 Control experiments



On the basis of the obtained experimental results, a plausible mechanism is proposed for this *N*-formylation (Scheme 2). Initially, $BrCF_2COOEt$ undergoes the amination reaction with *N*-methylaniline to furnish intermediate **A** in the presence of CuOAc, Cs_2CO_3 and X-phos. [26] Subsequently, the defluorinative hydrolysis of intermediate **A** affords intermediate oxoacetate **B**, which was proved in the control experiment (eq. 2, Scheme 1). Oxoacetate **B** is further hydrolyzed to give the oxoacetic acid **C**. Finally, the decarboxylation of intermediate **C** occurs to produce the *N*-formylated product **2a**. [27]

Scheme 2 Possible Mechanism



In conclusion, we have developed an efficient protocol of copper-catalyzed *N*-formylation of amines using ethyl bromodifluoroacetate as the *N*-formylating

reagent. A variety of amines including primary, secondary and cyclic amines, can participate in the *N*-formylation smoothly under ambient conditions, giving a series of *N*-formamides in moderate to excellent yields. Control experiments suggest that the *N*-formylation might proceed *via* the tandem amination/hydrolysis/decarboxylation process. The reaction represents the first utilization of ethyl bromodifluoroacetate as the *N*-formylating reagent.

Experimental Section

General Information:

Chemicals were either purchased or purified by standard techniques. ^{1}H NMR and ^{13}C NMR spectra were measured on a 500 MHz spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C) or a 400 MHz spectrometer (400 MHz for ^{1}H), using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS, the coupling constants *J* are given in Hz. High resolution mass spectra were recorded on an ESI-Q-TOF mass spectrometry. All reactions under air atmosphere were conducted using standard Schlenk techniques. Melting points were measured on X4 melting point apparatus and uncorrected after recrystallization from ethyl acetate. Column chromatography was performed using EM Silica gel 60 (300-400 mesh).

General Procedure for the Synthesis of formamides derivatives 2a-2y, 4a-4i.

1a-1y, 3a-3i (0.2 mmol), $BrCF_2COOEt$ (0.4 mmol), CuOAc (10 mol %), X-phos (20 mol%) (Bpy for **1t**), Cs_2CO_3 (1.0 eq.) and H_2O (6.0 eq.) were added to a Schlenk tube, and then solvent of dry DMF (2.0 mL) was added. The mixture was then stirred at 110 °C for 12 h under air atmosphere. After the reaction was complete, the mixture was poured into ethyl acetate and evaporated under vacuum. The resulting crude product was purified by flash column chromatography on silica gel using petroleum ether/ethyl acetate (10:1 to 5:1) as the eluent to give the pure products **2a-2y, 4a-4i**.

Procedure for the Conversion of 5 to 2u.

5 (0.2 mmol), CuOAc (10 mol %), X-phos (20 mol%), Cs_2CO_3 (1.0 eq.), H_2O (6.0 eq.) and dry DMF (2.0 mL) were added to a Schlenk tube. The mixture was stirred at 110 °C for 2 h under air atmosphere, then 2 M HCl (1 mL) was added and heated for another 12 h. After the reaction was finished, the mixture was poured into ethyl acetate and evaporated under vacuum. The residue was purified by flash column chromatography using petroleum ether/ethyl acetate (5:1) to afford the desired product **2u**.

N-methyl-N-phenylformamide **(2a)** [18f]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a Yellow oil (22.2 mg, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 7.2 Hz, 2H), 3.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 142.4, 129.7, 126.5, 122.5, 32.2. GC-MS (EI, 70 eV) m/z (%) 134.75 (60.08), 105.85 (100.00), 93.85 (28.25), 78.90 (17.38), 77.90 (9.21), 50.90 (14.94).

N-methyl-N-(p-tolyl)formamide (**2b**) [18f]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a Yellow oil (25.3 mg, 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 8.0 Hz, 2H), 3.21 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 139.8, 136.4, 130.2, 122.7, 32.3, 20.9. GC-MS (EI, 70 eV) m/z (%) 148.75 (50.05), 119.90 (100.00), 107.85 (41.74), 79.90 (14.94), 64.90 (13.0).

N-(4-methoxyphenyl)-N-methylformamide (**2c**) [18f]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a Yellow oil (26.4 mg, 80% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.08 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 9.0 Hz, 2H), 3.80 (s, 3H), 3.25 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.5, 158.4, 135.4, 124.8, 114.9, 55.7, 32.8. GC-MS (EI, 70 eV) m/z (%) 164.75 (67.51), 121.90 (100.00), 107.90 (14.62), 93.90 (25.27), 64.90 (13.88), 51.90 (6.12).

N-(4-fluorophenyl)-N-methylformamide (**2d**) [18f]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the

title compound as a Yellow oil (24.2 mg, 79% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.15 - 7.13 (m, 2H), 7.11 - 7.08 (m, 2H), 3.28 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 161.6 (d, *J* = 245.0 Hz), 138.6, 124.9, 116.7 (d, *J* = 22.5 Hz), 32.7. GC-MS (EI, 70 eV) m/z (%) 152.75 (39.89), 123.85 (100.00), 111.85 (34.00), 94.80 (18.98), 74.90 (13.55), 50.90 (2.93).

N-(4-chlorophenyl)-N-methylformamide (**2e**) [18f]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a Yellow solid (21.0 mg, 62% yield), m.p. 50 - 52 °C (uncorrected). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.31 (d, *J* = 8.5 Hz, 2H), 7.04 (d, *J* = 8.5 Hz, 2H), 3.22 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0, 140.9, 132.2, 129.9, 123.7, 32.2. GC-MS (EI, 70 eV) m/z (%) 168.70 (56.11), 141.75 (31.62), 139.80 (100.00), 127.80 (59.54), 74.90 (27.56), 50.95 (10.08).

N-(4-bromophenyl)-N-methylformamide (**2f**) [18e]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a White solid (26.0mg, 61% yield), m.p. 69 - 71 °C (uncorrected). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 8.8 Hz, 2H), 3.29 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0, 141.4, 132.9, 123.9, 119.9, 32.1. GC-MS (EI, 70 eV) m/z (%) 214.60 (100.00), 212.60 (98.28), 185.65 (73.23), 183.65 (74.99), 104.90 (85.48), 76.90 (45.87).

N-(4-iodophenyl)-N-methylformamide (**2g**) [28]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a White solid (27.1 mg, 52 % yield), m.p. 87 - 89 °C (uncorrected). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.29 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0, 142.1, 138.9, 124.1, 90.6, 32.0. GC-MS (EI, 70 eV) m/z (%) 260.55 (100.00), 231.60 (29.26), 219.55 (37.03), 130.85 (15.46), 105.90 (14.35), 76.95 (24.33), 50.95 (7.18).

N-methyl-N-(4-(trifluoromethyl)phenyl)formamide (**2h**) [18g]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a White solid (32.1 mg, 79% yield), m.p. 265 - 267 °C

(uncorrected). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 3.35 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0, 145.3, 128.4 (q, *J* = 32.5 Hz), 127.05, 124.0 (q, *J* = 268.8 Hz), 121.6, 31.8. GC-MS (EI, 70 eV) m/z (%) 202.65 (82.13), 173.70 (100.00), 144.70 (24.65), 133.80 (10.47), 94.85 (14.66), 74.90 (11.38).

N-(4-cyanophenyl)-N-methylformamide (**2i**) [29]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a White solid (11.2 mg, 35% yield), m.p. 96 - 98°C (uncorrected). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (s, 1H), 7.73 - 7.69 (m, 2H), 7.30 - 7.28 (m, 2H), 3.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5, 145.9, 133.7, 121.1, 118.1, 109.4, 31.3. GC-MS (EI, 70 eV) m/z (%) 159.80 (36.90), 130.85 (100.00), 103.90 (19.83), 76.95 (13.68), 50.95 (7.64).

N-methyl-N-(m-tolyl)formamide (**2j**) [29]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a Yellow oil (23.6 mg, 79% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.32 - 7.29 (m, 1H), 7.10 (d, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 2H), 3.32 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3, 142.2, 139.7, 129.4, 127.2, 123.1, 119.5, 32.0, 21.4. GC-MS (EI, 70 eV) m/z (%) 148.80 (62.26), 119.90 (100.00), 90.85 (33.40), 76.90 (18.33), 50.95 (7.19).

N-(3-methoxyphenyl)-N-methylformamide (**2k**) [30]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a White solid (24.8 mg, 75% yield)，m.p. 305 - 307 °C (uncorrected). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.33 - 7.29 (m, 1H), 6.82 - 6.80 (m, 1H), 6.77 - 6.75 (m, 1H), 6.70 - 6.69 (m, 1H), 3.82 (s, 3H), 3.30 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 160.7, 143.6, 130.5, 114.7, 111.6, 108.8, 55.6, 32.2. GC-MS (EI, 70 eV) m/z (%) 164.75 (71.64), 136.85 (55.72), 95.90 (100.00), 76.95 (23.38).

N-(3-chlorophenyl)-N-methylformamide (**2l**) [18e]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a Yellow oil (23.0 mg, 68% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ

8.50 (s, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.19 (s, 1H), 7.08 (d, *J* = 8.0 Hz, 1H), 3.31 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 143.5, 135.4, 130.7, 126.4, 122.3, 120.2, 31.9. GC-MS (EI, 70 eV) m/z (%) 168.70 (59.94), 141.75 (33.17), 139.80 (100.00), 127.80 (27.52), 99.85 (25.16), 76.95 (39.62).

N-(3-bromophenyl)-N-methylformamide (**2m**) [29]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a Yellow oil (29.4 mg, 69% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.34 (s, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 3.30 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 143.6, 130.9, 129.3, 125.2, 123.2, 120.6, 31.9. GC-MS (EI, 70 eV) m/z (%) 214.60 (98.79), 212.60 (100.00), 185.65 (69.10), 183.65 (67.90), 105.90 (89.62), 76.95 (76.82).

N-ethyl-N-phenylformamide (**2n**) [18e]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a Yellow oil (13.7 mg, 46% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.40 (t, *J* = 8.0 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 2H), 3.85 (q, *J* = 7.0 Hz, 2H), 1.15 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0, 140.9, 129.6, 126.8, 124.3, 40.1, 13.0. GC-MS (EI, 70 eV) m/z (%) 148.80 (37.09), 120.85 (40.59), 105.90 (100.00), 76.90 (40.21), 50.90 (14.75).

N-allyl-N-phenylformamide (**2o**) [18e]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a Yellow oil (16.4 mg, 51% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 5.80 - 5.72 (m, 1H), 5.12 - 5.07 (m, 2H), 4.33 (d, *J* = 5.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 141.2, 132.5, 129.6, 126.7, 123.6, 117.6, 47.9. GC-MS (EI, 70 eV) m/z (%) 160.75 (22.83), 132.75 (14.12), 131.85 (100.00), 105.90 (34.84), 103.90 (35.59), 76.90 (46.59), 50.90 (15.77).

N-phenyl-N-(prop-2-yn-1-yl)formamide (**2p**) [31]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a Yellow oil (16.9 mg, 53% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.25 (t, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 8.0 Hz,

2H), 4.47 (d, *J* = 2.0 Hz, 2H), 2.15 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 140.3, 129.6, 127.2, 123.8, 78.3, 72.2, 34.4. GC-MS (EI, 70 eV) m/z (%) 158.75 (17.00), 157.80 (15.52), 131.85 (45.72), 129.85 (100.00), 105.90 (17.11), 103.90 (29.78), 76.90 (61.63), 50.90 (23.12).

N-(cyanomethyl)-N-phenylformamide (**2q**) [18e]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a Yellow oil (15.4 mg, 48% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 2H), 4.68 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7, 139.0, 130.3, 128.4, 124.2, 114.9, 33.2. GC-MS (EI, 70 eV) m/z (%) 159.55 (36.06), 130.75 (44.99), 104.80 (100.00), 103.85 (50.83), 91.80 (49.58), 76.90 (48.45), 50.90 (23.63).

N,N-diphenylformamide (**2r**) [32]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a Yellow oil (12.6 mg, 32% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.35 - 7.31 (m, 4H), 7.25 - 7.19 (m, 4H), 7.10 (d, *J* = 7.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 141.0, 138.9, 128.9, 128.3, 126.2, 126.0, 125.3, 124.3. GC-MS (EI, 70 eV) m/z (%) 196.75 (100.00), 167.80 (62.40), 166.85 (34.56), 103.90 (30.73), 66.95 (45.96), 50.95 (30.25).

N-benzyl-N-phenylformamide (**2s**) [19]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a Yellow oil (23.2 mg, 55% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.25 - 7.22 (m, 2H), 7.18 - 7.13 (m, 6H), 7.00 (d, *J* = 7.3 Hz, 2H), 4.90 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.4, 141.1, 136.8, 129.6, 128.7, 128.0, 127.5, 126.9, 124.2, 48.9. GC-MS (EI, 70 eV) m/z (%) 210.75 (36.35), 90.90 (100.00), 76.95 (13.46), 64.95 (14.48), 50.95 (5.20).

N-phenyl-N-(3-(p-tolyl)prop-2-yn-1-yl)formamide (**2t**): Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a White solid (37.9 mg, 76% yield)， m.p. 48 - 50^{o}C (uncorrected). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.41 - 7.37 (m, 2H), 7.30 - 7.28 (m, 3H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 7.6 Hz, 2H), 4.71 (s, 2H), 2.27

(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 140.5, 138.6, 131.7, 129.7, 129.1, 127.2, 124.0, 119.4, 84.1, 83.1, 35.4, 21.5. HRMS (ESI) Calcd for $C_{17}H_{15}NNaO^+$ ($[M + Na]^+$) 272.1046, Found: 272.1038.

Indoline-1-carbaldehyde (**2u**) [18e]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a White solid (19.1 mg, 65% yield), m.p. 57 - 59°C (uncorrected). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (major rotamer, s, 1H), 7.31 - 7.28 (m, 1H), 7.25 - 7.20 (m, 2H), 7.11 - 7.07 (m, 1H), 4.11 (t, J = 8.5 Hz, 2H), 3.20 (t, J = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 157.7, 141.4, 141.3, 132.1, 127.78, 127.75, 126.2, 125.0, 124.7, 124.4, 116.9, 109.6, 47.1, 44.8, 27.9, 27.4. GC-MS (EI, 70 eV) m/z (%) 146.80 (42.48), 117.90 (100.00), 90.90 (27.34), 64.90 (9.74), 50.90 (3.62).

2-methylindoline-1-carbaldehyde (**2v**) [33]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a Yellow oil (19.7 mg, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (s, 1H), 7.23 - 7.12 (m, 3H), 7.06 - 7.02 (m, 1H), 4.77 - 4.42 (m, 1H), 3.35 - 3.33 (m, 1H), 2.76 - 2.63 (m, 1H), 1.42 - 1.34 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5, 157.6, 140.6, 140.5, 130.8, 130.4, 127.7, 126.4, 125.1, 124.6, 124.4, 116.9, 109.7, 54.8, 53.3, 36.4, 36.0, 23.4, 20.5. GC-MS (EI, 70 eV) m/z (%) 160.80 (37.66), 117.90 (100.00), 90.90 (28.43), 64.90 (12.55), 50.90 (5.54).

3,4-dihydroquinoline-1(2H)-carbaldehyde (**2w**) [32]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a Yellow oil (23.8 mg , 74% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (d, J = 8.5 Hz, 1H), 7.11 - 7.00 (m, 4H), 3.73 - 3.71 (m, 2H), 2.74 - 2.71 (m, 2H), 1.88 - 1.86 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1, 137.4, 129.7, 129.0, 127.2, 124.6, 117.1, 40.4, 27.2, 22.4. GC-MS (EI, 70 eV) m/z (%) 160.80 (53.02), 131.85 (100.00), 117.90 (37.13), 76.95 (25.83), 50.90 (12.10).

2H-benzo[b][1,4]thiazine-4(3H)-carbaldehyde (**2x**) [34]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a White solid (25.8 mg, 72% yield), m.p. 65 - 67°C (uncorrected). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.22 - 7.20 (m, 1H), 7.12 - 7.10 (m,

2H), 7.06 - 7.04 (m, 1H), 4.06 - 4.04 (m, 2H), 3.13 - 3.11 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.2, 135.2, 127.6, 126.6, 125.9, 125.4, 120.7, 38.6, 27.4. GC-MS (EI, 70 eV) m/z (%) 178.70 (67.41), 135.80 (100.00), 163.70 (29.87), 108.85 (38.80), 76.95 (21.97), 50.95 (12.61).

2H-benzo[b][1,4]oxazine-4(3H)-carbaldehyde (**2y**) [14]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a Yellow oil (26.1 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.08 (t, *J* = 8.4 Hz, 1H), 6.96 - 6.91 (m, 2H), 4.24 (t, *J* = 4.8 Hz, 2H), 3.93 (t, *J* = 4.8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 159.2, 145.7, 145.5, 125.8, 125.7, 125.1, 122.1, 121.5, 121.1, 118.2, 117.2, 116.5, 65.4, 65.1, 44.0, 37.7. GC-MS (EI, 70 eV) m/z (%) 162.75 (96.79), 117.90 (64.25), 119.90 (100.00), 105.90 (36.20), 76.95 (33.02), 50.90 (25.82).

N-phenylformamide (**4a**) [18e]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a Yellow oil (13.3 mg, 55% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.36 (s, 1H), 7.80 (br, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.37 - 7.30 (m, 2H), 7.20 - 7.09 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 159.3, 137.1, 136.9, 129.9, 129.2, 125.4, 124.9, 120.2, 119.0. GC-MS (EI, 70 eV) m/z (%) 120.85 (100.00), 92.85 (71.91), 65.90 (53.31), 64.90 (23.80), 50.90 (7.46).

N-p-Tolylformamide (**4b**) [18f]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 7:1, v/v) affords the title compound as a White solid (16.5mg, 61% yield), m.p. 53 - 55 ^{o}C (uncorrected). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, *J* = 9.6 Hz, 0.5H), 8.63 (d, *J* = 11.2 Hz, 0.5H), 8.31 (s, 0.5H), 8.01 (s, 0.5H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.15 - 7.10 (m, 2H), 6.99 (d, *J* = 8.4 Hz, 1H), 2.32 and 2.30 (s and s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 159.4, 135.2, 134.54, 134.48, 134.3, 130.3, 129.6, 120.3, 119.2, 20.9, 20.8. GC-MS (EI, 70 eV) m/z (%) 135.10 (50.44), 111.10 (13.87), 106.10 (100.00), 79.10 (13.58), 51.05 (6.28).

N-(4-methoxyphenyl)formamide (**4c**) [18e]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 7:1, v/v) affords the title compound as a

Yellow oil (22.7 mg, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (br, 1H), 8.29 (s, 0.5H), 7.76 (s, 0.5H), 7.44 (d, *J* = 8.8 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 1H), 6.89 - 6.83 (m, 2H), 3.79 and 3.77 (s and s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 157.7, 156.8, 130.1, 129.7, 122.0, 121.7, 115.0, 114.3, 55.7, 55.6. GC-MS (EI, 70 eV) m/z (%) 151.14 (100.00), 122.15 (16.02), 108.19 (92.05), 80.12 (32.40), 53.15 (11.16).

N-(4-(tert-butyl)phenyl)formamide (**4d**) [35]：Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 7:1, v/v) affords the title compound as a Yellow oil (29.7 mg, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.34 (br, 0.5H), 7.83 (br, 0.5H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.38 - 7.33 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 1H), 1.31 and 1.30 (s and s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 159.3, 148.6, 147.9, 134.5, 134.3, 126.7, 126.0, 120.0, 119.0, 34.5, 31.4. GC-MS (EI, 70 eV) m/z (%) 177.10 (26.50), 162.10 (100.00), 135.10 (25.64), 94.10 (12.24), 65.10 (8.82).

N-(4-fluorophenyl)formamide (**4e**) [36]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 7:1, v/v) affords the title compound as a White solid (14.7 mg, 53% yield)，m.p. 63 - 65 °C (uncorrected). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (br, 0.5H), 8.36 (s, 0.5H), 8.16 (br, 0.5H), 7.53 - 7.49 (m, 1H), 7.38 (s, 0.5H), 7.08 - 7.01 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8 (d, *J* = 248.8 Hz), 161.6, 159.8 (d, *J* = 236.3 Hz), 159.0, 132.97, 132.95, 122.0, 121.5, 116.7 (d, *J* = 22.5 Hz), 116.0 (d, *J* = 22.5 Hz). GC-MS (EI, 70 eV) m/z (%) 139.00 (100.00), 111.15 (90.35), 84.16 (59.33), 83.00 (43.19), 57.10 (19.05).

N-(4-chlorophenyl)formamide (**4f**) [36]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 7:1, v/v) affords the title compound as a White solid (20.2 mg, 65% yield)，m.p. 100 - 102 °C (uncorrected). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 0.5H), 8.70 (s, 0.5H), 8.37 (s, 0.5H), 8.15 (s, 0.5H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.35 - 7.28 (m, 2H), 7.07 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 159.5, 135.6, 135.5, 130.9, 130.0, 129.9, 129.2, 121.5, 120.2. GC-MS (EI, 70 eV) m/z (%) 155.01 (84.32), 129.26 (33.56), 127.00 (100.00), 99.00 (19.05), 92.18 (28.36).

N-(4-bromophenyl)formamide (**4g**) [36] Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 7:1, v/v) affords the title compound as a White solid (25.9 mg, 65% yield)，m.p. 114 - 116 °C (uncorrected). ^{1}H NMR (400 MHz, DMSO) δ 10.36 (br, 1H), 8.32 (s, 1H), 7.59 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 165.0, 143.1, 142.8, 137.3, 136.9, 126.4, 124.6, 120.6, 120.4. GC-MS (EI, 70 eV) m/z (%) 198.9 (100.00), 173.31 (81.45), 171.49 (83.65), 92.16 (55.23), 65.16 (54.32).

N-(4-(trifluoromethyl)phenyl)formamide (**4h**) [18e] : Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 7:1, v/v) affords the title compound as a White solid (15.1 mg, 40% yield)，m.p. 191 - 193 °C (uncorrected). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (br, 1H), 8.60 and 8.44 (s and s, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.64 - 7.58 (m, 2H), 7.20 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.1, 159.2, 140.0, 127.3, 126.9 (q, *J* = 33.8 Hz), 126.6, 124.1 (q, *J* = 270.0 Hz), 119.8, 118.1. GC-MS (EI, 70 eV) m/z (%) 189.00 (100.00), 161.00 (67.99), 111.05 (79.21), 66.05 (25.58), 63.00 (15.44).

N-methyl-N-phenethylformamide (**4i**) [37]: Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 7:1, v/v) affords the title compound as a Colourless oil (11.4 mg, 35% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 0.5H), 7.83 (s, 0.5H), 7.36 - 7.31 (m, 2H), 7.28 - 7.25 (m, 2H), 7.17 (d, *J* = 7.2 Hz, 1H), 3.60 and 3.50 (t and t, *J* = 7.2 Hz, 2H), 2.93 - 2.85 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 162.6, 138.7, 137.9, 128.9, 128.83, 128.78, 128.6, 126.9, 126.6, 51.3, 46.1, 35.1, 35.0, 33.3, 29.9. GC-MS (EI, 70 eV) m/z (%) 163.10 (22.86), 104.10 (82.83), 91.05 (13.51), 72.10 (100.00), 51.05 (3.99).

Ethyl 2-(indolin-1-yl)-2-oxoacetate (**5**): Purification by column chromatography on silica gel (petroleum ether/ ethyl acetate = 10:1, v/v) affords the title compound as a Yellow oil (5.7 mg, 13% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.0 Hz, 1H), 7.31 - 7.27 (m, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 4.43 (q, *J* = 7.2 Hz, 2H), 4.29 (t, *J* = 8.4 Hz, 2H), 3.26 (t, *J* = 8.3 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 157.7, 141.7, 132.0, 127.7, 125.2, 124.7, 117.9, 62.3, 48.5, 28.3, 14.0. HRMS (ESI) Calcd for $C_{12}H_{13}NNaO_3^+$ ($[M + Na]^+$) 242.0788, Found:

242.0792.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for product **2a-2y, 4a-4i**, and **5.** These materials are available free of charge *via* the Internet at http://pubs.acs.org.

Acknowledgment. We thank the National Natural Science Foundation of China (No. 21302144 and 21272177) and Natural Science Foundation of Zhejiang Province (No. LR15B020002) for financial support.

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