Microwave-Assisted, Metal-Free, Chemoselective *N*-Formylation of Amines using 2-Formyl-1,3-dimethyl-1*H*-imidazol-3-ium Iodide and *In Situ* Synthesis of Benzimidazole and Isocyanides

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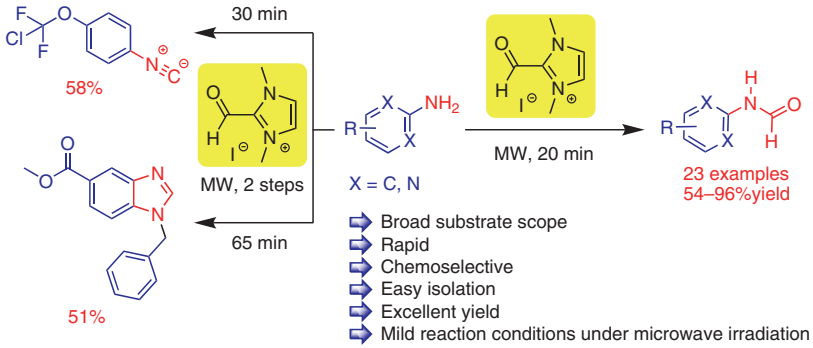


Received: 20.03.2022
Accepted after revision: 27.04.2022
Published online: 08.06.2022
DOI: 10.1055/s-0041-1737605; Art ID: so-2022-d0011-op

Crowd-Reviewed

Abstract An efficient, environmentally benign, chemoselective, microwave-assisted *N*-formylation protocol of aromatic, aliphatic, alicyclic, benzylic amines, inactivated aromatic amines and sterically demanding heterocyclic amines using 2-formyl-1,3-dimethyl-1*H*-imidazol-3-ium iodide has been developed. This affords a series of *N*-substituted formamides with good to excellent yields (23 examples, 53–96% yield) and can be readily scaled. The methodology can be further extended to synthesize benzimidazole and isocyanide derivatives.

Key words *N*-formylation, *N*-formamide, microwave-assisted synthesis, 2-formyl-1,3-dimethyl-1*H*-imidazol-3-ium iodide, isocyanide, benzimidazole

Formamides are an important class of organic compounds having diverse applications in synthetic organic chemistry[1] and medicinal chemistry.[2] Pharmaceuticals containing the *N*-formamide group are on the market and others are in clinical trials (Figure 1).

The formyl group is widely used as a protecting group for amines in peptide synthesis because the amine can be readily deprotected under acidic or basic conditions.[3,4] Furthermore, *N*-formamides are important precursors in the preparation of isocyanides,[5,6] formamides,[7] oxazolidinones,[8–10] benzimidazoles, and quinazolinones.[11] Formamides play an important role in the fields of biochemistry and molecular biology, especially in the area of nucleotides and polynucleotides.[12–15]

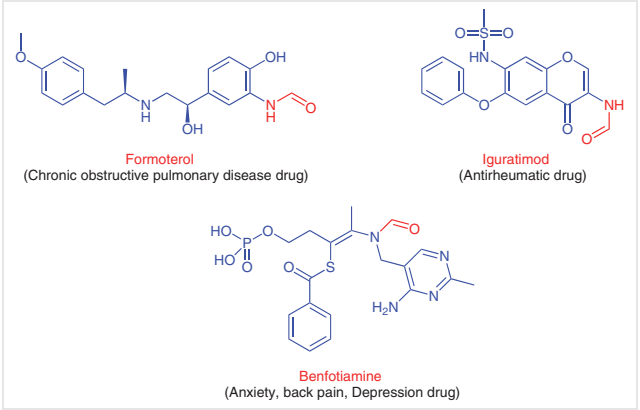


Figure 1 Structures of *N*-formyl group containing pharmaceutical drugs

Direct *N*-formylation of various amines can be achieved using different formylating reagents such as formic acetic anhydride,[16] formic acid in the presence of coupling reagents such as T3P[17] and DCC,[18] Weinreb formamide,[19] methanol,[20] formyloxyacetoxyphenylmethane (FAPM),[21] carbon monoxide,[22] carbon dioxide,[23–25] ammonium formate,[26] *N*-formylbenzotrizole,[27] and organic and inorganic catalysis.[28–30]

However, many of these methods have limitations such as long reaction times, harsh reaction conditions, low yields, expensive reagents, lack of selectivity or generality, and decrease in turnover number of the catalyst. In continuation of our research in the area of development of novel methods for the synthesis of amides,[31] *o*-uredobenzonitriles,[32] bioactive heterocyclic small molecules,[33] and synthetic applications of T3P[34–39] and dithioesters,[40] we have developed a microwave-assisted *N*-formylation protocol for

various amines including poorly reactive amines using 2-formyl-1,3-dimethyl-1*H*-imidazol-3-ium iodide to overcome many of the challenges with existing formylating reagents.

Our group has also identified several benzimidazole-based anticancer agents;[41–43] hence, we examined this *N*-formylation protocol for the synthesis of benzimidazole derivatives as well as for production of isocyanides.

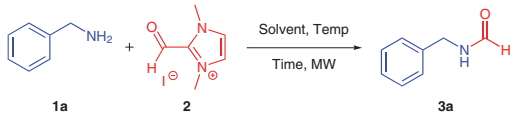
In initial studies (Table 1), we chose benzylamine **1a** (1.0 mmol) and 2-formyl-1,3-dimethyl-1*H*-imidazol-3-ium iodide **2** (1.0 mmol), synthesized by using the reported procedure with slight modifications,[44–46] as model substrates to identify optimal reaction conditions. To begin with, we performed the reaction in the presence of THF as a solvent at 30 °C (entry 1) under microwave irradiation, but obtained very little product. However, we observed an increased yield of product when the reaction was carried out at 40 °C for 60 minutes (entry 2). Upon increasing the temperature to 50 °C and 60 °C, a gradual improvement of yield was observed (entries 3 and 4). When the reaction was carried out at 70 °C under microwave irradiation, we observed complete conversion of starting materials with good yield of product (entry 5). With a further increase in temperature to 80 °C, no improvement in the yield was observed (entry 6). The effect of solvent in terms of the yield was screened (entries 7–11). Upon increasing the amount of formylating agent to 1.1 and 1.2 equivalents, no improvement in the yield was observed (entries 12 and 13). Thus, the optimized conditions for the reaction use benzylamine **1a** (1.0 mmol) and formylating agent **2** (1.0 mmol) in THF for 20 minutes at 70 °C under microwave irradiation (entry 5).

When the reaction was performed with conventional heating at 70 °C for 3 hours, the starting material **1a** was completely consumed but the isolated yield of product was lower compared to those observed under microwave conditions. The yield under conventional heating was 78%; whereas under microwave irradiation the yield was 95%.

With the optimized conditions established, we explored the scope and generality of the reaction using various amines; the results are summarized in Scheme 1. Benzylic, alicyclic, and aliphatic amines resulted in the desired products in good to excellent yields ranging from 53 to 96%. Our results revealed that substrates having an electron-releasing group on the aromatic ring give the respective *N*-substituted formamides with higher yields, whereas amines having electron-withdrawing groups on the aromatic ring resulted in relatively low yields. We also found that benzylic amines produced *N*-substituted formamides in better yields compared to aliphatic and alicyclic amines.

We subsequently extended the scope of the reaction to piperidine, pyrrolidine, and dibenzylamine. This protocol is also scalable, with **3a** being synthesized at the 1.0 g scale and being obtained in 90% yield, compared to 95% yield when synthesized at 1.0 mmol scale.

Table 1 Optimization of the Reaction Conditions for the Synthesis of **3a**



Entry	Solvent	Reagent (equiv)	Temp (°C)	Time (min)	Yield (%)
1	THF	1.0	30	60	15
2	THF	1.0	40	60	20
3	THF	1.0	50	60	30
4	THF	1.0	60	30	86
5[a]	THF	1.0	70	20	95
6	THF	1.0	80	20	91
7	methanol	1.0	65	30	12
8	DCM	1.0	40	30	38
9	acetonitrile	1.0	82	30	43
10	1,4-dioxane	1.0	100	30	63
11	DMF	1.0	150	30	60
12	THF	1.1	70	20	95
13	THF	1.2	70	20	93

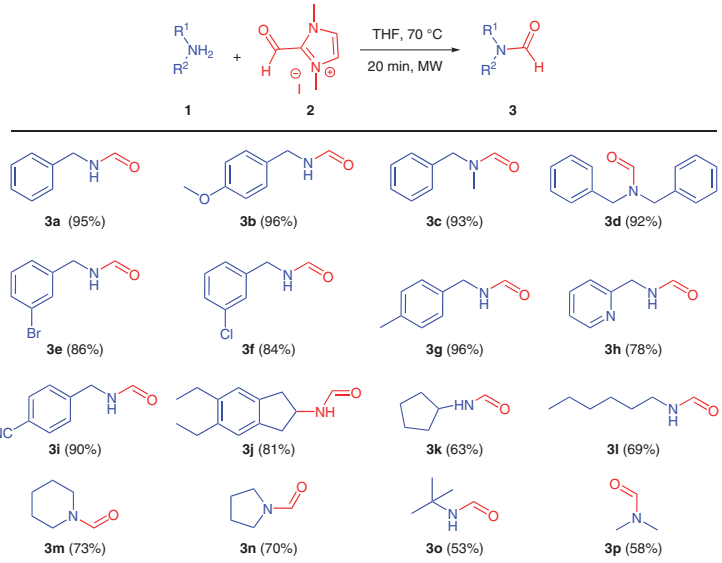
[a] Reaction conditions (General procedure A): **1a** (1.0 mmol), **2** (1.0 mmol), THF (13 vol), 70 °C, 20 min, MW.

However, aromatic amines produced low yields of the corresponding *N*-substituted formamides following the optimized conditions. Thus, we further evaluated the best reaction conditions for *N*-formylation of aromatic amines (Table 2) using aniline **4a** (1.0 mmol) and **2** (1.0 mmol) with different organic and inorganic bases (entries 2–4) under microwave irradiation. We found triethylamine (0.9 mmol) to be the most suitable base.

With these optimized conditions, we explored the scope and generality of the reaction using various aromatic amines; the results are summarized in Scheme 2. These conditions resulted in the desired products in good to excellent yields ranging from 53 to 72% (seven examples). The results revealed that substrates having electron-donating groups on the aromatic ring gave the respective *N*-substituted formamides in higher yields compared to substrates having electron-withdrawing groups on the aromatic ring.

Substrate Scope

In further efforts to extend the application of this formylation protocol, we developed methods for in situ synthesis of isocyanide (**6a**, **6b**) and benzimidazole (**6c**) derivatives from the corresponding amines under microwave irradiation.



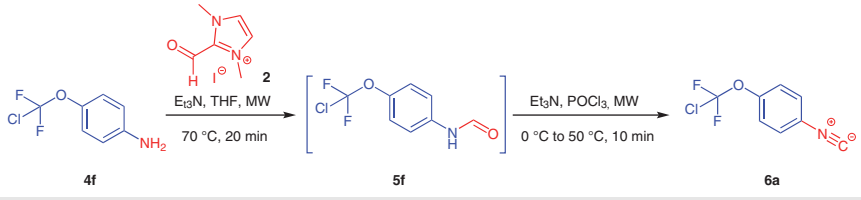
Scheme 1 Substrate scope for the synthesis of N-substituted formamides

Isocyanide **6a** was obtained by reacting amine **4f** in THF with formylating agent **2** in the presence of triethylamine at 70 °C for 20 minutes under microwave irradiation to furnish the corresponding *N*-formamide intermediate **5f**, which was treated with triethylamine and phosphorus oxychloride at 50 °C for 10 minutes under microwave irradiation to give **6a** in 58% isolated yield over two steps (Scheme 3).

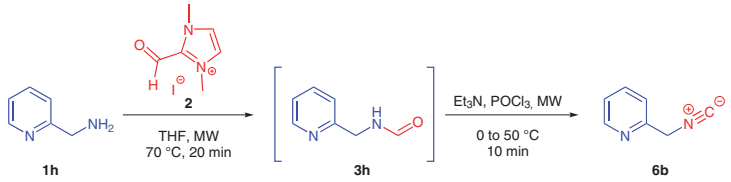
Isocyanide **6b** was similarly obtained by reacting amine **1h** in THF with **2** at 70 °C for 20 minutes under microwave irradiation, giving *N*-formamide intermediate **3h** (Scheme 4). On treatment with triethylamine and phosphorus oxychloride at 50 °C, **6b** was isolated in 66% yield over two steps.

Equally, benzimidazole derivative **6c** was obtained by reacting amine **4g** in THF with **2** in the presence of triethylamine at 70 °C for 20 minutes under microwave irradiation to give the corresponding *N*-formamide intermediate **5g**. The in situ generated **5g** was then cooled to 0 °C and glacial acetic acid was added. The resulting mixture was heated to 80 °C for 45 minutes under microwave irradiation to give methyl 1-benzyl-1*H*- benzo[*d*]imidazole-5-carboxylate **6c** in 51% isolated yield over two steps (Scheme 5).

We propose that the lone pair of electrons present on the nitrogen of the amine attacks the carbonyl carbon of formylating agent **2**, eliminating **C** (Scheme 6). Subsequent charge neutralization leads to the formation of *N*-substituted formamide and by-product **D**. In the case of aromatic amines, triethylamine was necessary to facilitate the attack on **2**. We isolated the highly hygroscopic by-product **D**, and its structure was confirmed by ^{1}H NMR and ^{13}C NMR analysis.

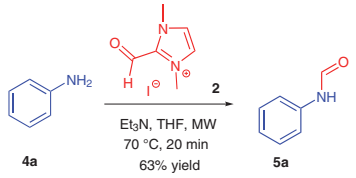


Scheme 3 Synthesis of 1-(chlorodifluoromethoxy)-4-isocyanobenzene **6a**



Scheme 4 Synthesis of 2-(isocyanomethyl)pyridine **6b**

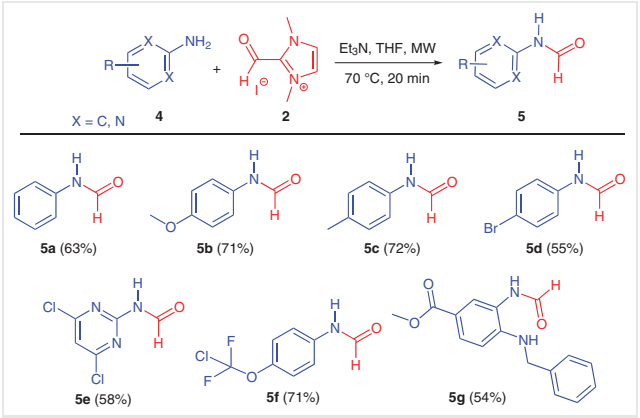
Table 2 Optimization of the Reaction Conditions for the Synthesis of *N*-Phenylformamide (**5a**)



Entry	Solvent	Base	Base (equiv)	Temp (°C)	Time (min)	Yield (%)
1	THF	DIPEA	1.0	70	20	51
2	THF	Et_3N	1.0	70	20	56
3	THF	K_2CO_3	1.0	70	20	40
4	THF	Cs_2CO_3	1.0	70	20	48
5	THF	Et_3N	1.3	70	20	50
6[a]	THF	Et_3N	0.9	70	20	63
7	THF	Et_3N	0.8	70	20	60

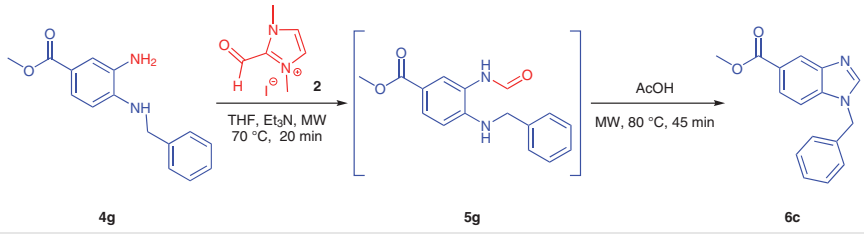
[a] Reaction conditions (General procedure B): **4a** (1.0 mmol), **2** (1.0 mmol), Et_3N (0.9 mmol), THF (13 vol), 70 °C, 20 min.

In conclusion, we have developed an efficient microwave-assisted protocol for *N*-formylation of amines, including aromatic amines, with a diversity of functional groups using a novel formylating agent 2-formyl-1,3-dimethyl-1*H*-imidazol-3-ium iodide. This method provides rapid access to *N*-formylated products under metal-free, chemoselective, mild conditions with good to excellent yields and broad substrate scope. We have also demonstrated the synthesis of benzimidazole derivatives and substituted isocyanides via in situ generated *N*-substituted formamides.

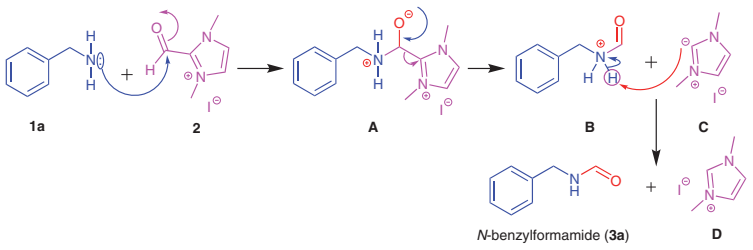


Scheme 2 Substrate scope for the synthesis of *N*-substituted formamides of aryl amines

Starting materials, reagents, and solvents were purchased from commercial sources and used as received unless stated otherwise. Moisture- or air-sensitive reactions were conducted under a nitrogen atmosphere in oven-dried glass apparatus. The microwave instrument used was an Anton Paar, Monowave 200. Reaction progress was monitored by thin-layer chromatography (TLC) on pre-coated silica gel plates (Silica gel 60 F_{254}; Merck) and visualization was accomplished with UV light or potassium permanganate followed by heating. Solvents were removed under reduced pressure using a rotary evaporator. Purification of intermediates and final compounds was carried out using silica gel 230–400 mesh (particle size 40–63 µm) column chromatography. NMR spectra were recorded with Bruker 400 MHz, 300 MHz and 100 MHz spectrometers (DMSO-d_6 and $CDCl_3$). Chemical shifts are reported in ppm using the TMS as internal standard. Multiplicities are reported as, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, with coupling constants in Hz. LCMS analyses



Scheme 5 Synthesis of methyl 1-benzyl-1*H*-benzo[*d*]imidazole-5-carboxylate **6c**



Scheme 6 Proposed reaction mechanism of *N*-formylation

were performed with an Agilent Technologies Infinity 1290. HRMS analyses were performed with a Waters SYNAPTG2. HPLC analyses were performed with an Agilent, Infinity II LC System.

Synthesis of *N*-Substituted Formamides 3a–p; General Procedure A

To a solution of **1a–p** (1.0 equiv) in THF in a 5 mL microwave reaction vial was added 2-formyl-1,3-dimethyl-1*H*-imidazol-3-ium iodide **2** (1.0 equiv) at room temperature under nitrogen atmosphere. The resulting reaction mixture was sealed, pre-stirred for 3 minutes and then heated at 70 °C for 20 minutes under microwave irradiation (ca. 100 W of initial power). Subsequently, the reaction mixture was cooled to room temperature, quenched with water and the organic phase was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with water and brine. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to obtain the crude product. The crude product was purified by column chromatography (silica gel 230–400 mesh, eluting with 1–6% methanol in dichloromethane) to obtain pure compounds **3a–p**.

Synthesis of Compounds 5a–g; General Procedure B

To a solution of the aromatic amine **4a–g** (1.0 equiv) in THF in a 5 mL microwave reaction vial were added triethylamine (0.9 equiv) and 2-formyl-1,3-dimethyl-1*H*-imidazol-3-ium iodide **2** (1.0 equiv) at room temperature under nitrogen atmosphere. The resulting mixture was sealed, pre-stirred for 3 minutes and then heated at 70 °C for 20 minutes under microwave irradiation (ca. 100 W of initial power). Then, the reaction mixture was cooled to room temperature, quenched with water and the organic phase was extracted with ethyl acetate (3 × 10 mL). The combined organic phases were washed with water and saturated brine, the organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to obtain the crude product. The crude product was purified by column chromatography (silica gel 230–400 mesh, eluting with 1–3% MeOH in dichloromethane) to obtain pure compounds **5a–g**.

N-Benzylformamide 3a

Yield: 94%; off-white solid; TLC R_f = 0.44 (petroleum ether/ethyl acetate 5:5 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.50 (s, 1 H, N-H), 8.13–8.14 (t, J = 0.8 Hz,1 H, -CHO), 7.23–7.25 (m, 5 H, Ar-H), 4.29–4.31 (d, J = 6.0 Hz, 2 H, -CH_2)

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.50, 139.45, 128.91, 128.74, 127.82, 127.76, 127.34, 41.17.

MS (ESI): m/z [M + H]$^+$ calcd for C_8H_9NO: 136.06; found: 136.2.

LCMS purity = 98.802%.

HRMS (ESI): m/z [M + H]$^+$ calcd for C_8H_9NO: 136.0684; found: 136.1210.

N-(4-Methoxybenzyl)formamide 3b

Yield: 96%; pale-yellow solid; TLC R_f = 0.38 (petroleum ether/ethyl acetate 5:5 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.42 (s, 1 H, -NH), 8.10 (s, 1 H, -CHO), 7.18–7.20 (d, J = 8.40 Hz, 2 H, Ar-H), 6.88–6.92 (t, J = 8.60 Hz, 2 H, Ar-H), 4.22–4.23 (d, J = 6.0 Hz, 2 H, -CH_2), 3.73 (s, 3 H, -OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.35, 158.74, 131.40, 129.12, 128.82, 114.31, 114.20, 55.52, 40.02.

MS (ESI): m/z [M + H]$^+$ calcd for $C_9H_{11}NO_2$: 166.08; found: 166.1.

LCMS purity = 99.6%.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_9H_{11}NO_2$: 166.0790; found 166.1051.

N-Benzyl-*N*-methylformamide 3c

Yield: 93%; colorless oil; TLC R_f = 0.33 (petroleum ether/ethyl acetate 5:5 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ (mixture of *cis-trans*-rotamers, 1: 0.65) = 8.29 (s, 1 H, -CHO), 7.30–7.40 (m, 5 H, Ar-H), 4.45 (s, 2 H, -CH_2), 2.50 (s, 3 H, -CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.27, 137.38, 129.13, 129.01, 128.16, 128.14, 52.57, 34.10.

MS (ESI): m/z [M + H]$^+$ calcd for $C_9H_{11}NO$: 150.08; found: 150.1.

LCMS purity = 99.3%.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_9H_{11}NO$: 150.0841; found: 150.1369.

HPLC (0.1% TFA in Water: Acetonitrile): R_t = 10.062 min.

N,*N*-Dibenzylformamide 3d

Yield: 92%; white solid; TLC R_f = 0.58 (petroleum ether/ethyl acetate 5:5 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.47 (s, 1 H, -CHO), 7.34–7.40 (m, 5 H, Ar-H), 7.31–7.33 (m, 1 H, Ar-H), 7.25–7.30 (m, 2 H, Ar-H), 7.17–7.23 (m, 2 H, Ar-H), 4.36 (s, 2 H, -CH_2), 4.28 (s, 2 H, -CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 163.70, 137.14, 137.01, 129.16, 128.99, 128.28, 128.17, 127.72, 50.14, 44.64.

MS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{15}NO$: 226.12; found: 226.1.

LCMS purity = 99.9%.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{15}NO$: 226.1154; found: 226.1756.

N-(3-Bromobenzyl)formamide 3e

Yield: 86%; off-white solid; TLC R_f = 0.33 (petroleum ether/ethyl acetate 5:5 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.54 (s, 1 H, -NH), 8.14–8.15 (d, J = 1.6 Hz, 1 H, -CHO), 7.44–7.49 (m, 2 H, Ar-H), 7.26–7.32 (m, 2 H, Ar-H), 4.29–4.33 (d, J = 15.2 Hz, 2 H, -CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.07, 139.93, 130.78, 130.69, 130.34, 126.33, 122.78, 41.48.

^{13}C NMR-DEPT135 (400 MHz, DMSO-d_6): δ = 40.60 (CH_2).

MS (ESI): m/z [M + H]$^+$ calcd for C_8H_8BrNO [^{79}Br]: 213.98; found: 214.0.

LCMS purity = 99.99%.

HRMS (ESI): m/z [M + H]$^+$ calcd for C_8H_8BrNO [^{79}Br] [M + H]$^+$: 213.9789, C_8H_8BrNO [^{81}Br] [M + H]$^{+2}$: 215.9789; found: 213.9573 [^{79}Br] [M + H]$^+$, 215.8934 [^{81}Br] [M + H]$^{+2}$.

N-(3-Chlorobenzyl)formamide 3f

Yield: 84%; off-white solid; TLC R_f = 0.26 (petroleum ether/ethyl acetate 5:5 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.54 (s, 1 H, -NH), 8.152–8.155 (t, J = 0.6 Hz, 1 H, -CHO), 7.30–7.39 (m, 3 H, Ar-H), 7.22–7.26 (m, 1 H, Ar-H), 4.30–4.34 (d, J = 14.8 Hz, 2 H, -CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.16, 139.68, 134.58, 130.07, 127.81, 127.74, 125.82, 41.52.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for C_8H_8ClNO: 170.03; found: 170.1.

LCMS purity = 99.91%.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for C_8H_8ClNO: 170.0294; found: 170.0378.

***N*-(4-Methylbenzyl)formamide 3g**

Yield: 96%; white solid; TLC R_f = 0.25 (petroleum ether/ethyl acetate 5:5 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.45 (s, 1 H, -NH), 8.114–8.118 (t, *J* = 0.8 Hz, 1 H, -CHO), 7.12–7.16 (m, 4 H, Ar-H), 4.24–4.25 (d, *J* = 6.0 Hz, 2 H, -CH_2), 2.27 (s, 3 H, -CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.39, 136.40, 129.32, 127.75, 40.28, 21.11.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{11}NO$: 150.08; found: 150.1.

LCMS purity = 98.25%.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_{11}NO$: 150.0841; found: 150.1778.

***N*-(Pyridin-2-ylmethyl)formamide 3h**

Yield: 78%; pale-yellow liquid; TLC R_f = 0.30 (dichloromethane/methanol 9:1 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.59 (s, 1 H, -NH), 8.50–8.53 (t, *J* = 6.4 Hz, 1 H, -CHO), 8.17 (s, 1 H, Ar-H), 7.75–7.80 (m, 1 H, Ar-H), 7.26–7.31 (m, 2 H, Ar-H), 4.39–4.41 (d, *J* = 6.4 Hz, 2 H, -CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.73, 158.40, 149.34, 137.24, 122.67, 121.58, 43.22.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_7H_8N_2O$: 137.06; found: 137.0.

LCMS purity = 99.81%.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_7H_8N_2O$: 137.0637; found: 137.1333.

***N*-(4-Cyanobenzyl)formamide 3i**

Yield: 90%; off-white solid; TLC R_f = 0.48 (dichloromethane/methanol 9:1 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.62 (s, 1 H, -NH), 8.184–8.188 (d, *J* = 1.6 Hz, 1 H, -CHO), 7.80–7.83 (m, 2 H, Ar-H), 7.45–7.47 (d, *J* = 8.8 Hz, 2 H, Ar-H), 4.38–4.40 (d, *J* = 6.4 Hz, 2 H, -CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.83, 145.41, 132.78, 128.52, 119.32, 110.10, 40.19.

MS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_9H_8N_2O$: 159.06; found: 159.0.

LCMS purity = 99.71%.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_9H_8N_2O$: 161.0637; found: 161.1165.

***N*-(5,6-Diethyl-2,3-dihydro-1*H*-inden-2-yl)formamide 3j**

Yield: 81%; pale-yellow solid; TLC R_f = 0.27 (petroleum ether/ethyl acetate 5:5 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.33 (s, 1 H, -NH), 7.95 (s, 1 H, -CHO), 6.97–7.00 (d, *J* = 14.4 Hz, 2 H, Ar-H), 4.46–4.51 (m, 1 H, -CH), 3.08–3.14 (m, 2 H, -CH_2), 2.66–2.72 (m, 2 H, -CH_2), 2.53–2.59 (m, 4 H, -2CH_2), 1.15–1.11 (t, *J* = 7.6 Hz, 6 H, -2CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.17, 139.94, 139.87, 138.99, 138.72, 124.96, 124.69, 49.24, 40.12, 27.28, 25.34, 16.10.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{19}NO$: 218.15; found: 218.2.

LCMS purity = 97.47%.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{19}NO$: 218.1467; found: 218.1622.

***N*-(Cyclopentylmethyl)formamide 3k**

Yield: 64%; pale-yellow liquid; TLC R_f = 0.26 (petroleum ether/ethyl acetate 5:5 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.02 (s, 1 H, -NH), 7.91 (s, 1 H, -CHO), 4.06–4.01 (m, 1 H, -CH), 1.81–1.77 (m, 2 H, -CH_2), 1.60–1.64 (m, 4 H, –2CH_2), 1.52–1.51 (m, 2 H, -CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.78, 49.33, 32.75, 32.72, 23.83, 23.80.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_6H_{11}NO$: 114.08; found: 114.2.

LCMS purity = 99.93%.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_6H_{11}NO$: 114.0841; found: 114.1295.

***N*-Hexylformamide 3l**

Yield: 69%; colorless liquid; TLC R_f = 0.29 (petroleum ether/ethyl acetate 5:5 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.97 (s, 2 H, -NH and -CHO), 3.02–3.08 (m, 2 H, -CH_2), 1.36–1.38 (d, *J* = 6.3 Hz, 2 H, -CH_2), 1.24 (s, 6 H, -3CH_2), 0.83–0.86 (d, *J* = 6.6 Hz, 3 H, -CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.27, 37.50, 31.37, 29.42, 26.47, 22.49, 14.32.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_7H_{15}NO$: 130.12; found: 130.2.

LCMS purity = 100%.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_7H_{15}NO$: 130.1154; found: 130.1651.

Piperidine-1-carbaldehyde 3m

Yield: 73%(145 mg); colorless liquid; TLC R_f = 0.2 (petroleum ether/ethyl acetate 5:5 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.95 (s, 1 H, -CHO), 3.28–3.35 (m, 4 H, -2CH_2), 1.58–1.63 (m, 2 H, -CH_2), 1.46–1.50 (m, 2 H, -CH_2), 1.38–1.44 (m, 2 H, -CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.04, 46.21, 26.69, 25.35, 24.69.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_6H_{11}NO$: 114.08; found: 114.1.

LCMS purity = 99.83%.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_6H_{11}NO$: 114.0841; found: 114.1295.

Pyrrolidine-1-carbaldehyde 3n

Yield: 70%; colorless liquid; TLC R_f = 0.65 (dichloromethane/methanol 9:1 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.17 (s, 1 H, -CHO), 3.43–3.46 (t, *J* = 6.2 Hz, 2 H, -CH_2), 3.20–3.24 (t, *J* = 6.6 Hz, 2 H, -CH_2), 1.77–1.83 (t, *J* = 12 Hz, 4 H, -2CH_2).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.06, 45.81, 43.13, 24.91, 24.23.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for C_5H_9NO: 100.07; found: 100.3.

LCMS purity = 99.82%.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for C_5H_9NO: 100.0684; found: 100.1117.

***N*-*tert*-Butylformamide 3o**

Yield: 53%; colorless liquid; TLC R_f = 0.29 (petroleum ether/ethyl acetate 5:5 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.847–7.843 (d, J = 1.6 Hz, 1 H, -CHO), 7.69 (s, 1 H, -NH), 7.26 (s, 9 H, -3CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 161.79, 50.26, 28.99.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_5H_{11}NO$: 102.08; found: 102.3.

LCMS purity = 99.34%.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_5H_{11}NO$: 102.0841; found: 102.0932.

***N*,*N*-Dimethylformamide 3p**

Yield: 58%; colorless liquid; TLC R_f = 0.74 (dichloromethane/methanol 9:1 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.95 (s, 1 H, -CHO), 2.89 (s, 3 H, -CH_3), 2.737–2.738 (d, 3 H, -CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.76, 36.22, 31.21.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for C_3H_7NO: 74.05; found: 147.2 [M + H × 2, dimer mass]$^+$.

LCMS purity = 97.31%.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for C_3H_7NO: 74.0528; found: 74.0906.

***N*-Phenylformamide 5a**

Yield: 63%; off-white solid; TLC R_f = 0.45 (petroleum ether/ethyl acetate 5:5 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.18 (s, 1 H, -NH), 8.27–8.28 (d, *J* = 1.6 Hz, 1 H, -CHO), 7.58–7.60 (d, *J* = 7.6 Hz, 2 H, Ar-H), 7.30–7.34 (t, *J* = 8.0 Hz, 2 H, Ar-H), 7.06–7.11 (m, 1 H, -Ar-H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.04, 138.71, 129.33, 124.07, 119.59.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for C_7H_7NO: 122.05; found: 122.2.

LCMS purity = 99.88%.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for C_7H_7NO: 122.0528; found: 122.1004.

***N*-(4-Methoxyphenyl)formamide 5b**

Yield: 71%; pale-brown solid; TLC R_f = 0.32 (petroleum ether/ethyl acetate 5:5 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.00 (s, 1 H, -NH), 8.19–8.20 (d, *J* = 2.0 Hz, 1 H, -CHO), 7.48–7.52 (m, 2 H, Ar-H), 6.87–6.91 (m, 2 H, Ar-H), 3.72 (s, 3 H, -OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.50, 155.86, 131.92, 120.16, 114.43, 55.63.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_9NO_2$: 152.06; found: 152.2.

LCMS purity = 99.81%.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_9NO_2$: 152.0633; found: 152.1145.

***N*-*p*-Tolylformamide 5c**

Yield: 72%; pale-brown solid; TLC R_f = 0.45 (petroleum ether/ethyl acetate 5:5 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.07 (s, 1 H, -NH), 8.222–8.227 (d, *J* = 2.0 Hz, 1 H, -CHO), 7.45–7.48 (m, 1 H, Ar-H), 7.05–7.12 (m, 3 H, Ar-H), 2.24 (s, 3 H, -CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 159.77, 136.22, 133.15, 132.97, 129.66, 119.55, 20.89.

MS (ESI): *m*/*z* [M + H]$^+$ calcd for C_8H_9NO: 136.07; found: 136.1.

LCMS purity = 99.94%.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for C_8H_9NO: 136.0684; found: 136.1183.

***N*-(4-Bromophenyl)formamide 5d**

Yield: 55%; off-white solid; TLC R_f = 0.41 (petroleum ether/ethyl acetate 5:5 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.32 (s, 1 H, -NH), 8.293–8.298 (d, *J* = 2.0 Hz, 1 H, -CHO), 7.54–7.58 (m, 2 H, Ar-H), 7.48–7.52 (m, 2 H, Ar-H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.22, 138.04, 132.15, 121.55, 115.64.

MS (ESI): *m*/*z* [M – H]$^{-2}$ calcd for C_7H_6BrNO: 199.96; found: 200.1.

LCMS purity = 99.16%.

HRMS (ESI): *m*/*z* calcd for C_7H_6BrNO [^{79}Br]$^+$ [M + H]$^+$: 199.9633, [^{81}Br] [M + H]$^{+2}$: 201.9633; found: 200.0219 [M + H]$^+$, 202.0183 [M + H]$^{+2}$.

***N*-(4,6-Dichloropyrimidin-2-yl)formamide 5e**

Yield: 48%; off-white solid; TLC R_f = 0.64 (petroleum ether/ethyl acetate 5:5 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.52 (s, 1 H, -NH), 9.06 (S, 1 H, -CHO), 7.38 (S, 1 H, Ar-H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 162.63, 161.48, 159.06, 107.05.

MS (ESI): *m*/*z* calcd for $C_5H_3Cl_2N_3O$ [M + H]$^+$: 191.97, $C_5H_3Cl_2N_3O$ [M + H]$^{+2}$: 193.97; found: 192.0 [M + H]$^+$, 194.0 [M + H]$^{+2}$.

LCMS purity = 97.68%.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_5H_3Cl_2N_3O$: 191.9653; found: 192.0220.

***N*-(4-(Chlorodifluoromethoxy)phenyl)formamide 5f**

Yield: 66%; pale-yellow solid; TLC R_f = 0.45 (petroleum ether/ethyl acetate 5:5 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.40 (s, 1 H, -NH), 8.305–8.309 (d, *J* = 1.6 Hz, 1 H, -CHO), 7.69–7.72 (m, 2 H, Ar-H), 7.31–7.34 (d, *J* = 8.4 Hz, 2 H, Ar-H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.24, 145.37, 137.92, 125.43, 123.15, 122.58, 120.92, 119.13.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –24.85.

MS (ESI): *m*/*z* [M – H]$^-$ calcd for $C_8H_6ClF_2NO_2$: 220.01; found: 220.0.

LCMS purity = 99.77%.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_8H_6ClF_2NO_2$: 222.0055; found: 222.0668.

Methyl 4-(Benzylamino)-3-formamidobenzoate 5g

Yield: 54%; pale-brown solid; TLC R_f = 0.47 (petroleum ether/ethyl acetate 5:5 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.53 (s, 1 H, -NH), 8.306–8.309 (d, *J* = 1.2 Hz, 1 H, -CHO), 7.86–7.87 (d, *J* = 2.0 Hz, 1 H, -NH), 7.55–7.58 (m, 1 H, Ar-H), 7.31–7.38 (m, 4 H, Ar-H), 7.22–7.26 (m, 1 H, Ar-H), 6.56–6.59 (m, 1 H, Ar-H), 6.478 (s, 1 H, Ar-H), 4.41–4.43 (d, *J* = 6.0 Hz, 2 H, -CH_2), 3.74 (s, 3 H, -CH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.50, 164.41, 146.47, 139.44, 128.94, 127.54, 127.39, 121.91, 116.42, 110.43, 51.87, 46.34.

MS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{16}N_2O_2$: 285.12; found: 285.1.

LCMS purity = 99.90%.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{16}N_2O_2$: 285.1161; found: 285.1861.

1-(Chlorodifluoromethoxy)-4-isocyanobenzene 6a

To a solution of compound **4f** (150 mg, 0.774 mmol, 1.0 equiv) in THF (2 mL) in a 10 mL microwave reaction vial, 2-formyl-1,3-dimethyl-1*H*-imidazol-3-ium iodide **2** (198 mg, 0.785 mmol, 1.0 equiv) and triethylamine (0.1 mL, 0.716 mmol, 0.9 equiv) were added at room temperature under a nitrogen atmosphere. The resulting reaction mixture was pre-stirred for 1 minute and then it was heated at 70 °C for 20 minutes under microwave irradiation. Then the reaction mixture was cooled to 0 °C, triethylamine (0.36 mL, 2.581 mmol, 3.3 equiv) and phosphorus oxychloride (0.08 mL, 0.858 mmol, 1.1 equiv) were added and the mixture was stirred for 1 minute and then heated at 50 °C for 10 minutes under microwave irradiation. After that, the reaction mixture was cooled to room temperature, quenched with ice cold water and the organic phase was extracted with ethyl acetate (3 × 15 mL). The combined organic phases were washed with water and brine, the organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to obtain the crude product. The crude product was purified by silica gel column chromatography eluting with 15–20% ethyl acetate in petroleum ether to obtain **6a** as a dark gum in 58% yield (91 mg).

TLC R_f = 0.92 (petroleum ether/ethyl acetate 5:5 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.74–7.78 (m, 2 H, Ar-H), 7.50–7.54 (m, 2 H, Ar-H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.82, 149.97, 149.95, 129.11, 127.91, 125.04, 123.34, 122.17.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –25.27.

MS (ESI): m/z [M + H]$^+$ calcd for $C_8H_4ClF_2NO$: 203.99; found 203.9.

LCMS purity = 96.10%.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_8H_4ClF_2NO$: 203.9944; found: 204.0218.

2-(Isocyanomethyl)pyridine 6b

To a solution of **1h** (150 mg, 1.237 mmol) in THF (2 mL) in a 10 mL microwave reaction vial, 2-formyl-1,3-dimethyl-1*H*-imidazol-3-ium iodide **2** (313 mg, 1.241 mmol, 1.0 equiv) was added at room temperature under a nitrogen atmosphere. The resulting reaction mixture was pre-stirred for 1 minute and then it was heated at 70 °C for 20 minutes under microwave irradiation. Then the reaction mixture was cooled to 0 °C, triethylamine (0.58 mL, 4.158 mmol, 3.3 equiv) and phosphorus oxychloride (0.13 mL, 1.394 mmol, 1.1 equiv) were added, the mixture was stirred for 1 minute and then it was heated at 50 °C for 10 minutes under microwave irradiation. After that, the reaction mixture was cooled to room temperature, quenched with ice cold water and the organic phase was extracted with ethyl acetate (3 × 15 mL). The combined organic phases were washed with water and brine. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to obtain the crude product. The crude product was purified by silica gel column chromatography using 60–70% ethyl acetate in petroleum ether to obtain pure compound **6b** as an off-white solid in 66% yield (121 mg).

TLC R_f = 0.26 (petroleum ether/ethyl acetate 5:5 V/V).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (s, 1 H, Ar-H), 7.93–7.95 (m, 1 H, Ar-H), 7.43–7.47 (m, 2 H, Ar-H), 6.70–6.74 (m, 1 H, -CH_2), 6.55–6.59 (m, 1 H, -CH_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.28, 127.56, 122.31, 119.79, 119.00, 118.40, 112.73.

MS (ESI): m/z [M + H]$^+$ calcd for $C_7H_6N_2$: 119.05; found: 119.0.

LCMS purity = 92.36%.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_7H_6N_2$: 119.0531; found: 119.1021.

Methyl 1-Benzyl-1*H*-benzo[*d*]imidazole-5-carboxylate 6c

To a solution of **4g** (150 mg, 0.585 mmol, 1.0 mmol) in THF (2 mL) in a 10 mL microwave reaction vial, 2-formyl-1,3-dimethyl-1*H*-imidazol-3-ium iodide **2** (148 mg, 0.587 mmol, 1.0 equiv), and triethylamine (0.08 mL, 0.573 mmol, 1.0 equiv) were added at room temperature under a nitrogen atmosphere. The resulting reaction mixture was pre-stirred for 1 minute and then it was heated at 70 °C for 20 minutes under microwave irradiation. The reaction mixture was cooled to room temperature then glacial acetic acid (1.0 mL) was added. The resulting mixture was stirred for 3 minutes and then heated at 80 °C for 45 minutes under microwave irradiation and then cooled to room temperature. The reaction was quenched with ice cold water, the organic phase was extracted with ethyl acetate (3 × 15 mL) and the combined organic phases were washed with water and brine. The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to obtain the crude product. The crude product was purified by silica gel column chromatography eluting with 30–35% ethyl acetate in petroleum ether to obtain pure **6c** as a pale-yellow solid in 51% yield (79 mg).

TLC R_f = 0.52 (petroleum ether/ethyl acetate 5:5 V/V).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.58 (s, 1 H, Ar-H), 8.26–8.27 (d, J = 1.2 Hz, 1 H, Ar-H), 7.84–7.87 (m, 1 H, Ar-H), 7.64–7.66 (m, 1 H, Ar-H), 7.28–7.37 (m, 5 H, Ar-H), 5.56 (s, 2 H, -CH_2), 3.73 (s, 3 H, -OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.14, 146.93, 143.63, 137.49, 137.05, 129.24, 128.34, 127.88, 123.95, 123.81, 121.70, 111.37, 52.48, 48.27.

MS (ESI): m/z [M + H]$^+$ calcd for $C_{16}H_{14}N_2O_2$: 267.11; found: 267.1.

LCMS purity = 94.62%.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{16}H_{14}N_2O_2$: 267.1055; found: 267.1755.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding Information

Financial support from the Vision Group on Science and Technology, Government of Karnataka (No. VGST/SMYSR/GRD-426) is gratefully acknowledged.

Acknowledgment

We thank the NMR, LCMS & HRMS Facility, Institute of Excellence, University of Mysore, Manasagangotri, Mysuru-570006, India, for analyses.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0041-1737605. Included are the synthetic procedure for the synthesis of formylating agent **2** as well as ^{1}H NMR, ^{13}C NMR, LCMS, HRMS data for formylating agent **2** and final compounds **3a–p**, **5a–g**, **6a**, **6b** and **6c**.

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