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Article

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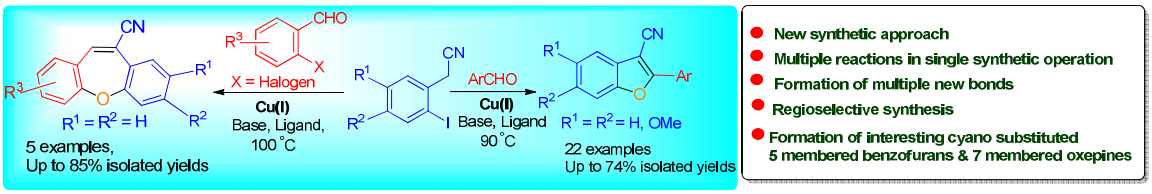
Copper Catalyzed Cascade Synthesis of 2-Aryl-3-cyanobenzofuran and Dibenzo[*b,f*]oxepine-10-carbonitrile Derivatives

Bharath Kumar Villuri,[a] Sachin S. Ichake,[a] Sabbasani Rajasekhara Reddy,[a,b] Veerababurao Kavala,[a] Vijayalakshmi Bandi,[a] Chun-Wei Kuo[a] and Ching-Fa Yao[a]*

[a]Department of Chemistry, National Taiwan Normal University, 88, Section 4, Ting-Chow Road, Taipei 116, Taiwan, R.O.C.

[b]Department of Chemistry, School of Advanced Sciences, VIT University, Vellore-632014, India.

Supporting Information Placeholder



ABSTRACT: The copper catalyzed reaction of aryl aldehydes with 2-iodobenzylcyanides afforded 2-aryl-3-cyanobenzofurans in isolated yields of up to 74% in a cascade manner, which involves Knoevenagel condensation, aryl hydroxylation, oxa-Michael addition and aromatization reactions. Conversely, 2-halo benzaldehydes as reacting partners with 2-iodobenzylcyanide furnished regioselectively dibenzo[*b,f*]oxepine-10-carbonitrile derivatives up to 85% isolated yields *via* tandem Knoevenagel condensation, aryl hydroxylation and Ullmann coupling reactions.

Introduction

Benzofuran scaffolds are components of a wide variety of therapeutic drugs.[1] Notably, 2-aryl-3-cyanobenzofuran moieties are key intermediates in the synthesis of bioactive inhibitors of the hepatitis C virus (HCV).[2] These moieties also have desirable mechanochromic properties, giving them the potential for serving as applications in organic light emitting diodes (OLEDs).[3] Although, many strategies have been developed for the construction of 2-aryl-3-cyanobenzofurans, some alternate and convenient protocols are needed to broaden the scope for the synthesis of different types of substituted 2-aryl-3-cyanobenzofuran derivatives. These include, the direct cyanation of benzofurans,[4] functional group inter-conversion (FGI) from 2-aryl-3-amidobenzofurans,[5] an aromatic ring umpolong reaction of catechols with $PhCOCH_2CN$,[6] the cycloaddition of benzyne with iodonium yillide,[7] and by the intramolecular joining of a pre-existing oxygen (-O-) containing moiety on the side chain to its benzene ring at the ortho position through C-O bond formation.[8] Ruihu Wang *et al*. recently reported on the synthesis of 2-phenylbenzofuran through the hydroxyintermediate **I,** for use in the hydroxylation of iodoarenes (**Scheme 1**, eq 1).[9] Fan and coworkers also synthesized 3-cyano-1H-indoles using *o*-bromobenzylcynide and arylaldehydes as starting materials through the amine intermediate **II**, in which, ammonium hydroxide was used as a nitrogen source (**Scheme 1**, eq 2).[10] Yanguang Wang *et al*.[11a] and other groups reported on the synthesis of 2-aryl-3-cyanobenzofurans using pre-installed oxygen (-O-) containing arenes through the formation of the intermediate **III** (**Scheme 1**, eq 3).[11]

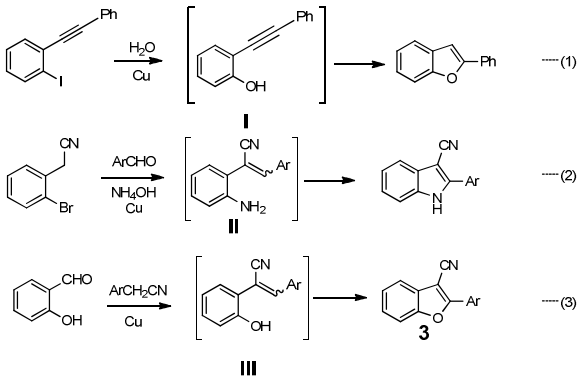
In a continuation of our research efforts in exploring additional synthetic aspects of 2-Iodobezylcyanide surrogates for the construction of various valuable heterocyles[12] and based on clues provided in literature cited above (**Scheme 1**, eq1-eq3), we hypothesized that if might be possible to prepare, 2-aryl-3-cyanobenzofuran derivatives through the *in situ* generation of the hydroxyl intermediate **III** from iodoarene, using 2-iodobenzylcyanides **2a** and benzaldehyde **1a** as starting materials (**Scheme 2**, eq4). This might be achieved through Knoevenagel condensation, aryl hydroxylation, oxa-Michael addition and aromatization reactions in a cascade manner by utilizing some previously reported copper mediating protocols.[13] We further, hypothesized that the reaction of 2-halobenzaldehydes with **2a,** could result in the formation of either seven membered oxepines **4** or benzofurans **3** (**Scheme 2**, eq5).

Results and Discussion

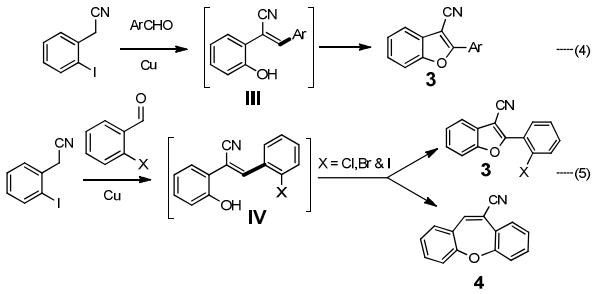
In order to verify our hypothesis for producing the proposed 2-aryl-3-cyanobenzofurans (**Scheme 2,** eq 4), a set of experiments was initially carried out by using 20 mol% of CuI as a standard catalyst along with 3 equiv of Cs_2CO_3 in 2 ml of DMSO solvent at 100 °C, and varying the amount of benzal-

dehyde **1a,** with 2-iodobenzylcyanide **2a,** ligands and additives. The results are presented in **Table 1**.

Scheme 1. Recent relevant strategies for the synthesis of Indole and benzofurans

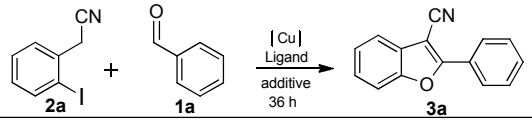


Scheme 2. Current hypothesis

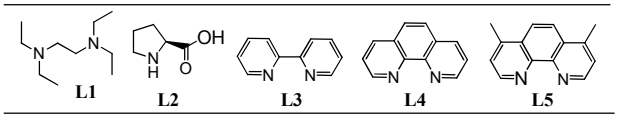


An initial experiment, which was carried using standard reagents (20 mol% of CuI, 3 equiv of Cs_2CO_3 in 2 ml of DMSO), with 1.1 equiv of 1a and 0.5 mmol of 2a, resulted in the decomposition of the compound 2a, while compound 1a remained unreacted (entry 1). When 1.4 equiv of 2a and 0.5 mmol of 1a were used a trace amount of the blue colored illuminiscent 3a was observed under UV light (entry 2). Thus, all further reactions were carried out using an excess amount of compound 2a (1.4 equiv). In order to increase product yield, 50 mol% of a series of different ligands such as tetraethylethane-1,2-diamine (L1), proline (L2), 2,2'-bipyridine (L3), 1,10-phenanthroline (L4) and 4,7-dimethyl-1,10-phenanthroline (L5) were examined under standard reagent conditions with 0.5 mmol of 1a and 1.4 equiv of 2a. Among all of the ligands tested, L5 was found to be the best, giving a maximum yield of the product 3a of 55% (entries 3 and 7). To our delight, the characteristic data (^1H & ^{13}C NMR) of this isolated compound was found to be same as that of the previously reported 2-aryl-3-cyanobenzofuran. To further improve the yield in the reaction, we used 0.5 equiv of TBAB (Tetra butyl ammonium bromide) as an additive. The yields were increased to 59% with L4 and to 67% with L5 (entries 8 and 9). A second set of experiments in which 20 mol% of var ious other copper salts were used, i.e., CuCl, CuBr, $Cu(OAc)_2$ and $Pd(OAc)_2$ along with 50 mol% of the additive. The results revealed that, CuCl gave the maximum yield of the product at 71% (entry, 10) and CuBr gave a moderate yield of the product, while the others resulted in trace amounts of the product or decomposition (entries, 12&13). A third set of experiments was directed at the effect of strong and weak bases such as tBuOK and K_2CO_3, which resulted in the decomposition of the reactants or a low product yield (Entries 14 & 15). In a fourth set of experiments, designed to examine the effect of other polar solvents such as DMF and DMAc, the use of DMF resulted a 20 % product yield and no reaction was observed in DMAc (Entries 16 &17). The final set of experiments involved investigating various additives other than TBAB and included TBAC (Tetra butyl ammonium chloride, TBAI (Tetra butyl ammonium iodide), and CTAB (Cetyl trimethyl Ammonium bromide), none of which were satisfactory (Entries 18 - 20).

Table 1.Optimization of the synthesis of 2-aryl 3-cyanobenzofurans **3**



Entry[a]	Catalyst (20 mol %)	Base (3 equiv)	Solvent (2 ml)	Ligand (50 mol %)	Additive (0.5 equiv)	Yield (%)[b,e] 3a
1[d]	CuI	Cs_2CO_3	DMSO	--	--	ND
2	CuI	Cs_2CO_3	DMSO	--	--	Trace
3	CuI	Cs_2CO_3	DMSO	L1	--	--
4	CuI	Cs_2CO_3	DMSO	L2	--	7
5	CuI	Cs_2CO_3	DMSO	L3	--	35[c]
6	CuI	Cs_2CO_3	DMSO	L4	--	40
7	CuI	Cs_2CO_3	DMSO	L5	--	55
8	CuI	Cs_2CO_3	DMSO	L4	TBAB	59
9	CuI	Cs_2CO_3	DMSO	L5	TBAB	67
10	**CuCl**	**Cs_2CO_3**	**DMSO**	**L5**	**TBAB**	**71**
11	CuBr	Cs_2CO_3	DMSO	L5	TBAB	44
12	$Cu(OAc)_2$	Cs_2CO_3	DMSO	L5	TBAB	Trace
13	$Pd(OAc)_2$	Cs_2CO_3	DMSO	L5	TBAB	ND
14	CuCl	*t*-BuOK	DMSO	L5	TBAB	ND
15	CuCl	K_2CO_3	DMSO	L5	TBAB	18
16	CuCl	Cs_2CO_3	DMF	L5	TBAB	20
17	CuCl	Cs_2CO_3	DMAc	L5	TBAB	--
18	CuCl	Cs_2CO_3	DMSO	L5	TBAC	66
19	CuCl	Cs_2CO_3	DMSO	L5	TBAI	52
20	CuCl	Cs_2CO_3	DMSO	L5	CTAB	41



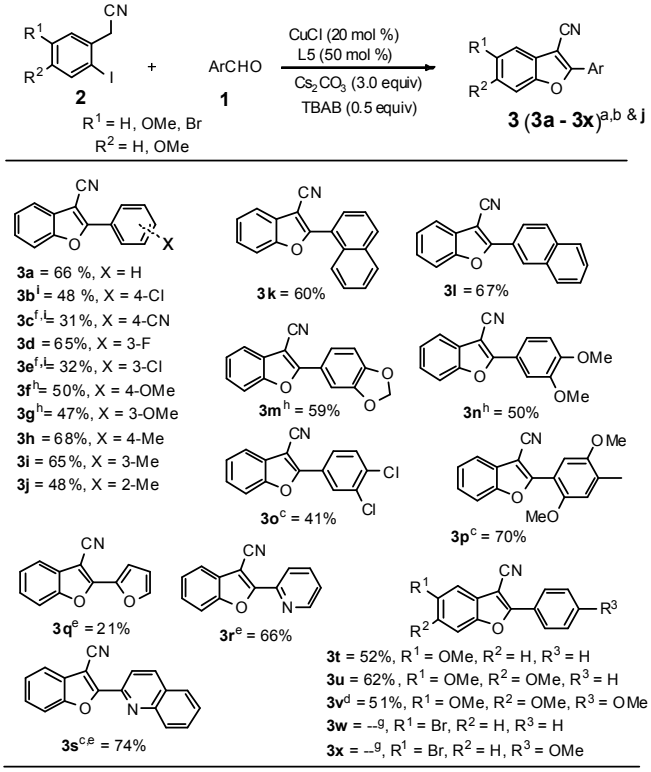
(a) All reactions were performed on a 0.5 mmol scale of **1a** and 1.4 equiv of **2a** at 90 °C under an open air atmosphere; (b) NMR yields; (c) Isolated yield; (d) **2a** (0.5 mmol) and **1a** (1.1 equiv). (d) N.D: not determined (due to decomposion of **2a**); (e) In all the entries, 5-50 % of unreacted benzaldehyde **1a** was recovered due to the decomposition of **2a** at 90 °C, except in the case of entries 9,10 & 18.

Entry 10, in **Table 1** provides information on the optimized reaction conditions, based on the above observations.

Having the afore mentioned reaction conditions in hand, the scope of the methodology with diverse aldehydes and 2-iodobenzylcyanide substrates was examined (**Table 2**). Reactions of benzaldehyde **1** derivatives containing electron withdrawing groups Cl and CN at para positions and 2-iodobenzylcyanide furnished **3b** and **3c** in 48% and 31% yield, respectively. The decreased yield of **3c** can be attributed to the strong deactivating effect of the 4-CN group. F and Cl substituents at the meta positions afforded **3d** in 65% and **3e** in 32% yields. In the case of a strong electron donating group (OMe) at the para position, the corresponding 3-cyano-2-phenylbenzofuran derivatives were produced in 50 % yield. A meta methoxy substituted aldehyde gave the desired product **3g** in 47% yield. Next, the effects of moderate electron donating groups (Me) in aldehyde substrates such as 4-Me, 3-Me and 2-Me benzaldehydes with 2-iodobenzylcyanide were investigated. The reaction of the 4-methylbenzaldehyde sub-

strate gave the desired product **3h** in 68 % and 3-methylbenzaldehyde afforded the corresponding product **3i** in 65%, while, 2-methylbenzaldehyde provided a slightly lower yield (48%) of the desired product **3j** compared with the reactions of 4-methyl and 3-methylbenzaldehyde derivatives, which likely due to the effect of the ortho methyl group. We next examined the reactions of 1-naphthyladehyde and 2-naphthylaldehyde with 2-iodobenzylcyanide under the optimized conditions. In both the cases, the desired 3-cyano-2-phenylbenzofuran derivatives (**3k, 3l**) were obtained in good yields. The reactions of disubstituted benzaldehydes containing the electron donating groups (OMe) and methylenedioxy with 2-iodobenzylcyanide were studied. The reactions afforded the corresponding 3-cyano-2-phenylbenzofuran derivatives **3m** and **3n** in 59% and 50%, respectively. However, the reaction of 3,4-dichlorobenzaldehyde gave only a 41% of the 3-cyano-2-phenylbenzofuran derivative (**3o**). It is noteworthy that chloro substituted compounds other than at the meta position resulted in moderate yields of the products (**3b** & **3o**). In particular, a chloro substitution at the meta position delivered a lower yield (**3e**). We subsequently examined the reaction of a benzaldehyde containing a tri electron releasing group and 2-iodobenzylcyanide under the optimized conditions. The reaction furnished the desired product (**3p**) in good yield (70%). Consequently, we investigated the reactions of various heterocyclic rings containing aldehyde groups and 2-iodobenzylcyanide. With furaldehyde, the reaction resulted in the desired product (**3q**) in 21% yield, whereas with pyridine and quinoline substituents, the reactions provided the corresponding products (**3r**) and (**3s**) in 66% and 74% yields, respectively.

Table 2. Scope for the synthesis of 2-aryl-3-cyanobenzofurans **3**



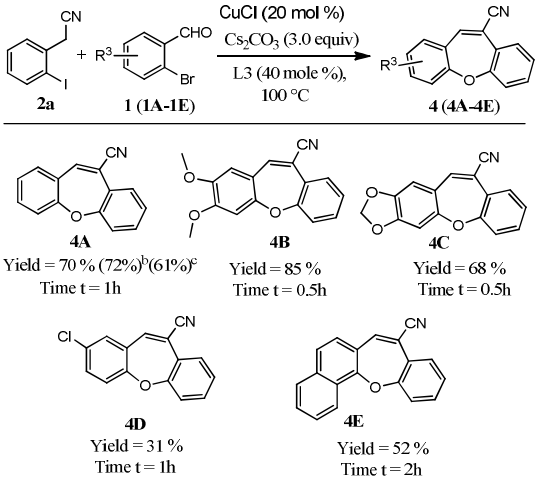
(a) Reaction conditions: 1 (1.0 mmol), 2 (1.4 equiv) and DMSO (4.0 ml) for 36 h at 90 °C under open air atmosphere; (b) Isolated yields based on 1; (c) The additive TBAB was not added; (d) Reaction performed on a 0.4 mmol scale for 4-OMe benzaldehyde; (e) Reaction time is 10 h; (f) Reaction time is 12 h; (g) mixture of compounds; (h) 1.8 equivof 2a was used; (i) 10 - 15 % of unidentified mixture of compounds were absorved; (j) Traces amounts to 5% of corresponding aldehyde **1** along with **3** were absorved in some of the reactions.

We also tested the scope of the methodology with respect to substituted 2-iodobenzylcyanide substrates and benzaldehyde. The reaction between 2-iodobenzylcyanide equipped with methoxy group and benzaldehyde, produced the corresponding product (**3t**) in a 52% yield. In addition, 3,4-dimethoxy substituted 2-iodobenzylcyanide reacted with benzaldehyde in the present reaction to give the desired 3-cyano-2-phenylbenzofuran derivative (**3u**) in 62% yield, whereas the desired product (**3v**) was produced in 51% yield in the case of 4-methoxybenzaldehyde. Unfortunately, the developed protocol failed to produce (**3w**) and (**3x**) and resulted in a mixture of compounds when bromo substituted 2-iodobenzylcyanide was used.

The developed catalytic system was tested for the synthesis of either seven membered oxepines **4** or benzofurans **3** as per our proposed hypothesis (**Scheme 2**, eq5). Apart from benzofuran scaffolds, dibenzo[b,f]oxepine-10-carbonitrile derivatives are also known to be valuable derivatives in medicinal chemistry.[14b] In spite of this, only a few synthetic methods using 2-hydroxybenzylcyanide as reacting partner with 2-halo benzaldehydes have been reported.[15] Unlike these reports, the synthesis of dibenzo[b,f]oxepine-10-carbonitrile derivatives **4** using 2-iodo benzylcyanides **2a** as the reaction partner with 2-halo benzaldehydes which includes 2-bromo, 2-chloro and 2-iodo benzaldehyde derivatives proceeded well.

In all three cases, dibenzo[*b,f*]oxepine-10-carbonitrile (**4A**) was produced exclusively in yields of 70%, 72% and 61%, respectively, within a short period of time (1 h). Hence, the synthesis of dibenzo[*b,f*]oxepine-10-carbonitrile derivatives **4** gave the expected products in 31-85% isolated yields using 2-iodobenzylcyanide **2a** as a reacting partner with the 2-bromobenzaldehydes (**1B–1E**), as shown in Table 3.

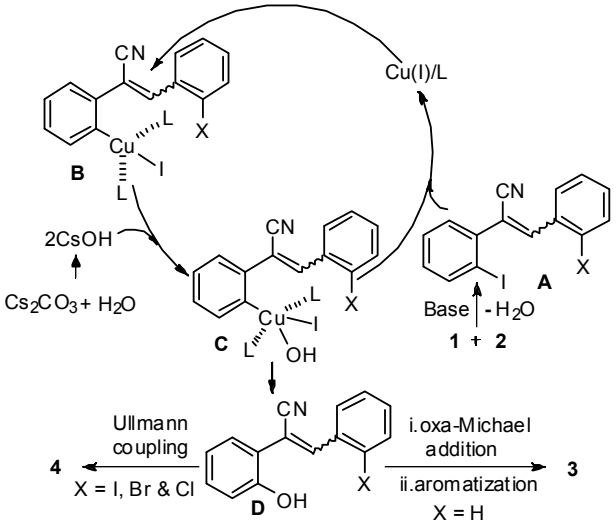
Table 3. Synthesis of dibenzo[b,f]oxepine-10-carbonitrile derivatives **4**[a]



(a) Reaction conditions: **1** (1.0 mmol), **2a** (1.1 equiv) and DMSO (3.0 ml) under open air atmosphere; (b) **1** is 2-iodo benzaldehyde; (c) **1** is 2-chloro benzaldehyde.

Consistent with earlier reports in the literature, based on the proposed mechanism by Deping Wang *et al.*[14a], a possible mechanism in which the reaction proceeds through Metal/L

catalyzed hydroxylation of aryl halides[14,9] is shown in **Scheme 3**. In addition, based on mechanistic studies of Xue and coworkers[14c], it was evident that upon aryl hydroxylation, the OH group of the resulting intermediate **D** originated from water. In addition, based on our observations, the formation of dibenzo[*b,f*]oxepine-10-carbonitrile derivatives **4** provides clear evidence that the formation of 2-aryl-3-cyanobenzofurans **3** proceeds through an aryl hydroxylation reaction. Considering the above aspects as mechanistic support, a possible mechanism was formulated in such a way that, in the initial step, the intermediate **A** is formed in the presence of a base *via* a Knoevenagel condensation reaction from **1** and **2** by releasing a water molecule. Intermediate **A** then undergoes oxidative addition to produce intermediate **B** by the Cu(I)/Ligand. Further, intermediate **B** undergoes nucleophilic addition by CsOH which is generated from Cs_2CO_3 and water to form intermediate **C**. Intermediate **C** then further undergoes reductive elimination to produce D, and re-initiates the [Cu(I)] catalytic cycle. Finally, Intermediate **D**, undergoes oxa-Michael addition and aromatization to produce the desired compound **3**.[13a] On the contrary, 2-halo benzaldehyde as reacting partner results in the Ullmann coupling product **4** from intermediate **D** as the major product.



Scheme 3. Possible reaction path way

CONCLUSION

In summary, we report on the synthesis of 2-aryl 3-cyanobenzofurans **3** and dibenzo[*b,f*]oxepine-10-carbonitrilederivatives **4** through Copper catalysis, using 2-iodobenzylcyanides **2** and 2-aryl aldehydes **1**. The new approach developed is regioselective and proceeds through a cascade one pot reaction to produce several substituted five membered benzofurans and seven membered oxepines through the formation of multiple new bonds under atmospheric oxygen.

EXPERIMENTAL SECTION

General Information

Unless otherwise stated, all reagents and solvents were purchased from commercial suppliers and were used directly without further purification. The 10 ml sealed vials were cleaned by drying in an oven overnight and cooled to room temperature prior to use. All reactions that required anhydrous conditions were conducted under an argon atmosphere. Flash column chromatography was performed on 63-200 mesh silica gel using freshly distilled *n*-hexane and ethyl acetate as eluents. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ascend spectrometer 600, 400 and 150, 100 MHz, respectively. Chemical shifts are reported in parts per million (ppm) on the δ scale by using $CDCl_3$ or d_6-DMSO as an internal standard. Multiplicities were indicated by using abbreviations such as s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. Coupling constants are expressed in Hertz (Hz). High Resolution Mass Spectra (HRMS) were recorded on ESI, EI+ve and EI–ve modes. The melting points (mp) were recorded on an Electro Thermal FARGO MP-2D capillary melting point apparatus.

i. General procedure for the synthesis of compounds **3a-3v**.

A 10 ml vial was charged with 1.0 mmol of aryl aldehyde, 1.4 mmol of 2-iodobenzylcyanide, 20 mol% of CuI, 50 mol % of ligand, 3.5 equiv of Cs_2CO_3 and 0.5 equivalents of TBAB and 4 ml of DMSO. The resulting reaction mixture was placed on an oil bath that was preheated to 90 ^{o}C and stirred for about 36 h under an open atmosphere. The progress of reaction was monitored by TLC at 2h time points. After the reaction reached completion, 10 ml of ethyl acetate was added and filtered from the salts. Brine was added to the filtrate and the solution and extracted with ethyl acetate (2 x 10 ml). The residue was purified by column chromatography on silica gel using n-Hexane/ethyl acetate as eluents to obtain the pure products **3a-3v**.

ii. General procedure for the synthesis of compounds **4A-4E**.

A 10 ml vial was charged with 1.0 mmol of aryl aldehyde, 1.4 mmol of 2-iodobenzylcyanide, 20 mol% of CuI, 40 mol % of ligand and 3.0 equiv of Cs_2CO_3 and 4 ml of DMSO. The resulted reaction mixture was placed on an oil bath that was preheated to 100 ^{o}C and stirred under an open atmosphere. The progress of the reaction was monitored by TLC. After the reaction reached completion, the reaction mixture was added to 10 ml of ethyl acetate and the salts removed by filtration. Brine was then added to the filtrate and the solution extracted with ethyl acetate (2 x 10 ml). The residue was purified by column chromatography on silica gel using n-Hexane/ethyl acetate as eluents to obtain pure products **4A-4E.**

iii. Analysis data of **3a-3v** and **4A- 4E**.

2-phenylbenzofuran-3-carbonitrile (**3a**)

Eluent: *n*-hexane (100%); Off White Solid; Yield: 144 mg (66%); Mp: 80–81 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.20 (dd, *J* = 8.0 Hz, 1.6 Hz, 2H), 7.71 (dd, *J* = 8.2 Hz, 1.6 Hz, 1H), 7.60-7.53(m, 4H), 7.43-7.39 (m, 2H. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.9, 153.6, 131.5, 129.4, 128.1, 127.5, 126.8, 126.7, 128.6, 124.9, 120.2, 114.5, 111.9, 88.4. HRMS (EI): Calcd for $C_{15}H_9NO$ $[M]^+$ 219.0684, found: 219.0686.

2-(4-chlorophenyl)benzofuran-3-carbonitrile (**3b)**

Eluent: *n*-hexane (100%); White Solid; Yield: 122 mg (48%); Mp: 132–133 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (dd, *J* = 8.8 Hz, 2.0 Hz, 2H), 7.71 (d, *J* = 7.2 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.51 (dd, *J* = 8.8 Hz, 2.0 Hz, 2H), 7.45-7.37 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.7, 153.6, 137.6, 129.8, 127.9, 127.3, 126.9, 126.5, 125.1, 120.3, 114.3, 111.9, 88.8. HRMS (EI): Calcd for $C_{15}H_8ClNO$ $[M]^+$ 253.0294, found: 253.0295.

2-(4-cyanophenyl)benzofuran-3-carbonitrile (**3c**)

Eluent: *n*-hexane / ethyl acetate (99 ml / 1 ml); White Solid; Yield: 76 mg (31%); Mp: 228-229 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.31 (d, *J* = 8.8 Hz, 2H), 7.84 (d, *J* = 7.6 Hz, 2H), 7.77 (d, *J* = 7.2 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H),7.52-7.43 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.0, 153.9, 133.1, 131.8, 127.8, 127.1, 126.9, 125.4, 120.6, 118.2, 114.5, 113.7, 112.2, 91.0. HRMS (EI): Calcd for $C_{16}H_8N_2O$ $[M]^+$ 244.0637, found: 244.0638.

2-(3-fluorophenyl)benzofuran-3-carbonitrile (**3d**)

Eluent: *n*-hexane (100%); White Solid; Yield: 154 mg (65%); Mp: 137-138 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01 (d, *J* = 7.6 Hz, 1H), 7.84 (dd, *J* = 9.2Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.54 -7.48 (m, 1H), 7.45 - 7.37 (m, 2H), 7.22 (t, *J* = 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.4 (d, J_{C-F} = 246.0 Hz), 160.2, 153.6, 131.2 (d, J_{C-F} = 8.0 Hz), 130.0, 129.9 (d, J_{C-F} = 8.0 Hz), 127.2, 127.1, 125.1, 122.5 (J_{C-F} = 3.0 Hz), 120.3, 118.5 (J_{C-F} = 21.0 Hz), 114.1, 113.7 (J_{C-F} = 24.0 Hz), 112.0, 89.3. HRMS (EI): Calcd for $C_{15}H_8FNO$ $[M]^+$ 237.0590, found: 237.0589.

2-(3-chlorophenyl)benzofuran-3-carbonitrile (**3e**)

Eluent: *n*-hexane (100%); White Solid; Yield: 81 mg (32%); Mp: 139-140 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14 (s, 2H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 4.4 Hz, 2H), 7.46-7.40 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.1, 153.7, 135.6, 131.7, 129.7, 127.3, 127.1, 126.6, 125.2, 124.8, 120.4, 114.0, 112.0, 89.3. HRMS (EI): Calcd for $C_{15}H_8ClNO$ $[M]^+$ 253.0294, found: 253.0293.

2-(4-methoxyphenyl)benzofuran-3-carbonitrile (**3f**)

Eluent: *n*-hexane / ethyl acetate (95 ml / 5 ml); White Solid; Yield: 124 mg (50%); Mp: 151-152 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.15 (d, *J* = 8.8 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.39 - 7.34 (m, 2H), 7.04 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.3, 162.1, 153.3, 128.6, 127.7, 126.1, 124.8, 128.7, 119.6, 114.9, 114.8, 111.7, 86.5, 55.7. HRMS (EI): Calcd for $C_{16}H_{11}NO_2$ $[M]^+$ 249.0790, found: 249.0789.

2-(3-methoxyphenyl)benzofuran-3-carbonitrile (**3g**)

Eluent: *n*-hexane / ethyl acetate (95 ml / 5 ml); White Solid; Yield: 118 mg (47%); Mp: 85-86 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, *J* = 6.8 Hz, 1H), 7.68 (s, 2H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.45 - 7.37 (m, 3H), 7.04 (d, *J* = 7.6 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.7, 160.2, 153.5, 130.5, 129.1, 127.4, 126.6, 124.9, 120.2, 119.2, 117.8, 114.5, 111.9, 111.3, 88.5, 55.7. HRMS (EI): Calcd for $C_{16}H_{11}NO_2$ $[M]^+$ 249.0790, found: 249.0792.

2-(p-tolyl)benzofuran-3-carbonitrile (**3h**)

Eluent: *n*-hexane (100%); White Solid; Yield: 158 mg (68%); Mp: 136-137 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 7.2 Hz, 1H), 7.42 - 7.33 (m, 4H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.3, 153.4, 142.0, 130.1, 127.6, 126.7, 126.4, 125.3, 124.8, 120.0, 114.7, 111.8, 87.5, 21.8. HRMS (EI): Calcd for $C_{16}H_{11}NO$ $[M]^+$ 233.0841, found: 233.0842.

2-(m-tolyl)benzofuran-3-carbonitrile (**3i**)

Eluent: *n*-hexane (100%); White Solid; Yield: 135 mg (58%); Mp: 70 -71 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (d, *J* = 8.4 Hz, 2H), 7.70 (dd, *J* = 6.6, 2.2 Hz, 1H), 7.56 (dd, *J* = 6.6, 1.4 Hz, 1H), 7.44 -7.37 (m, 3H), 7.35 (d, *J* = 6.4 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.1, 153.5, 139.2, 132.3, 129.3, 128.0, 127.5, 127.2, 126.5, 124.8, 124.0, 120.1, 114.6, 111.9, 88.2, 21.7. HRMS (EI): Calcd for $C_{16}H_{11}NO$ $[M]^+$ 233.0841, found: 233.0841.

2-(o-tolyl)benzofuran-3-carbonitrile (**3j**)

Eluent: *n*-hexane (100%); White Solid; Yield: 57 mg (50%); Mp: 67 - 68 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76 (d, *J* = 6.8 Hz, 2H), 7.59 (dd, *J* = 6.6, 2.2 Hz, 1H), 7.46 -7.42 (m, 3H), 7.39 - 7.26 (m, 2H), 2.54 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.5, 154.0, 138.0, 131.7, 131.3, 130.3, 127.4, 126.8, 126.5, 126.4, 124.8, 122.2, 114.0, 112.0, 91.7, 21.0. HRMS (EI): Calcd for $C_{16}H_{11}NO$ $[M]^+$ 233.0841, found: 233.0842.

2-(naphthalen-1-yl)benzofuran-3-carbonitrile (**3k**)

Eluent: *n*-hexane (100%); White Solid; Yield: 161 mg (60%); Mp: 126-127 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23 (d, J = 8.4 Hz, 1H), 8.09 (d, J = 7.2 Hz, 1H), 8.10-7.95 (m, 2H), 7.81 (d, J = 6.2 Hz, 1H), 7.68-7.59 (m, 4H), 7.49-7.46 (m, 2H).13C NMR (CDCl3, 100 MHz): δ 164.0, 154.3, 134.1, 131.6, 132.3, 130.8, 129.6, 129.0, 127.8, 126.9, 126.6, 125.5, 125.4, 125.2, 125.0, 120.4, 113.9, 112.2, 92.7. HRMS (EI): Calcd for $C_{19}H_{11}NO$ $[M]^+$ 269.0841, found: 269.0841.

2-(naphthalen-2-yl)benzofuran-3-carbonitrile (**3l**)

Eluent: *n*-hexane (100%); White Solid; Yield: 180 mg (67%); Mp: 128-129 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.67 (s, 1H), 8.25 (d, *J* = 7.6 Hz, 1H), 7.97 (s, 2H), 7.87 (s, 1H), 7.73 (d, *J* = 6.0 Hz, 1H), 7.57 (s, 3H), 7.41 (s, 2H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.9, 153.7, 134.6, 133.2, 129.3, 129.2, 128.2, 128.1, 127.6, 127.3, 127.2, 126.7, 125.3, 124.9, 122.9, 120.2, 114.6, 111.9, 88.6. HRMS (EI): Calcd for $C_{19}H_{11}NO$ $[M]^+$ 269.0841, found: 269.0841.

2-(benzo[*d*][1,3]dioxol-5-yl)benzofuran-3-carbonitrile (**3m**)

Eluent: *n*-hexane / ethyl acetate (98 ml / 2 ml); White Solid; Yield: 155 mg (59%); Mp: 143-144 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.67 (dd, *J* = 6.2, 2.6 Hz, 1H), 7.62 (d, *J* = 1.2 Hz, 2H), 7.54 - 7.52 (m, 1H), 7.39 - 7.35 (m, 2H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.07 (s, 2H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.8, 153.3, 150.4, 148.6, 127.6, 126.3, 124.8, 122.1, 122.1, 119.9, 114.8, 111.7, 109.2, 106.7, 102.1, 87.0. HRMS (EI): Calcd for $C_{16}H_9NO_3$ $[M]^+$ 263.0582, found: 263.0582.

2-(3,4-dimethoxyphenyl)benzofuran-3-carbonitrile (**3n**)

Eluent: *n*-hexane / ethyl acetate (95 ml / 5 ml); White Solid; Yield: 139 mg (50%); Mp: 162-163 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.82 (dd, *J* = 8.4, 2.0 Hz, 2H), 7.70 - 7.67 (m, 2H), 7.56 -7.54 (m, 1H), 7.39 -7.36 (m, 2H), 6.99 (d, *J* = 8.4 Hz, 1H), 4.01 (s, 3H) 3.97 (s, 3H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.2, 153.3, 151.8, 149.5, 127.6, 126.1, 124.8, 120.8, 120.5, 119.9, 115.0, 111.7, 111.5, 109.2, 102.1, 86.7, 56.3, 56.2. HRMS (EI): Calcd for $C_{17}H_{13}NO_3$ $[M]^+$ 279.0895, found: 279.0894.

2-(3,4-dichlorophenyl)benzofuran-3-carbonitrile (**3o**)

Eluent: *n*-hexane (100%); White Solid; Yield: 118 mg (41%); Mp: 136 - 137 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.24 (d, *J* = 1.6 Hz, 1H), 8.07 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.23 (t, *J* = 7.2 Hz, 1H), 7.63 - 7.58 (m, 2H), 7.48 - 7.40 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.1, 153.7, 135.7, 134.1, 131.5, 128.3, 127.8, 127.3, 127.1, 125.6, 125.3, 120.4, 113.9, 112.1, 89.6. HRMS (EI): Calcd for $C_{15}H_7C_{l2}NO$ $[M]^+$ 286.9905, found: 286.9904.

2-(2,5-dimethoxy-4-methylphenyl)benzofuran-3-carbonitrile (**3p**)

Eluent: *n*-hexane / ethyl acetate (95 ml / 5 ml); White Solid; Yield: 205 mg (70%); Mp: 127 - 128 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.40 - 7.36 (m, 2H), 7.28 (s, 1H), 6.87 (s, 1H), 3.97 (s, 3H) 3.88 (s, 3H) 2.31 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.0, 153.2, 152.0, 151.8, 132.5, 128.4, 126.1, 124.5, 120.1, 114.7, 114.6, 114.2, 111.6, 110.7, 91.6, 56.3, 55.4, 17.1. HRMS (ESI): Calcd for $C_{18}H_{16}NO_3$ $[M+H]^+$ 294.1125, found: 294.1130.

2-(furan-2-yl)benzofuran-3-carbonitrile (**3q**)

Eluent: *n*-hexane / ethyl acetate (95 ml / 5 ml); Brown Solid; Yield: 44 mg (21%); Mp: 86 - 87 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69 (s, 2H), 7.55 (d, *J* = 6.8 Hz, 1H), 7.39 (s, 2H), 7.22 (s, 1H), 6.64 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.7, 153.6, 145.7, 143.7, 126.7, 126.6, 125.1, 120.2, 113.5, 113.4, 112.7, 111.9, 87.2. HRMS (EI): Calcd for $C_{13}H_7NO_2$ $[M]^+$ 209.0477, found: 209.0477.

2-(pyridin-2-yl)benzofuran-3-carbonitrile (**3r**)

Eluent: *n*-hexane / ethyl acetate (95 ml / 5 ml); Pale green Solid; Yield: 145 mg (66%); Mp: 136 - 137 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.82 (d, *J* = 4.4 Hz, 1H), 8.08 (d, *J* = 8.0, 1H), 7.87 (t, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 1H) 7.48 -7.39 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.1, 154.0, 150.6, 127.3, 125.1, 125.1, 121.5, 120.6, 113.8, 112.2, 91.3. HRMS (ESI): Calcd for $C_{14}H_9N_2O$ $[M+H]^+$ 221.0709, found: 221.0715.

2-(quinolin-2-yl)benzofuran-3-carbonitrile (**3s**)

Eluent: *n*-hexane / ethyl acetate (95 ml / 5 ml); Pale green Solid; Yield: 200 mg (74%); Mp: 181-182 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.35 - 8.29 (m, 2H), 8.2 (d, *J* = 8.8 Hz, 1H), 7.88 - 7.78 (m, 3H), 7.68 (d, *J* = 8.4 Hz, 5H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.52 - 7.43 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.2, 154.3, 148.4, 146.6, 137.5, 130.7, 130.4, 128.4, 128.3, 127.8, 127.5, 125.5, 120.8, 118.4, 113.9, 112.4, 92.2. HRMS (ESI): Calcd for $C_{18}H_{11}N_2O$ $[M+H]^+$ 271.0866, found: 271.0873.

5-methoxy-2-phenylbenzofuran-3-carbonitrile (**3t**)

Eluent: *n*-hexane / ethyl acetate (90 ml / 10 ml); Yellow Solid; Yield: 129 mg (52%); Mp: 119 - 120 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.17 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.56 - 7.51 (m, 3H), 7.46 (d, *J* = 8.8 Hz, 1H), 7.13 (d, *J* = 8.8 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 7.00 (dd, *J* = 9.0, 2.6 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.4, 157.6, 148.5, 131.3, 129.4, 128.3, 128.2, 126.6, 116.0, 114.7, 112.6, 101.8, 88.5, 56.2. HRMS (EI): Calcd for $C_{16}H_{11}NO_2$ $[M]^+$ 249.0790, found: 249.0789.

5,6-dimethoxy-2-phenylbenzofuran-3-carbonitrile (**3u**)

Eluent: *n*-hexane / ethyl acetate (90 ml / 10 ml); Yellow Solid; Yield: 173 mg (62%); Mp: 147 - 148 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (d, *J* = 7.2 Hz, 2H), 7.52 - 7.47 (m, 3H), 7.10 (d, *J* = 6.0 Hz, 2H), 3.97 (d, *J* = 4.4 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.8, 149.9, 148.5, 148.4, 130.7, 129.3, 128.5, 126.1, 119.6, 114.8, 100.8, 95.7, 88.4, 56.7, 56.6. HRMS (EI): Calcd for $C_{17}H_{13}NO_3$ $[M]^+$ 279.0895, found: 279.0893.

5,6-dimethoxy-2-(4-methoxyphenyl)benzofuran-3-carbonitrile (**3v**)

Eluent: *n*-hexane / ethyl acetate (90 ml / 10 ml); White Solid; Yield: 63 mg (51%); Mp: 198-199 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 6.0 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 3.96 (d, *J* = 5.2 Hz, 6H), 3.89 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.6, 161.2, 149.4, 148.2, 148.1, 127.9, 121.2, 119.7, 115.3, 114.8, 100.7, 95.7, 86.6, 56.7, 56.6, 55.7. HRMS (EI): Calcd for $C_{18}H_{15}NO_4$ $[M]^+$ 309.1001, found: 309.1004.

dibenzo[*b*,*f*]oxepine-10-carbonitrile (**4A**)

Eluent: *n*-hexane / ethyl acetate (95 ml / 5 ml); Pale Yellow Solid; Yield: 153 mg (70%); Mp: 162 - 163 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.57 (d, *J* = 8.0, 1H), 7.45-7.41 (m, 3H), 7.26 - 7.19 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.5, 157.6, 142.5, 133.0, 132.1, 130.6, 128.5, 128.2, 126.4, 125.8, 125.6, 122.1, 121.9, 118.7, 114.2. HRMS (EI): Calcd for $C_{15}H_9NO$ $[M]^+$ 219.0684, found: 219.0684.

2,3-dimethoxydibenzo[*b*,*f*]oxepine-10-carbonitrile (**4B**)

Eluent: *n*-hexane / ethyl acetate (90 ml / 10 ml); Yellow Solid; Yield: 237 mg (85 %); Mp: 139 - 140 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55 (d, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.37 (s, 1H), 7.26 - 7.18 (m, 2H), 7.76 (s, 1H), 6.66 (s, 1H), 3.92 (s, 3H), 3.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.4, 152.3, 148.7, 131.6, 131.1, 130.3, 129.3, 128.8, 128.6, 128.6, 126.2, 123.5, 114.1, 111.9, 105.5, 99.2, 96.9, 81.2. HRMS (EI): Calcd for $C_{17}H_{13}NO_3$ $[M]^+$ 279.0895, found: 279.0894.

[1,3]dioxolo[4',5':4,5]benzo[1,2-*b*]benzo[*f*]oxepine-10-carbonitrile (**4C**)

Eluent: *n*-hexane / ethyl acetate (90 ml / 10 ml); Yellow Solid; Yield: 179 mg (68 %); Mp: 176 - 177 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 1H), 7.31 (s, 1H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 6.75 (s, 1H), 6.64 (s, 1H), 6.00 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.4, 152.3, 148.7, 131.6, 131.1, 130.3, 129.3, 128.8, 128.6, 128.6, 126.2, 123.5, 114.1, 111.9, 105.5, 99.2, 96.9, 81.2. HRMS (EI): Calcd for $C_{16}H_9NO_3$ $[M]^+$ 263.0582, found: 263.0582.

2-chlorodibenzo[*b*,*f*]oxepine-10-carbonitrile (**4D**)

Eluent: *n*-hexane (100%); Yellow Solid; Yield: 79 mg (31 %); Mp: 144 - 145 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60 (d, *J* = 1.9 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.39 (s, 1H), 7.31 - 7.17 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.4, 152.3, 148.7, 131.6, 131.1, 130.3, 129.3, 128.8, 128.6, 128.6, 126.2, 123.5, 114.1, 111.9, 105.5, 99.2, 96.9, 81.2. HRMS (EI): Calcd for $C_{15}H_8ClNO$ $[M]^+$ 253.0294, found: 253.0293.

benzo[*b*]naphtho[2,1-*f*]oxepine-8-carbonitrile (**4E**)

Eluent: *n*-hexane / ethyl acetate (95 ml / 5 ml);Yellow Solid; Yield: 140 mg (52 %); Mp: 199-200 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.59 (d, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 7.2, 1H), 7.62 (t, *J* = 8.4 Hz, 4H), 7.58 (s, 1H), 7.46 -7.41 (m, 2H),7.27 (d, *J* = 9.2 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.4, 152.3, 148.7, 131.6, 131.1, 130.3, 129.3, 128.8, 128.6, 128.6, 126.2, 123.5, 114.1, 111.9, 105.5, 99.2, 96.9, 81.2. HRMS (EI): Calcd for $C_{19}H_{11}NO$ $[M]^+$ 269.0841, found: 269.0841.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

X-ray crystallographic data for **3d**, **3k** and **4B**; ^{1}H and ^{13}C NMR spectral data for representative compounds (PDF)

Accession Codes

CCDC 1825548 for **3d**, CCDC 1825549 for **3k** and CCDC 1835897 for **4B** are the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

*E-mail: cheyaocf@ntnu.edu.tw.

ORCID

Ching-Fa Yao: 0000-0002-8692-5156

Notes

The authors declare no competing financial interest.

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