RSC Advances

Ligand-free copper-catalyzed efficient one-pot access of benzo[b]pyrido[3,2-f][1,4]oxazepinones through O-heteroarylation-Smiles rearrangement-cyclization cascade

Journal:	*RSC Advances*
Manuscript ID:	RA-ART-09-2014-011128.R1
Article Type:	Paper
Date Submitted by the Author:	20-Oct-2014
Complete List of Authors:	Ganguly, Nemai; Kalyani University, Chemistry Mondal, Pallab; University of Kalyani, Chemistry Roy, Sushmita; University of Kalyani, Chemistry Mitra, Partha; Indian Association for the Cultivation of Science, Inorganic Chemistry

Ligand-free copper-catalyzed efficient one-pot access of benzo[*b*]pyrido[3,2-*f*][1,4]oxazepinones through *O*-heteroarylation-Smiles rearrangement-cyclization cascade

Nemai C. Ganguly,[‡]* Pallab Mondal,[‡] Sushmita Roy,[‡] Partha Mitra[†]

[‡]Department of Chemistry, University of Kalyani, Kalyani 741235, India

[†]Department of Inorganic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata 700032, India

E-mail: nemai_g@yahoo.co.in, fax: +91-33-25828282

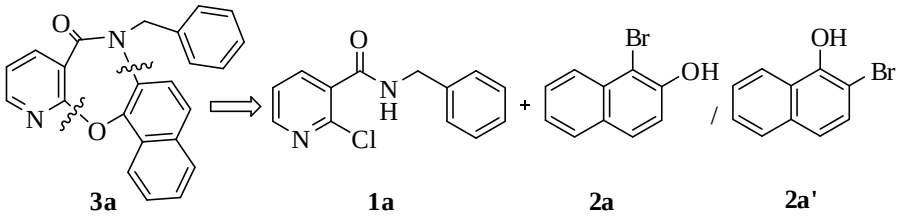
Abstract : Efficient synthesis of a library of novel benzopyrido[1,4]oxazepinones was accomplished by Cs_2CO_3-mediated one-pot coupling of *N*-substituted-*o*-chloronicotinamides and *o*-halogenated phenols under cuprous oxide catalysis in DMF at 120^{o}C through *O*-heteroarylation-Smiles rearrangement-cyclization cascade (16 examples). The C-N bond construction process is biased in favour of Smiles rearrangement allowing regioselective generation of these tricyclic molecular architectures essentially free from Goldberg-*N*-arylation products in good to excellent yields.

Keywords : Benzopyrido[1,4]oxazepinones, *N*-substituted-*o*-chloronicotinamide, *o*-halogenated phenols, *O*-heteroarylation-Smiles rearrangement-annulation cascade, cuprous oxide catalyst.

Introduction

Benzo- and heteroaryl-fused [1,4]oxazepinones exhibit broad and diverse range of biological properties. Dibenzoxazepinones, particularly those with a pendant *N*-substituent, are endowed with HIV-1 RT inhibition[1], anti-cancer,[2] anti-tumor[3] and anti-inflammatory[4] activities. Several CNS-active compounds showing anti-depressant,[5] anti-psychotic activities[6] and β-secretase inhibitors[7] feature this privileged heterocyclic motif. Installation of heterocyclic substructures at this scaffold profoundly modulate its biological space. The heteroaryl-annulated oxazepinones showed anticonvulsant,[8] antimicrobial,[9] anti-ischemic[10] and integrin antagonism activities.[11] The promising biological profile attracted considerable synthetic interest in [1,4]oxazepinones and several initiatives are reported to generate collections of these compounds for biological screening. Dibenzoxazepinones were accessed from substituted *ortho*-bromophenols and secondary benzamides under ligand-assisted copper catalysis.[12] In another approach functionalised *N*-benzylsalicylamides and 1,2-difluoronitrobenzene were utilized as reaction

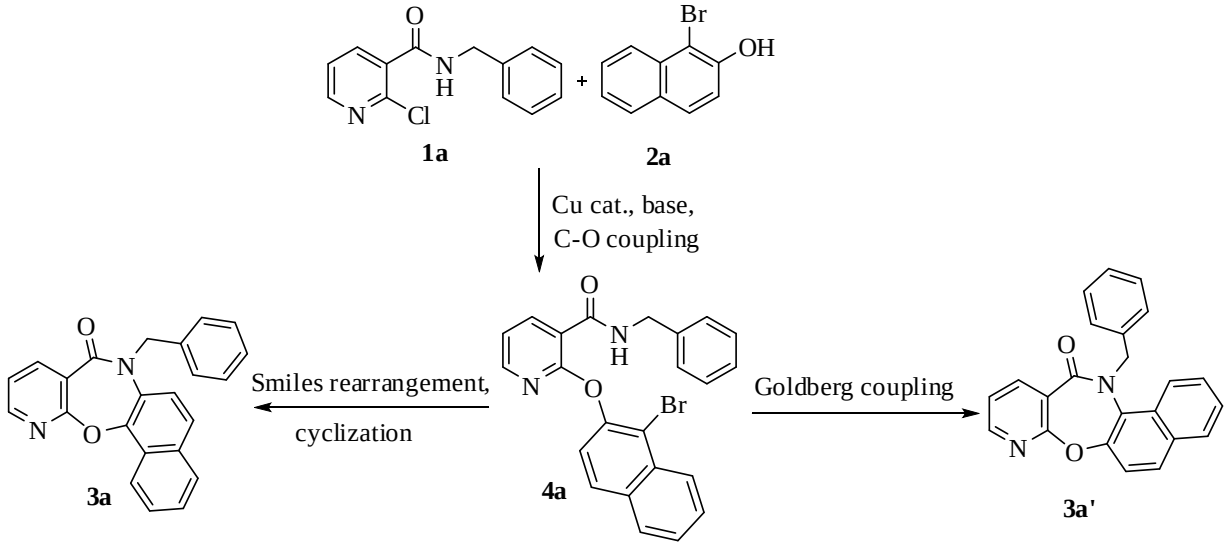
partners under K_2CO_3-mediated transition metal free one-pot process to synthesize these compounds.[13] These methods basically rely on domino C-O and regioselective C-N bond formations *via* Smiles rearrangement. A good number of biologically relevant heterocycles[14] have been synthesized using Smiles rearrangement in a key step. In continuation of our interest in the construction of structurally and functionally diversified targets with a privileged heterocyclic core,[15] we embarked on synthesis of [1,4]oxazepinones that share pyridine and benzene/naphthalene substructures, the former being connected to the carbonyl flank to its secondary amide core. Deconstruction of a conceived target **3a** reveals *N*-benzylated-*o*-chloronicotinamide (**1a**) and 1-bromo-2-naphthol (**2a**) as building blocks assuming Smiles rearrangement-based exchange of relationship of OH and Br of **2a** onto **3a** (Scheme1).



Scheme 1 Deconstruction of target structure **3a**

1a is readily accessible from 2-chloronicotinic acid which served as a versatile intermediate for synthesis of a number of agrochemicals and pharmaceuticals including the anti-HIV drug nevarapine.[16] Notwithstanding the reluctance of aryl chlorides towards Ullmann etherification,[17] the labile nature of chlorine in 2-chloropyridine is expected to favour nucleophilic displacement process. However, subsequent *N*-arylation of **4a** can deliver two regioisomeric products **3a′** and **3a** depending on direct Goldberg reaction[18] or Smiles rearrangement[19]-based coupling. The successful entry to **3a** hinges on finding out suitable reaction conditions that preclude Goldberg reaction and biased in favour of Smiles rearrangement. The proposed reaction pathway leading to **3a** is depicted in Scheme 2. Both *O*- and *N*-arylations are feasible under base-mediated copper-catalysis and, therefore, can be integrated in a one-pot synthetic operation. Copper-catalyzed methods are cost effective than its Pd-, Ni-variants and several methods are available that utilize copper sources at low catalyst levels under mild conditions, with and without ligands, [20,21] as also in bimetallic form (Fe-Cu).[21] Herein, we disclose our results of Cs_2CO_3-mediated ligand-free

copper-catalyzed synthesis of benzo[*b*]pyrido[3,2-*f*][1,4]oxazepinones using *N*-substituted-2-chloronicotinamides and *o*-halogenated naphthols/phenols as coupling partners.



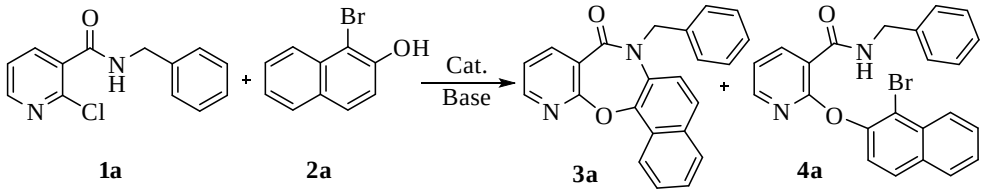
Scheme 2 Plausible reaction route to benzopyrido[1,4]oxazepinone **3a**

Results and discussion

First, 2-chloronicotinic acid was converted to its acid chloride by oxalyl chloride in DMF-CH_2Cl_2 followed by treatment with benzylamine in the presence of triethylamine to give *N*-benzyl-2-chloronicotinamide (**1a**). For preliminary survey, an assembly of **1a** and 1-bromo-2-naphthol (**2a**) was submitted to a set of basic reaction conditions. Cs_2CO_3 was the base of choice in view of its proven competence for promoting both C-O and C-N cross coupling reactions[17c,22] The mild base is compatible with DMF primarily due to its appreciable solubility and this combination is reported to effectively mediate several Smiles rearrangement-based entry to heterocycles.[14d,e,h] The results of these exploratory experiments are presented in Table 1. Initially, a mixture of **1a** and **2a** in 1:1.1 molar ratio was heated with Cs_2CO_3 (2 mol equiv) in DMF at 120 ^oC without any catalyst resulting in isolation of the tricyclic product **3a** in 40% exclusive yield (entry 1, Table 1). Addition of 5 mol% of CuI to the above reaction mixture substantially improved the reaction performance and a decent 77% yield in shorter reaction time (3 h) was accomplished revealing the implication of Cu(I) catalyst (entry 2). A few other copper sources such as CuBr, $Cu(OAc)_2$, $Cu(OTf)_2$ and Cu_2O were screened at identical catalyst level (5 mol%) (entries 3-6). Copper triflate was least effective and cuprous oxide surpassed all delivering 85% yield (entry 6). Optimization of catalyst concentration revealed that lowering it to 2 mol%

resulted in erosion of yield to 62% (entry 7). On the other hand, its increment to 10 mol% as also the use of an excess of base (4 mol equiv) did not improve the yield (entries 8, 9). Encouraged by the reported promotion of *N*-arylation by nitrogen and oxygen ligands such as diamines and β-diketones,[18b] we explored the effect of ligand additives on the reaction outcome. Performing the reaction in the presence of 10 mol% of dibenzoylmethane (dbm) or acetylacetone did not significantly affect the reaction outcome (entries 10, 11). Plausibly, in-built ligating ability of pyridine moiety accounts for the insensitivity of the protocol towards additional ligands. A few other bases (K_2CO_3, K_3PO_4 and DBU) were also screened; K_2CO_3 and DBU gave poor results whereas K_3PO_4 proved more effective affording **3a** in 76% yield (entries 12-14). Replacing DMF with acetonitrile provided 32% sole yield of **4a** in a sluggish reaction (8 h; entry 15). The reaction in toluene was similarly interrupted in the *O*-heteroarylation stage. But remarkably 90% yield of **4a** was scored in a rapid and efficient reaction (entry 16).

Table 1: Optimization experiments for coupling of **1a** and **2a**



1a **2a** **3a** **4a**

Entry	Catalyst (mol%)	Additive (mol%)	Base	Solvent	Time[a] (h)	Yield[b] (%) **3a**	**4a**
1	-	-	Cs_2CO_3	DMF	5	40	-
2	CuI (5)	-	Cs_2CO_3	DMF	3	77	-
3	CuBr (5)	-	Cs_2CO_3	DMF	3	72	-
4	$Cu(OAc)_2$ (5)	-	Cs_2CO_3	DMF	5	57	-
5	$Cu(OTf)_2$ (5)	-	Cs_2CO_3	DMF	5	55	-
6	Cu_2O (5)	-	Cs_2CO_3	DMF	3	85	-
7	Cu_2O (2)	-	Cs_2CO_3	DMF	3	62	-
8	Cu_2O (10)	-	Cs_2CO_3	DMF	3	83	-
9	Cu_2O (5)	-	Cs_2CO_3[c]	DMF	3	84	-
10	Cu_2O (5)	dbm (10)	Cs_2CO_3	DMF	3	81	-
11	Cu_2O (5)	acetylacetone (10)	Cs_2CO_3	DMF	3	75	-
12	Cu_2O (5)	-	K_2CO_3	DMF	5	45	-
13	Cu_2O (5)	-	K_3PO_4	DMF	3	76	-
14	Cu_2O (5)	-	DBU	DMF	3	20	10
15	Cu_2O (5)	-	Cs_2CO_3	MeCN[d]	8	-	32
16	Cu_2O (5)	-	Cs_2CO_3	PhMe[d]	3	-	90

[a]Reactions were performed on 1 milimolar scale; reaction conditions: **1a** and **2a** (1: 1.1 ratio), base (2 equiv.), copper catalyst, solvent (3 mL), 120 ^oC.
[b]Refers to isolated yield after chromatographic purification.
[c]4 mol equiv. of Cs_2CO_3 was used.
[d]Reactions were performed under refluxing condition.

To assess the scope and generality of the protocol, an assortment of *N*-substituted-2-chloronicotinamides (**1a**-**1d**) were reacted with *ortho*-halogenated phenols under optimized reaction conditions [5 mol% Cu_2O, Cs_2CO_3 (2 mol equiv), DMF at 120 ^oC] to build a library of this novel class of compounds. These results are exhibited in Table 2. The *o*-bromophenol (**2b**) reacted much slowly compared to its naphthol counterpart (**2a**); however, the regioselectivity of *N*-arylation could not be ascertained in this case in absence of any ring substituent.

Table 2: Reactions of *N*-substituted-2-chloronicotinamide and *o*-halogenated phenols under copper-catalyzed basic conditions

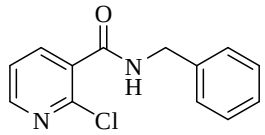
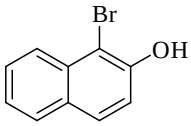
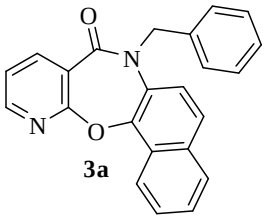
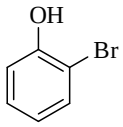
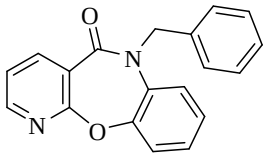
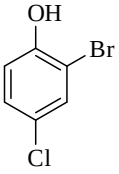
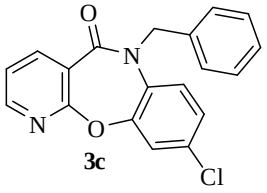
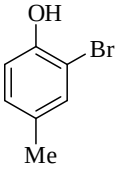
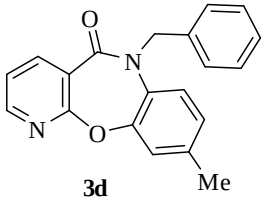
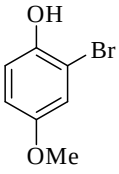
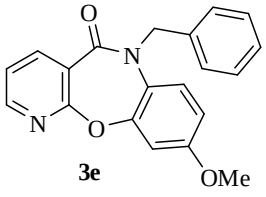
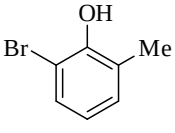
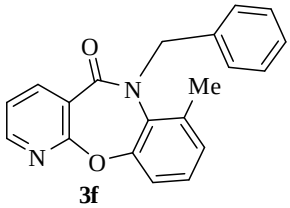
Entry	Secondary amide	*o*-Halogenated phenol	Product[a]	Time (h)	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	3	85
2	**1a**	 **2b**	 **3b**	6	72
3	**1a**	 **2c**	 **3c**	3	90
4	**1a**	 **2d**	 **3d**	5	78
5	**1a**	 **2e**	 **3e**	6	65
6	**1a**	 **2f**	 **3f**	6	35

Table 2: Reactions of *N*-substituted-2-chloronicotinamide and *o*-halogenated phenols under copper-catalyzed basic conditions

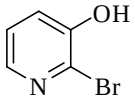
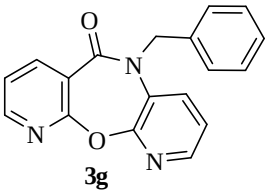
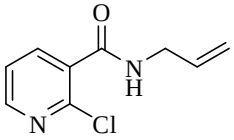
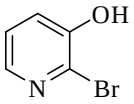
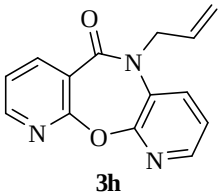
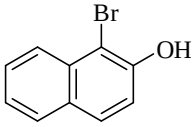
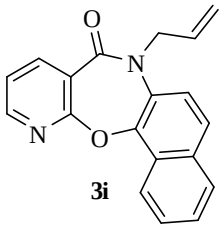
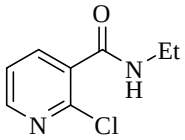
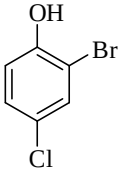
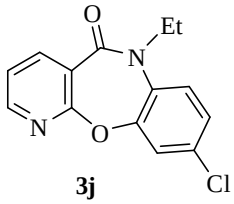
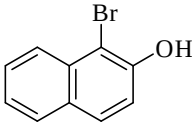
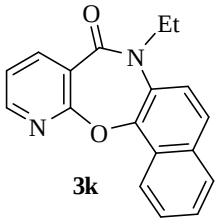
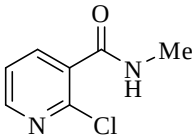
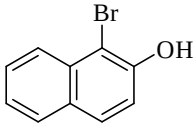
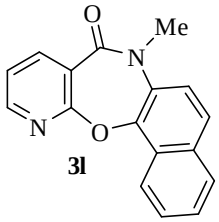
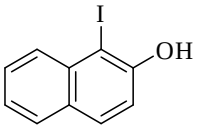
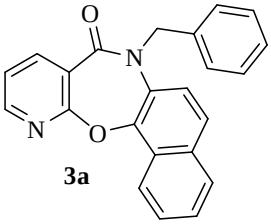
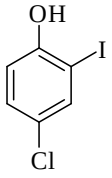
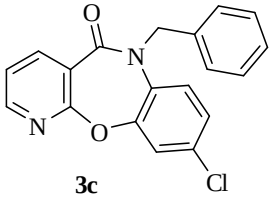
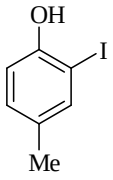
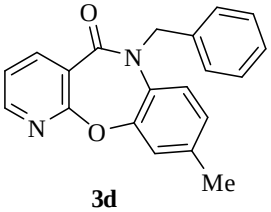
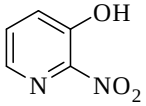
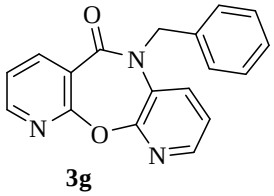
Entry	Secondary amide	*o*-Halogenated phenol	Product[a]	Time (h)	Yield[b] (%)
7	**1a**	 **2g**	 **3g**	3	93
8	 **1b**	 **2g**	 **3h**	3	90
9	**1b**	 **2a**	 **3i**	3	78
10	 **1c**	 **2c**	 **3j**	3	85
11	**1c**	 **2a**	 **3k**	3	80
12	 **1d**	 **2a**	 **3l**	3	82

Table 2: Reactions of *N*-substituted-2-chloronicotinamide and *o*-halogenated phenols under copper -catalyzed basic conditions

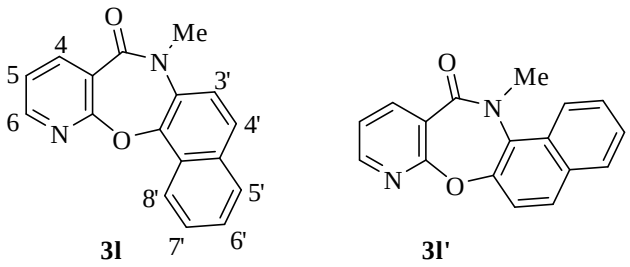
Entry	Secondary amide	*o*-Halogenated phenol	Product[a]	Time (h)	Yield[b] (%)
13	**1a**	 **2h**	 **3a**	3	88
14	**1a**	 **2i**	 **3c**	2	90
15	**1a**	 **2j**	 **3d**	3	82
16	**1a**	 **2k**	 **3g**	10	77

[a] The products were characterized by their spectral features (FTIR, ^{1}H- and ^{13}C-NMR, MS) and XRD analysis.
[b] Refers to isolated yields after column chromatographic purification.

The presence of an additional electron-withdrawing *p*-chloro substituent in the bromophenol component **2c** helped rate enhancement and attainment of relatively high yields (entries 3, 10, Table 2). In contrast, the presence of *p*-Me/–OMe groups afforded lower yields and required longer exposures (entries 4, 5). In case of sterically congested 2-bromo-6-methylphenol (**2f**), the yield plummeted to 35% in a sluggish reaction (6 h) which might be attributed to steric impediment to the nucleophilic attack of the phenoxide ion during etherification (entry 6). 2-Bromo-3-hydroxypyridine (**2g**) was also well-tolerated and proved to be an efficient phenol partner (entries 7, 8). Expectedly, the activating effect of electron-withdrawing pyridine moiety

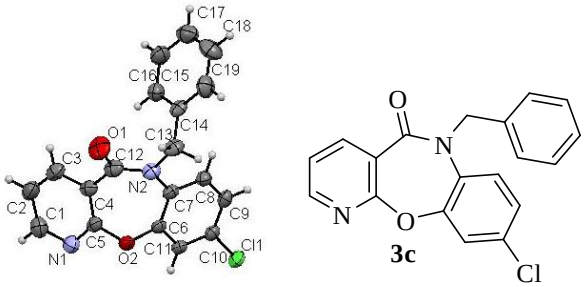
facilitates the Smiles rearrangement. 1-Iodo-2-naphthol (**2h**) and *o*-iodophenols (**2i, 2j**), to our surprise, responded well providing excellent yields of corresponding target structures, despite the poor activation level of iodine towards Smiles rearrangement event (entries 13-15). Conversely, 2-nitro-3-hydroxypyridine (**2k**) was found to be a rather reluctant partner (entry 16).

The ^{1}H-NMR spectra of the tricyclic products allowed assignment of their structures as **3a**-**3l**. A representative product **3l**, for example, exhibited discrete signals in the aromatic range for nine protons of which pyridine ring protons appeared at characteristic positions[23] at δ 8.40 (dd, *J*= 4.8, 1.6 Hz, 1H, H-6), δ 8.30 (dd, *J*= 7.2, 1.6 Hz, 1H, H-4) and δ 7.22 (dd, *J*= 7.2, 4.8 Hz, 1H, H-5) respectively. The most downfield one-proton doublet signal at δ 8.75 (d, *J*= 8.4 Hz) was assigned to H-8′ of the naphthalene ring that is *peri* to the ether oxygen bridge. Of the other two *peri*-proton signals that appeared relatively upfield from the rest *viz*, δ 7.36 (d, *J*= 8.8 Hz, 1H, H-3′), δ 7.51 (t, *J*= 7.6 Hz, H-6') and δ 7.65 (t, *J*= 7.6 Hz, H-7′), the one due to H-4' corresponded to δ 7.69 (d, *J*= 8.8 Hz, 1H) and was shifted upfield from H-5′ signal at δ 7.80 (1H, d, *J*= 8 Hz) due to the presence of electron-releasing ether oxygen at its *para* position. Notably, the regioisomeric Goldberg *N*-arylation product **3l'** lacks analogous *peri*-proton in *para* relationship to oxygen. This discrimination of the three *peri*-proton signals in term of chemical shift was observed to a general feature in ^{1}H-NMR spectra of all products embodying a naphthalene moiety. The ^{13}C-NMR spectra and HRMS data were also supportive of their assigned structures.



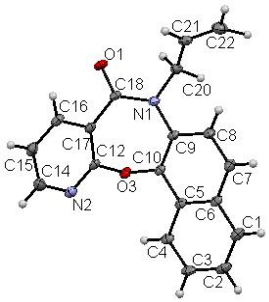
Scheme 3 Structures of regioisomeric products **3l** and **3l'** formed *via* Smiles rearrangement and Goldberg N-arylation respectively

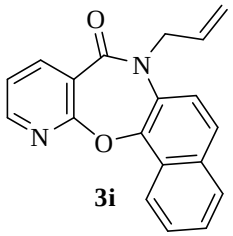
The structure of two representative products **3c** and **3i** were unambiguously confirmed by their single crystal XRD studies. The corresponding ORTEP diagrams are depicted below (Figure 1).



3c

3c



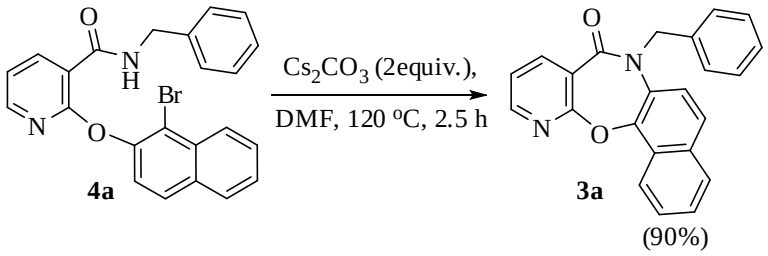


3i

3i

Figure 1 ORTEP diagrams of **3c** and **3i**, respectively. Ellipsoids are drawn at the 50% probability level.

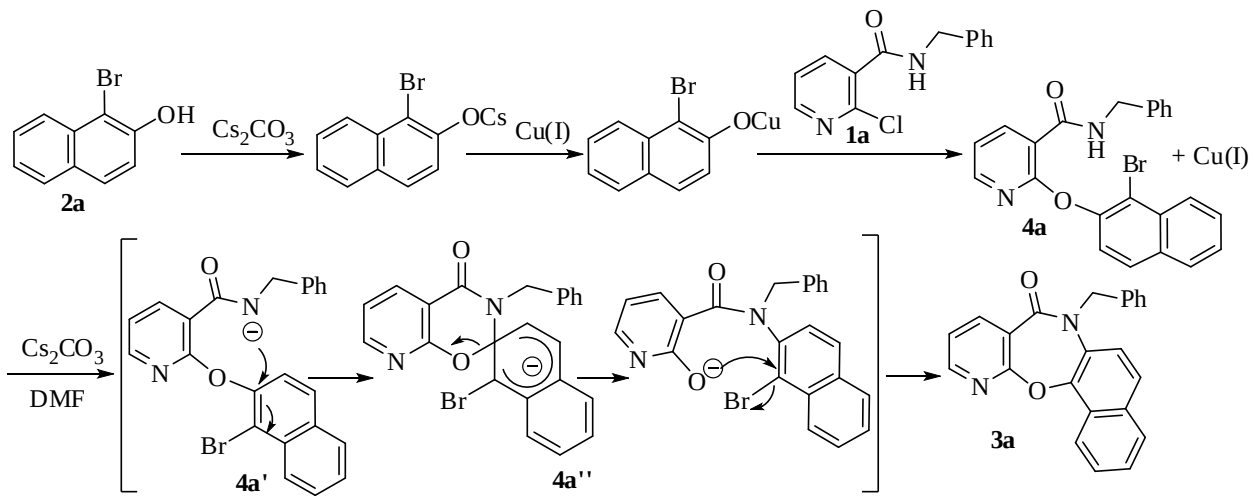
To gain an insight into the mechanistic scenario of the reactions, *N*-benzyl-2-(1-bromonaphthalen-2-yloxy)nicotinamide (**4a**) was separately prepared by treatment of a mixture of *N*-benzyl-2-chloronicotinamide (**1a**) and 1-bromo-2-naphthol (**2a**) in the presence of 5 mol% of Cu_2O and Cs_2CO_3 (2 mol equiv) in toluene at reflux (entry 16, Table 1). It was then exposed to Cs_2CO_3 in DMF without copper catalyst at 120 ^oC to afford **3a** in 86% yield in 2.5 h (Scheme 4).



Scheme 4 Control experiment for the *N*-arylation step

This result is consistent with intermediacy of **4a** on route to the target compound **3a** and also demonstrated that *N*-arylation event did not necessarily require support of copper catalysis.

Cesium carbonate plays crucial facilitatory role in both heteroarylation and Smiles rearrangement. The greater solubility of the cesium phenoxide or phenolate-copper complex compared to its potassium/sodium counterpart in organic solvents[24] is particularly important for etherification process. The unactivated aryl chlorides are poor reaction partners of phenols as the cleavage of C-Cl bond in rate determining step of Ullmann process[17a] is not very facile. But this cleavage is greatly facilitated in 2-chloropyridine because electron-deficient nature of pyridine enables it to support the developing negative charge due to nucleophilic attack of oxyanion. The success of the domino sequence is crucially dependent on the nature of solvent used. The superior performance of toluene providing ether **4a** (entry 16, Table 1) is substantiated by literature precedence.[17c] However, the apolar nature of toluene did not allow it to generate and stabilize the conjugate anion of the weak secondary amide base that is essentially required for Smiles rearrangement.[25] The polar aprotic solvent DMF outperforms others because, in addition to its supportive role in etherification, it strongly stabilizes the nitrogen anion **4a′** and the subsequent Meisenheimer complex **4a″** (Scheme 5). Acetonitrile proved ineffective for coupling of relatively inactivated phenol partner, 1-bromo-2-naphthol (**2a**) in our case. Similar failure was previously observed for analogous coupling of *N*-chloroacetamides with bromophenol.[14a] Recent DFT studies for analogous S-N type Smile rearrangement suggest that this route has much lower activation energy barrier than direct nucleophilic displacement route (Goldberg *N*-arylation)[14h,i] and, therefore, energetically favoured over the latter. The following mechanistic pathway is proposed for formation of **3a**.



Smiles rearrangement

Scheme 5 Plausible mechanism for the formation of **3a**

Conclusions

To summarize, one-pot coupling of readily accessible building blocks *viz.* *N*-substituted-*o*-chloronicotinamides and *o*-halogenated naphthols /phenols in the presence of Cs_2CO_3 (2 equiv) and Cu_2O (5 mol%) catalyst in DMF at 120 ^oC provided facile regioselective entry to hitherto unprecedented benzo[*b*]pyrido[3,2-*f*][1,4]oxazepinones through *O*-heteroarylation-Smiles rearrangement-cyclization cascade. It represents rare cases of Smiles rearrangement using unactivated *o*-bromo- and –iodophenols without the support of electron-withdrawing groups. The present optimized protocol delivered a new library of the designed tricyclic targets (16 examples) of potential biological relevance in good to excellent yields and its scope has been demonstrated for a range of electronically and sterically discriminated substrates. The use of inexpensive air-stable cuprous oxide catalyst, operational simplicity and ease of isolation of products are the notable advantages of the method.

Experimental:

Typical procedure for the synthesis of oxazepinone 3c:

To a stirring solution of *N*-benzyl-2-chloronicotinamide (**1a**) (246 mg, 1.00 mmol) and 1-bromo-4-chlorophenol (**2c)** (210 mg, 1.01 mmol) in DMF (3 mL) were added Cu_2O (7 mg, 0.05 mmol) and cesium carbonate (650 mg, 2.00 mmol). Then the reaction mixture was heated at 120 °C for 3 hours. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to room temperature and extracted with EtOAc (3x10 mL). The combined organic layer was

washed with brine water (2x5 mL), dried over $MgSO_4$, and evaporated under reduced pressure to give the crude product. It was purified by column chromatography on silica gel using EtOAc-light petrol (1: 9) as eluent to afford the desired product **3c** as off-white solid (302 mg, 90%). m.p. 210-212 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.45 (dd, J = 4.8, 2 Hz, 1H), 8.33 (dd, J = 7.6, 2 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.35-7.28 (m, 6H), 7.16 (d, J = 8.8 Hz, 1H), 7.09 (dd, J = 8.8, 2.4 Hz, 1H), 5.31 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 163.7, 152.2, 151.9, 143.0, 136.3, 132.9, 131.9, 128.9, 127.5, 126.8, 126.5, 123.8, 123.0, 122.5, 120.9, 52.5; IR (KBr): 1652, 1594, 1491, 1427, 1383, 1323, 1288, 1219, 1084, 817 cm^{-1}; HRMS (ESI) *m/z*: Calcd. for $C_{19}H_{13}ClN_2O_2Na$ $[M+Na]^+$: 359.0564. Found 359.0563.

Oxazepinone 3a: Brown liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 8.76 (d, J = 8 Hz, 1H), 8.43 (dd, J = 4.8, 2 Hz, 1H), 8.34 (dd, J = 7.6, 1.6 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.64 (t, J = 8 Hz, 1H), 7.60 (d, J = 9.2 Hz, 1H), 7.51 (t, J = 8 Hz, 1H), 7.38-7.35 (m, 3H), 7.32-7.20 (m, 4H), 5.43 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 164.7, 151.6, 146.9, 142.8, 136.7, 132.3, 129.6, 128.8, 127.7, 127.6, 127.4, 127.3, 127.0, 126.9, 126.1, 122.7, 122.1, 121.8, 120.7, 52.0; IR (KBr): 3063, 2926, 2852, 1649, 1592, 1459, 1422, 1341, 1220, 1100, 815, 752 cm^{-1}; HRMS (ESI) *m/z*: Calcd. for $C_{23}H_{17}N_2O_2$ $(M+H)^+$: 353.1290. Found: 353.1219.

Oxazepinone 3b: Off-white solid; m.p. 102-104 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.43 (d, J = 4 Hz, 1H), 8.33 (d, J = 7.2 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.33-7.23 (m, 7H), 7.18-7.10 (m, 2H), 5.34 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 164.1, 151.9, 151.7, 142.9, 136.7, 134.2, 128.8, 127.3, 127.1, 126.8, 126.3, 123.1, 122.6, 122.1, 121.2, 52.7; IR (KBr): 3058, 2923, 2852, 1646, 1591, 1568, 1421, 1392, 1222, 1190, 984, 791, 759 cm^{-1}; HRMS (ESI) *m/z*: Calcd. for: $C_{19}H_{15}N_2O_2$ $(M+H)^+$: 303.1133. Found: 303.1142.

Oxazepinone 3d: Pale yellow liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 8.42 (dd, J = 4.4, 2 Hz, 1H), 8.31 (dd, J = 7.6, 2 Hz, 1H), 7.32-7.23 (m, 7H), 7.11 (d, J = 8 Hz, 1H), 6.92 (d, J = 8 Hz, 1H), 5.31 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 164.2, 151.8, 151.6, 142.9, 137.6, 136.8, 131.4, 128.7, 127.3, 127.0, 126.8, 122.9, 122.7, 122.1, 121.4, 52.5, 20.6; IR (KBr): 3031, 2921, 1646, 1592, 1509, 1425, 1386, 1323, 1221, 1029, 801 cm^{-1}; HRMS (ESI) *m/z*: Calcd. for $C_{20}H_{17}N_2O_2$ $(M+H)^+$: 317.1290. Found: 317.1290.

Oxazepinone 3e: Pale yellow solid; m.p. 84-86 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.42 (dd, J = 4.4, 2 Hz, 1H), 8.33 (dd, J = 7.6, 2 Hz, 1H), 7.32-7.24 (m, 6H), 7.13 (d, J = 9.2 Hz, 1H), 6.95 (d,

J = 2.8 Hz, 1H), 6.67 (dd, *J* = 8.8, 2.8 Hz, 1H), 5.29 (s, 2H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 158.3, 153.0, 151.5, 142.9, 136.8, 128.7, 127.3, 127.0, 126.9, 126.8, 123.7, 122.2, 121.4, 112.9, 106.9, 55.7, 52.5; IR (KBr): 3063, 2935, 1646, 1590, 1507, 1460, 1416, 1392, 1296, 1215, 1100, 798 cm^{-1}; HRMS (ESI) *m/z*: Calcd. for $C_{20}H_{17}N_2O_3$ $(M+H)^+$: 333.1239. Found: 333.1235.

Oxazepinone 3f: Pale yellow solid; m.p. 148-150 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (dd, *J* = 4.8, 2 Hz, 1H), 8.24 (dd, *J* = 7.6, 2 Hz, 1H), 7.33-7.24 (m, 6H), 7.23-7.21 (m, 1H), 7.13 (t, *J* = 8 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 5.76 (d, *J* = 14.8 Hz, 1H), 4.46 (d, *J* = 14.8 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 165.0, 155.4, 151.3, 142.4, 136.5, 134.8, 133.1, 129.1, 128.5, 127.8, 127.6, 127.5, 122.1, 121.7, 119.7, 53.5, 19.6; IR (KBr): 3023, 1639, 1591, 1459, 1431, 1397, 1321, 1213, 1096, 953, 782 cm^{-1}; HRMS (ESI) *m/z*: Calcd. for $C_{20}H_{17}N_2O_2$ $(M+H)^+$: 317.1290. Found: 317.1298.

Oxazepinone 3g: Dark brown solid; m.p. 138-140 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.35 (dd, *J* = 7.6, 2 Hz, 1H), 8.15 (d, *J* = 4.4 Hz, 1H), 7.60 (dd, *J* = 8, 1.2 Hz, 1H), 7.35-7.24 (m, 6H), 7.15 (dd, *J* = 8, 4.8 Hz, 1H), 5.32 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 162.2, 156.5, 152.5, 145.3, 142.7, 136.0, 132.3, 129.2, 129.0, 127.7, 126.8, 122.6, 122.5, 120.4, 52.4; IR (KBr): 3065, 1645, 1592, 1414, 1393, 1323, 1215, 1185, 743 cm^{-1}; HRMS (ESI) *m/z*: Calcd. for $C_{18}H_{14}N_3O_2$ $(M+H)^+$: 304.1086. Found: 304.1080.

Oxazepinone 3h: Pale yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (dd, *J* = 4.8, 2 Hz, 1H), 8.31 (dd, *J* = 7.6, 2 Hz, 1H), 8.21 (dd, *J* = 4.4, 1.6 Hz, 1H), 7.79 (dd, *J* = 8, 1.6 Hz, 1H), 7.32 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.26 (dd, *J* = 8, 4.4 Hz, 1H), 6.09-5.99 (m, 1H), 5.34-5.30 (m, 2H), 4.67 (dd, *J* = 3.6, 1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 162.1, 156.1, 152.4, 145.1, 142.7, 132.6, 132.1, 129.5, 122.7, 122.4, 120.4, 117.7, 52.1; IR (KBr): 3079, 3010, 2924, 2852, 1654, 1592, 1415, 1318, 1215, 1100, 761 cm^{-1}; HRMS (ESI) *m/z*: Calcd. for $C_{14}H_{12}N_3O_2$ $(M+H)^+$: 254.0929. Found: 254.0937.

Oxazepinone 3i: Off-white solid; m.p. 104-106 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (d, *J* = 8.4 Hz, 1H), 8.45 (dd, *J* = 4.8, 2 Hz, 1H), 8.33 (dd, *J* = 7.2, 2 Hz, 1H), 7.83 (d, *J* = 8 Hz, 1H), 7.72-7.67 (m, 2H), 7.56 (t, *J* = 8 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H), 7.30-7.27 (m, 1H), 6.14-6.05 (m, 1H), 5.40 (d, *J* = 17.2 Hz, 1H), 5.30 (d, *J* = 10.4 Hz, 1H), 4.81 (d, *J* = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 164.6, 151.5, 146.5, 142.7, 133.0, 132.2, 129.8, 127.7, 127.6, 127.3,

126.9, 126.1, 122.7, 122.1, 121.8, 120.6, 117.4, 51.6; IR (KBr) ν_{max}: 3054, 2921, 2851, 1644, 1630, 1591, 1425, 1396, 1313, 1219, 1097, 1012, 804 cm^{-1}; HRMS (ESI) *m/z*: Calcd. for $C_{19}H_{15}N_2O_2$ $(M+H)^+$: 303.1133. Found: 303.1126

Oxazepinone 3j: Off-white solid; m.p. 132-134 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, *J* = 2.8 Hz, 1H), 8.25 (d, *J* = 7.2 Hz, 1H), 7.45 (s, 1H), 7.29-7.19 (m, 3H), 4.12 (q, *J* = 6.8 Hz, 2H), 1.34 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 163.6, 152.6, 151.6, 142.8, 132.8, 131.7, 126.6, 123.7, 123.1, 122.4, 121.3, 44.2, 13.6; IR (KBr): 3061, 2939, 1649, 1628, 1591, 1460, 1437, 1371, 1337, 1220, 1166, 1044, 898, 803 cm^{-1}; HRMS (ESI) *m/z*: Calcd. for $C_{14}H_{12}ClN_2O_2$ $(M+H)^+$: 275.0587. Found: 275.0584.

Oxazepinone 3k:

Off-white solid; m.p. 132-134 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.77 (d, *J* = 8.4 Hz, 1H), 8.40-8.39 (m, 1H), 8.27 (d, *J* = 7.6 Hz, 1H), 7.81 (d, *J* = 8 Hz, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.66 (t, *J* = 8 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 1H), 7.23 (dd, *J* = 4.8, 7.2 Hz, 1H), 4.26 (s, 2H), 1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 164.7, 151.3, 147.2, 142.6, 132.2, 129.3, 127.8, 127.6, 127.3, 126.9, 126.1, 122.7, 122.1, 122.0, 120.8, 43.6, 13.8; IR (KBr): 3061, 2939, 1649, 1628, 1591, 1460, 1437, 1371, 1337, 1220, 1166, 1044, 898, 803 cm^{-1}; HRMS (ESI) *m/z*: Calcd. for $C_{18}H_{15}N_2O_2$ $(M+H)^+$:291.1133. Found: 291.1127.

Oxazepinone 3l:

Off-white solid; m.p. 162-164 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, *J* = 8.4 Hz, 1H), 8.40 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.30 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.80 (d, *J* = 8 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.22 (dd, *J* = 7.2, 4.8 Hz, 1H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 164.5, 151.5, 145.8, 142.8, 132.1, 130.6, 127.6, 127.4, 126.8, 126.2, 122.6, 122.0, 121.4, 120.2, 36.6; IR (KBr): 3051, 2995, 2922, 1651, 1635, 1595, 1478, 1417, 1342, 1304, 1223, 1115, 1037, 799 cm^{-1}; HRMS (ESI) *m/z*: Calcd. for $C_{17}H_{13}N_2O_2$ $(M+H)^+$: 277.0977. Found: 277.0980.

***N*-benzyl-2-(1-bromonaphthalen-2-yloxy)nicotinamide** (**4a)**: Brown liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 8.69 (dd, *J* = 7.6, 1.6 Hz, 1H), 8.32 (s, 1H), 8.21 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.90 (d, *J* = 8.8 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.58-7.47 (m, 3H), 7.38-7.27 (m, 5H), 7.18 (dd, *J* = 7.6, 4.8 Hz, 1H), 4.74 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 160.4, 150.1 (2C), 142.5, 138.2, 134.0, 131.4, 129.8, 128.8, 127.9, 127.6, 127.5

(2C), 126.8, 125.8, 121.6, 119.6, 118.5, 116.8, 44.0; IR (KBr): 3420, 3060, 2924, 2853, 1656, 1590, 1531, 1511, 1417, 1303, 1244, 1156, 963, 755 cm^{-1}; HRMS (ESI) *m/z*: Calcd. for $C_{23}H_{17}BrN_2O_2Na$ $(M+Na)^+$:455.0365. Found: 455.0385.

Acknowledgments

SR is thankful to UGC, New Delhi, India for financial assistance by way of research fellowship. We are grateful to DST-FIST and UGC-SAP programmes for providing infrastructural facilities to the Department of Chemistry, University of Kalyani.

Notes and references

Department of Chemistry, University of Kalyani, Kalyani-741235, India. Email: nemai_g@yahoo.co.in, Fax: +913325828282;

†Electronic Supplementary Information (ESI) available experimental details, spectroscopic data, copies of the ^1H NMR and ^{13}C NMR spectra of all final products.

1 S. Vilar, L. Santana, and E. Uriarte, *J. Med. Chem*., 2006, **49**, 1118-1124.

2 Eur. Patent 000463, 2005.

3 M. Binaschi, A. Boldetti, M. Gianni, C. A. Maggi, M. Gensini, M. Bigioni, M. Parlani, A. Giolitti, M. Fratelli, C. Valli, M. Terao and E. Garattini, *Med. Chem. Lett*., 2010, **1**, 411-415.

4 J. K. Chakrabarti and T. A. Hicks, *Eur. J. Med. Chem*., 1987, **22**, 161-163.

5 (*a*) K. Nagarajan, J. David, Y. S. Kulkarni, S. B. Hendi, S. J. Shenoy and P. Upadhyaya, *Eur. J. Med. Chem*., 1986, **21**, 21-26; (*b*) J. -F. F. Liégeois, F. A. Rogistert, J. Bruhwyler, J. Damas, T. P. Nguyen, M. –O. Inarejos, E. M. G. Chleide, M. G. A. Mercier and J. E. Delarget, *J. Med. Chem.*, 1994, **37**, 519-525.

6 Y. Liao, B. J. Venhuis, N. Rodenhuis, W. Timmerman and H. Wikström, *J. Med. Chem*., 1999, **42**, 2235-2244.

7 T. –H. Al-Tel, R. A. Al-Qawasmeh, M. F. Schmidt, A. Al-Aboudi, S. N. Rao, S. S. Sabri and W. Voelter, *J. Med. Chem*., 2009, **52**, 6484-6488.

8 X. –Q. Deng, C. –X. Wei, F. –N. Li, Z. -G. Sun and Z. –S. Quan, *Eur. J. Med. Chem*., 2010, 3080-3086

9. M. Sridhara, K. R. V. Reddy, J. Keshavayya, P. S. K. Goud, B. C. Somashekar, P. Bose, S. K. Peethambara and S. K. Gaddam, *Eur. J. Med. Chem*., 2010, 4983-4989.

10 (*a*) K. Kamei, N. Maeda, R. Ogino, M. Koyama, M. Nakajima, T. Tatsuaka, T. Ohno and T. Inoue, *Bioorg. Med. Chem. Lett*., 2001, **11**, 595-598; (*b*) K. Kamei, N. Maeda, K. Nomura, M. Shibata, R. Katsuragi-Ogino, M. Koyama, M. Nakajima, T. Inoue, T. Ohno and T. Tatsuoka, *Bioorg. Med. Chem*., 2006, **14**, 1978-1992.

11 (*a*) Y. Liu, Y. Ma, C. Zhan, A. Huang and C. Ma, *Synlett*, 2012, 255-258; (*b*) H. Fukui, S. Ikegami, M. Watanuki, T. Maruyama, Y. Sumita and K. Inoguchi, K. WO 0155121, 2001.

12 M. O. Kitching, T. E. Hurst and V. Snieckus, *Angew. Chem. Int. Ed*., 2012, **51**, 2925-2929.

13 Y. Liu, C. Chu, A. Huang, C. Zhan, Y. Ma and C. Ma, *ACS Comb. Sci*., 2011, **13**, 547-553.

14 (*a*) S. –D. Cho, Y. –D. Park, J. –J. Kim, S. –G. Lee, C. Ma, S. –Y. Song, W. –H. Joo, J. R. Falck, M. Shiro, D. –S. Shin and Y. –J. Yoon, *J. Org. Chem.*, 2003, **68**, 7918-7920; (*b*) S. –D. Cho, S. –Y. Song, Y. –D. Park, J. –J. Kim, W. –H. Joo, M. Shiro, J. R. Falck, D. -S. Shin and Y. –J. Yoon, *Tetrahedron Lett.*, 2003, **44**, 8995-8998; (*c*) C. Ma, Q. Zhang, K. Ding, L. Xin and D. Zhang, *Tetrahedron Lett.*, 2007, **48**, 7476-7479; (*d)* H. Zuo, L. Meng, M. Ghate, K. –H. Hwang, Y. K. Cho, S. Chandrasekhar, C. R. Reddy and D. –S. Shin, *Tetrahedron Lett*., 2008, **49**, 3827-3830; (*e*) H. Zuo, Z. –B. Li, F. –K. Ren, J. R. Falck, M. Lijuan, C. Ahn and D. –S. Shin, *Tetrahedron*, 2008, **64**, 9669-9674; (*f*) A. Huang, Z. Qiao, X. Zhang, W. Yu, Q. Zheng, Y. Ma and C. Ma, *Tetrahedron*, 2012, **68**, 906-912; (*g*) C. Zhan, J. Jia, B. Yang, A. Huang, Y. Liu and C. Ma, *RSC Adv.*, 2012, **2**, 7506-7512; (*h*) Y. Zhao, Y. Wu, J. Jia, D. Zhang and C. Ma, *J. Org. Chem*., 2012, **77**, 8501-8506; (*i*) B. Yang, X. Tan, R. Guo, S. Chen, Z. Zhang, X. Chu, C. Xie, D. Zhang and C. Ma, *J. Org. Chem*., 2014, **79**, 8040–8048.

15 (*a*) N. C. Ganguly, S. Roy, P. Mondal and R. Saha, *Tetrahedron Lett.*, 2012, **52**, 7067-7071; (*b*) N. C. Ganguly, P. Mondal and S. Roy *Tetrahedron Lett*., 2013, **54**, 2386-2390; (*c*) N. C. Ganguly, S. Roy and P. Mondal, *RSC Adv*., 2014, **4**, 42078-42086.

16 (*a*) V. J. Merluzzi, K. D. Hargrave, M. Labadia, K. Grozinger, M. Skoog, J. C. Wu, C. K. Shih, K. Eckner, S. Hattox and J. Adams *et al*., *Science*, 1990, **250**, 1411-1413; (*b*) J. C. Wu, T. C. Warren, J. Adams, J. Proudfoot, J. Skiles, P. Raghavan, C. Perry, I. Potocki, P. R. Farina and P. M. Grob, *Biochemistry*, 1991, **30**, 2022-2026.

17 (*a*) H. Weingarten, *J. Org. Chem*., 1964, **29**, 977-978; (*b*) J. Lindley, *Tetrahedron*, 1984, **40**, 1433-1456 (c) J–F. Marcoux, S. Doye and S. L. Buchwald, *J. Am. Chem. Soc*., 1997, **119**, 10539-10540.

18 (*a*) K. Kunz, U. Scholz and D. Ganzer, *Synlett*, 2003, 2428-2439; (*b*) E. Racine, F. Monnier, J–P. Vors and M. Taillefer, *Org. Lett.*, 2011, **13**, 2818-2821.

19 (*a*) W. E. Truce, E. M. Kreider and W. W. Brand *Org. React*., 1971, **18**, 99; (*b*) M. Schnurch, R. Flasik, A. F. Khan, M. Spina, M. D. Mihovilovic and P. Stanetty, *Eur. J. Org. Chem*., 2006, 3283-3307.

20 For reviews, see: (*a*) S. V. Ley and A.W. Thomas, *Angew. Chem. Int. Ed*., 2003, **42**, 5400-5449; (*b*) H. C. Goodbrandt, *J. Org. Chem*., 1999, **64**, 670-674; (*c*) A. Klapars, J. C. Antilla and S. L. Buchwald, *J. Am. Chem. Soc*., 2001, **123**, 7727-7729 and references cited therein.

21 M. Taillefer, N. Xia and A. Quali, *Angew. Chem. Int. Ed*., 2007, **46**, 934-936.

22 (*a*) M. Wolter, G. Nordmann, G. E. Job and S. L. Buchwald, *Org. Lett*., 2002, **4**, 973-976; (*b*) C. C. Malakar, A. Baskakova, J. Conrad and U. Beifuss, *Chem. Eur. J*., 2012, **18**, 8882-8885.

23 M. Hellal, G. D. Cuny, *Tetrahedron Lett*., 2011, **52**, 5508-5511.

24 (*a*) H. E. Zaugg, *J. Org. Chem.*, 1976, **41**, 3419-3421; (*b*) W. H. Kwizinga and R. M. Kellogg, *J. Chem. Soc., Chem. Commun.*, 1979, 286-288; (*c*) D. D. Hennings, S. Imasa and V. R. Rawal, *J. Org. Chem.*, 1997, **62**, 2-3

25 D. M. Schmidt and G. E. Bonvicino, *J. Org. Chem*., 1984, **49**, 1664-1666.

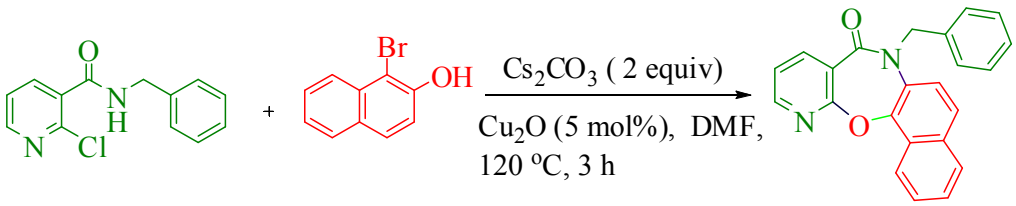
Ligand-free copper-catalyzed efficient one-pot access of benzo[*b*]pyrido[3,2-*f*][1,4]oxazepinones through *O*-heteroarylation-Smiles rearrangement-cyclization cascade

Nemai C. Ganguly,[‡]* Pallab Mondal,[‡] Sushmita Roy,[‡] Partha Mitra[†]

[‡]Department of Chemistry, University of Kalyani, Kalyani 741235, India

[†]Department of Inorganic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata 700032, India

E-mail: nemai_g@yahoo.co.in, fax: +91-33-25828282



16 examples

(85%)
(Yield upto 93%)

An optimized protocol towards synthesis of benzopyrido[1,4]oxazepinones of potential biological relevance is achieved by coupling of *N*-substituted-*o*-chloronicotinamides and *o*-halogenated naphthols/ phenols.