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AlCl₃ induced C-arylation/cyclization in a single pot: a new route to benzofuran fused *N*-heterocycles of pharmacological interest

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ABSTRACT

A new and one-pot synthesis of benzofuran fused *N*-heterocycles has been accomplished via AlCl₃mediated C–C followed by C–O bond formation between 2,3-dichloropyrazine or its derivatives and phenols. The methodology provided novel compounds as potential inhibitors of PDE4B. The single crystal X-ray data of a synthesized benzofuran derivative are presented. Scope of the methodology, in vitro pharmacological data of some of the synthesized compounds, along with docking study of an active compound are described.

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Conformational restriction of bioactive molecules offers the possibility of generating attractive structures that may provide valuable insights regarding the interaction of the precursory flexible molecule with the putative receptor or enzyme. A series of polycyclic derivatives **B** therefore were generated by introducing restrictions in the parent compounds **A** (Fig. 1).^{1a}

Since this strategy has been viewed as a potential opportunity for the identification of compounds possessing increased potency, we became interested in the synthesis and pharmacological evaluation of a series of nitrogen containing heterocycles C possessing benzofuran moiety as a central ring (Fig. 2). We were further encouraged by the pharmacological properties of similar class of compounds, for example, **D** (Elbfluorene-ALX-270-389) as selective inhibitor of cyclin-dependent kinase 1 (CDK1/cyclin B; $IC_{50} = 4.2 \ \mu M)^{1b}$ or a benzofuro[3,2-d]pyrimidine derivative MP-470 (E) as an inhibitor of multitargeted receptor tyrosine kinase (Fig. 2).² Both the compounds are presently undergoing phase 1 clinical trials. In our effort³ to identify novel inhibitors of PDE4 (phosphodiesterase 4) we were particularly interested in assessing PDE4 inhibitory properties of compounds C in vitro. While PDE4 inhibitory properties of benzofuran derivatives have been reported earlier^{4–6} to the best of our knowledge the use of benzofuran fused *N*-heterocycle has not been explored as a potential template for the discovery of novel PDE4 inhibitors.



Figure 1. Design of polycyclic structure B via conformational restriction of ether derivative A.



Figure 2. Benzofuran fused N-heterocycles: designed compound C and reported bioactive molecules D and E.

A number of methods have been reported for the synthesis of benzo[4,5]furo heterocycles^{1,7} which include (i) construction of the heterocyclic ring on the furan ring of benzofuran moiety, (ii) intramolecular cyclization (C–C bond formation) leading to a furan



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Scheme 1. One-pot synthesis of benzofuran fused N-heterocycles.

ring fused between the benzene and heterocyclic moiety pre-connected through an ether linkage, and (iii) intramolecular cyclization (C–O bond formation) of *o*-hydroxyaryl heteroarenes. All these approaches however require lengthy multistep synthesis or harsh reaction conditions or the use of special reagents/transition metal catalysts. While the third approach offers notable synthetic opportunities as its application in the synthesis of benzofuran fused *N*-heterocycles represented by **C** is less common.^{7a,8} Recently, we have observed that derivatives of 2,3-dichloropyrazine reacted smoothly with phenols in the presence of AlCl₃ to give benzofuran fused *N*heterocycles in a good yield. In this Letter we present our preliminary results of this AlCl₃ induced C–C followed by C–O bond formation leading to the compound **C** (or **3**, Scheme 1).

AlCl₃-induced C–C bond forming reaction between heteroaryl chlorides containing -C(Cl)=N- moiety and various arenes or heteroarenes has been explored by us earlier.⁹ We envisaged that

Table 1

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The reaction of **1a** with **2a** under various conditions^a



^a All the reactions were carried out using compound **1a** (1.0 equiv), **2a** (1.0 equiv) and AlCl₃ (1.0 equiv) in a solvent (5 mL) at 80 °C followed by addition of extra quantity of AlCl₃ (1.0 equiv) and then stirring again at 80 °C.

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^b Total time taken to yield the product **3a**.

Toluene

^c Isolated yield.

 $^{\rm d}$ The reaction was carried out at 40–60 °C for both the step.

a similar reaction between heteroaryl chlorides containing – N=C(CI)-C(CI)=N- moiety using phenols may proceed one-step further, that is, intramolecular cyclization via a C–O bond forma-

Table 2

Synthesis of benzofuran fused N-heterocycles (3) via AlCl₃-mediated C-C and C-O bond forming reaction between 1 and 2^a

Entry	Hetaryl chlorides (1)	Phenols (2)	Products (3)	Yield ^b (%)
1		OH 2a	$ \underbrace{ \bigvee_{N=1}^{N=1}}_{3a} $	85
2	1a	Br 2b		84
3	1a			80
4	1a	OH OMe 2d		78
5	1a	OH OEt 2e	$N \rightarrow O$ N O $N \rightarrow OEt$ 3e	78
6	1a	OPr-n 2f	$ \begin{array}{c} \begin{array}{c} \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} $	80
7	1a	OH OBu-n 2g	$ \begin{array}{c} \begin{array}{c} \begin{array}{c} \\ \end{array} \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \\ \\ \end{array} \\ \\ \end{array} \\ \\ \end{array} \\ \\ \end{array} \\ \\ \begin{array}{c} \\ \\ \\ \end{array} \\ \\ \\ \end{array} \\ \\ \\ \end{array} \\ \\ \\ \\ \end{array} \\ \\ \\ \\ \end{array} \\ \\ \\ \\ \\ \end{array} \\ \\ \\ \\ \end{array} \\$	75

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Table 2 (continued)	
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Entry	Hetaryl chlorides (1)	Phenols (2)	Products (3)	Yield ^b (%)
8	1a	HO 2h	$ \begin{array}{c} $	80
9	1a			80
10	1a	OH OCHEt Me 2j		75
11	1a		$N = \int_{N}^{0} \int_{0}^{0} \int_{0}^{0}$	80
12	1a	HO CO ₂ Et 2l		78
13	1a	O(CH ₂) ₇ CH ₃ 2m	$H_{3}C.$ $(CH_{2})_{7}$ $M = \int_{0}^{N} \int_{0}^{1} \int_{0}$	80
14	1a	OH OCH ₂ Ph 2n		80
15	$ \begin{array}{c} $	2a	N = 0 $N = 0$ $N = 0$ $3n$	78
16	1b	2b	$ \underset{N}{\overset{N=\overset{O}{\underset{N}{}{}}}{\underset{30}{}}} Br $	78
17	$ \begin{bmatrix} N & C \\ N & C \\ I \\ 1 \end{bmatrix} $	2a		75

^a All the reactions were carried out using compound **1** (1.0 equiv), **2** (1.0 equiv) and AlCl₃ (1.0 equiv) in 1,2-dichloroethane (5 mL) at 80 °C followed by addition of extra quantity of AlCl₃ (1.0 equiv) and then stirring again at 80 °C. ^b Isolated yield.



Figure 3. X-ray crystal structure of 3e (ORTEP diagram). Thermal ellipsoids are drawn at 50% probability level.



Scheme 2. Probable explanation for the regioselective formation of product **3n** and **3o**.

tion after the formation of initial C–C bond in the same pot. Accordingly, 2,3-dichloroquinoxaline¹⁰ (**1a**, 1.0 equiv) was reacted with 2-naphthol (**2a**, 1.0 equiv) in 1,2-dichloroethane (5 mL) in the presence of AlCl₃ (1.0 equiv) at 80 °C for 30 min.¹¹ Then the mixture was cooled to room temperature and additional quantity of AlCl₃ (1.0 equiv) was added. The mixture was stirred again at 80 °C for another 30 min when napthofuro[3,2-*b*]quinoxaline (**3a**) was obtained as the only product in an 89% yield (Table 1, entry 1). A decrease in reaction temperature increased the reaction time significantly (Table 1, entry 2). The use of other solvents was examined (entries 3–7) and found to be inferior in comparison to 1,2dichloroethane.

Having optimized reaction conditions in hand, we then examined the generality and scope of this $AlCl_3$ induced C-arylation/ cyclization process. Accordingly, a number of phenols (**2**) were reacted with a variety of dichloro *N*-heterocycles and the results are

summarized in Table 2. Phenols containing bromo (**2b**), hydroxy (**2c**), alkoxy (**2d–g**, **2j–n**), allyloxy (**2h**), and prop-2-ynyloxy (**2i**) groups were employed successfully to afford the desired products **3b–3m** (Table 2, entries 2–13) in good yields. Notably, corresponding debenzylated product was obtained when 2-benzyloxy phenol (**2n**) was used (Table 2, entry 14). The dichloro *N*-heterocycles used other than **1a** include 2,3-dichloropyrido[2,3-*b*]pyrazine¹⁰ (**1b**) and 2,3-dichloropyrazine (**1c**) (Table 2, entries 15–17). All the compounds synthesized were well characterized by spectral (NMR, MS, and IR) data. Additionally, the molecular structure of a representative compound **3e** was established unambiguously by single crystal X-ray diffraction (Fig. 3). ¹²

Mechanistically, the reaction seems to proceed (Scheme 2) via (i) complexation of one of the azomethine nitrogen [-C(CI)=N-]of **1** with AlCl₃ followed by (ii) nucleophilic attack by **2** at the adjacent chlorine bearing carbon atom, (iii) release of AlCl₃ affording the intermediate *o*-hydroxyaryl heteroarene, (iv) complexation of the other azomethine nitrogen [-C(CI)=N-] of *o*-hydroxyaryl heteroarene with AlCl₃ and finally (v) intramolecular cyclization via C–O bond formation to give **3**. The regioselective formation of products **3n** and **3o** can be explained based on the preferred transition state formed due to the complexation of AlCl₃ with **1b** as shown in Scheme 2.

To demonstrate the scope of this methodology ester **3I** was hydrolyzed using 1 N NaOH to give the corresponding acid **4** in an 85% yield (Scheme 3). The carboxylic acid obtained was then reacted with morpholine and an amino acid ester, that is, (*S*)-methyl 2-amino-3-phenylpropanoate separately in the presence of HBTU [2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] and diisopropyl ethyl amine to give the corresponding amide, that is, 2-(benzofuro[3,2-*b*]quinoxalin-3-yloxy)-1-morpholinoethanone (**5**) and (*S*)-methyl 2-(2-(benzofuro[3,2-*b*]quinoxalin-3-yloxy)acetamido)-3-phenylpropanoate (**6**) in 72% and 65%, yields, respectively.



Scheme 3. Preparation of amides 5 and 6 from ester 31.

We evaluated some of the compounds synthesized initially for their PDE4B inhibitory potential^{13,14} in vitro using PDE4B enzyme assay.¹⁵ Rolipram¹⁶ was used as a reference compound in this assay. A number of compounds showed inhibition at 30 µM (see Supplementary data) and **3p** being the best among them. The preliminary data indicated that compounds containing a substituent on the benzofuran moiety showed moderate activities and the presence of a smaller substituent was tolerated rather than a larger or bulky group in terms of PDE4 inhibition. The docking results of **3p** with PDE4B protein (see Supplementary data) showed H-binding of the benzofuran oxygen of **3p** with the -NH group of the GLU443 moiety of the PDE4B protein (binding energy -9.69 Kcal/ mol) indicating key role played by the benzofuran moiety in PDE4B inhibition. Since inhibitors of PDE4¹⁷ are expected to be beneficial for the treatment of inflammatory and immunological diseases the present class of compounds therefore may have therapeutic potential.

In conclusion, a direct synthesis of benzofuran fused *N*-heterocycles has been accomplished for the first time using AlCl₃-mediated C-arylation/cyclization strategy in a single pot. The methodology is operationally simple, does not require the use of expensive reagents or catalysts, and therefore amenable for scale-up preparation. This research also reveals the potential of benzofuran fused *N*-heterocycle as a new template for the discovery of PDE4 inhibitors.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.096.

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