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Vinylic amino group activation: a new and general strategy leading to functionalized fused heteroaromatics†

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A conceptually new and general strategy has been developed for the construction of a benzimidazole or a benzoxazole ring fused with isoquinolinone affording a diverse and unique class of small molecules as potential and novel inhibitors of PDE4.

The development of new and powerful chemical methodologies leading to fused heteroaromatics is of immense value as it allows access to the diversity based novel chemical space useful for pharmaceutical/drug discovery efforts. Through the generation of a combinatorial library of small molecules these methodologies often provide crucial breakthroughs in the discovery of new chemical entities (NCEs) required by pharmaceutical/agrochemical industries.

While benzimidazole or benzoxazole and isoquinolinone are well known structural motifs in drug discovery/medicinal chemistry their combined form *i.e.* (benzimidazo or benzoxazolo)isoquinolinones largely remained unexplored perhaps due to the limited or no accessibility of this class of compounds.[1] This prompted us to explore[2] a new and general method of accessing benzimidazo[1,2-*b*]isoquinolin-11-one/benzoxazolo[3,2-*b*]isoquinolin-11-one derivatives as potential inhibitors of phosphodiesterase 4 (PDE4). PDE4 inhibitors are known to be useful anti-inflammatory agents for the potential treatment of chronic obstructive pulmonary disease (COPD) and asthma.[3] Our target molecules **B** derived from a known anti-inflammatory agent[4] CP-77059 (Fig. 1) were designed based on the *in silico* docking studies of a representative compound **A** (Fig. 1) into the active site of PDE4B (Fig. 2). The study showed binding of **A** deep into the active site (docking score −22.07) along with an H-bond interaction of carbonyl oxygen of ester with the side chain amino group of Gln 443 (see ESI†).

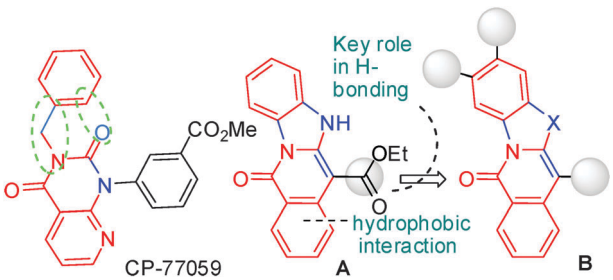

Fig. 1 Design of **A**/**B** as novel inhibitors of PDE4.

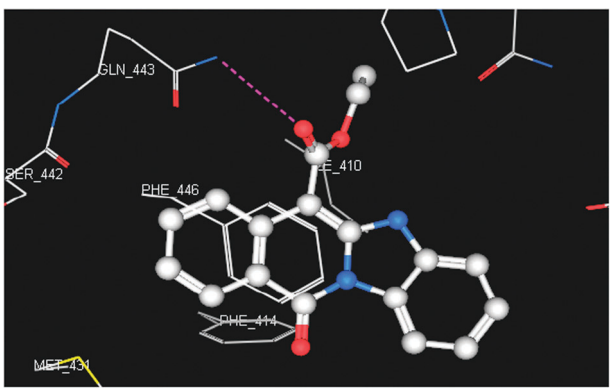

Fig. 2 Binding mode of **A** in PDE4B (PDB code-1XMY).

In view of the central role played by heterogeneous catalysts in various organic transformations,[5] inexpensive and commercially available Amberlyst-15 attracted our attention due to its non-hazardous nature and easy removal from the reaction mixture *e.g. via* simple filtration. We anticipated that Amberlyst-15 mediated activation of the vinylic amino group of 3-amino-2-(2-hydroxy/aminophenyl)isoquinolin-1(2*H*)-one could trigger its intramolecular cyclization leading to our target compounds **A**/**B**. Herein we report our preliminary results on intramolecular cyclization of 3-amino-2-(2-amino/hydroxyphenyl)isoquinolin-1(2*H*)-one derivative **3** leading to benzimidazo[1,2-*b*]isoquinolin-11-ones/benzoxazolo[3,2-*b*]isoquinolin-11-ones **4** (or **B**, Scheme 1).

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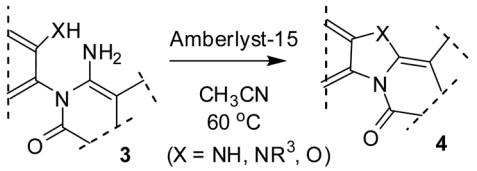
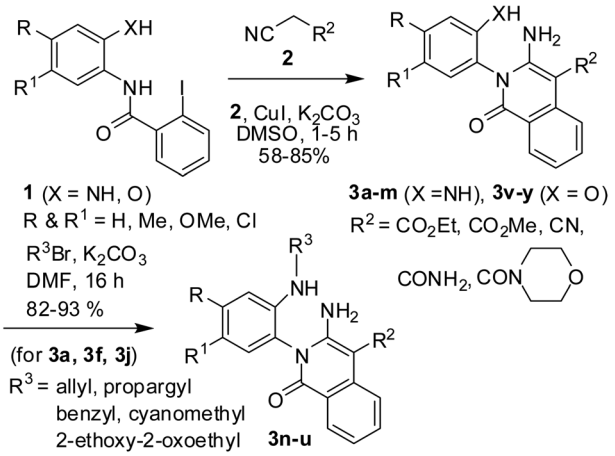
† Electronic supplementary information (ESI) available: Experimental procedures, spectral data for all new compounds, results of *in vitro* and docking studies. See DOI: 10.1039/c3cc41337c



Scheme 1 Amberlyst-15 mediated activation of a vinylic amino group.



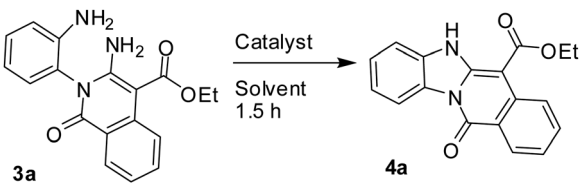
Scheme 2 Preparation of key starting material **3**.

To the best of our knowledge the use of this strategy leading to **4** is unprecedented.[1,6] The key starting material **3** (**3a–m;** X = NH and **3v–y;** X = O) required was prepared *via* Cu-mediated[2f,7] coupling–cyclization of 2-iodobenzamides **1** with appropriate cyano derivatives **2** in the same pot (followed by selective *N*-alkylation to prepare **3n–u**) (Scheme 2).

The Amberlyst-15 mediated intramolecular cyclization of **3a** was examined initially in a variety of solvents (Table 1). The reaction proceeded well in MeCN, PEG and MeOH (entries 1, 2 and 4, Table 1) but not in DMF (entry 3, Table 1). Notably, the reaction proceeded in water affording product **4a** albeit in lower yield (entry 5, Table 1). The reaction, however, did not proceed in the absence of Amberlyst-15 (entry 6, Table 1) or in the presence of another catalyst *i.e.* Amberlite (entry 7, Table 1) indicating the key role played by Amberlyst-15 in the present reaction. To test the recyclability of the catalyst, Amberlyst-15 was recovered by simple filtration and reused additional three times when **4a** was isolated without significant loss of its yield (entry 1, Table 1). Notably, all these reactions were performed without using any inert atmosphere. Overall, Amberlyst-15 in MeCN was found to be optimum for the preparation of **4a**.

We then examined the generality and substrate scope of the present reaction. A range of substituents *e.g.* Me, OMe, Cl on the *N*-aryl ring and ester, CN, amide on the isoquinolinone ring of **3** were well tolerated (Table 2). Moreover, the reaction proceeded well irrespective of the nature of participating amino groups (*e.g.* primary or secondary) on the *N*-aryl ring of **3**. Secondary amines possessing various R^3 groups like allyl, propargyl, benzyl, cyanomethyl or 2-ethoxy-2-oxoethyl participated well in the reaction. The generality of this methodology was demonstrated further by synthesizing benzoxazolo[3,2-*b*]isoquinolin-11-ones (**4v–y**) where the phenolic hydroxyl group of the *N*-aryl ring of **3** participated in the reaction. All the desired products were synthesized in good to excellent yields[8] and well characterized by spectral (NMR, IR and MS) data (see ESI†).

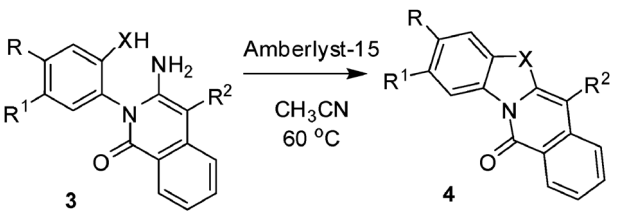
Table 1 Effect of conditions on Amberlyst-15 mediated synthesis of **4a**[a]



Entry	Catalyst	Solvent	Yield[b] (%)
1	Amberlyst-15	MeCN	98 (95, 90, 88)[c]
2	Amberlyst-15	PEG-800	92
3	Amberlyst-15	DMF	47
4	Amberlyst-15	MeOH	90
5	Amberlyst-15	H_2O	75[d]
6	No cat.	MeCN	No reaction
7	Amberlite	MeCN	No reaction

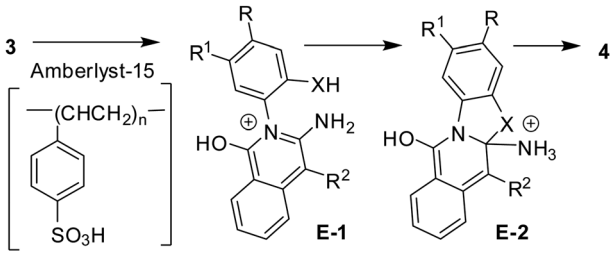
[a] Reaction was carried out using **3a** (1.0 mmol), catalyst (10%, w/w) in solvent (5 mL) at 60 °C. [b] Isolated yield. [c] Catalyst was reused for additional three runs and figures within parentheses indicate the corresponding yields for each run. [d] The reaction was carried out at 75 °C.

Table 2 Amberlyst-15 mediated synthesis of **4**[a]



Entry	X, R, R^1, R^2 substrate (**3**)	*t*/h	Product (**4**)	Yield[b] (%)
1	NH, H, H, CO_2Et **3a**	1.5	**4a**	98
2	NH, H, H, CO_2Me **3b**	2.0	**4b**	87
3	NH, H, H, CN **3c**	7.0	**4c**	71
4	NH, H, H, mor[c] **3d**	11.5	**4d**	63
5	NH, H, H, $CONH_2$ **3e**	8.5	**4e**	65
6	NH, CH_3, H, CO_2Et **3f**	1.5	**4f**	91
7	NH, CH_3, H, CO_2Me **3g**	2.0	**4g**	83
8	NH, CH_3, H, CN **3h**	7.0	**4h**	75
9	NH, CH_3, H, mor **3i**	12.0	**4i**	61
10	NH, OCH_3, H, CO_2Et **3j**	1.5	**4j**	92
11	NH, OCH_3, H, CO_2Me **3k**	2.0	**4k**	91
12	NH, Cl, Cl, CO_2Et **3l**	2.0	**4l**	93
13	NH, Cl, Cl, CO_2Me **3m**	2.0	**4m**	90
14	*N*-Allyl, H, H, CO_2Et **3n**	3.5	**4n**	89
15	*N*-Allyl, CH_3, H, CO_2Et **3o**	3.5	**4o**	91
16	*N*-Propargyl, H, H, CO_2Et **3p**	3.0	**4p**	89
17	*N*-Propargyl, CH_3, H, CO_2Et **3q**	3.0	**4q**	86
18	NBn, H, H, CO_2Et **3r**	4.5	**4r**	95
19	NBn, OCH_3, H, CO_2Et **3s**	4.0	**4s**	95
20	NCH_2CN, CH_3, H, CO_2Et **3t**	5.0	**4t**	96
21	NCH_2CO_2Et, CH_3, H, CO_2Et **3u**	6.0	**4u**	91
22	O, OCH_3, H, CO_2Et **3v**	5.0	**4v**	90
23	O, OCH_3, H, $CONH_2$ **3w**	8.0	**4w**	85
24	O, OCH_3, H, mor **3x**	8.0	**4x**	72
25	O, CH_3, H, CO_2Et **3y**	5.0	**4y**	93

[a] All the reactions were carried out using compound **3** (1 mmol) and Amberlyst-15 (10%, w/w) in CH_3CN (5 mL) at 60 °C. [b] Isolated yield. [c] mor = morpholine-4-carbonyl.



Scheme 3 The proposed reaction mechanism.

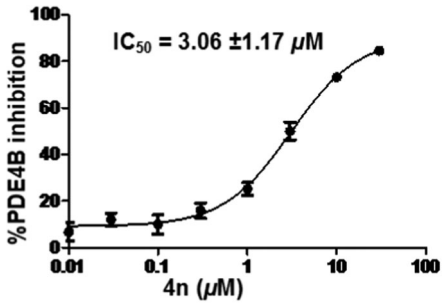


Fig. 3 Dose dependent inhibition of PDE4B by **4n**.

Amberlyst-15 (Scheme 3), a macro-reticular polystyrene-based ion exchange resin, possesses strongly acidic sulfonic groups. Thus, mechanistically (Scheme 3), the intramolecular cyclization of **3** seemed to proceed *via* a two-step process involving (i) a nucleophilic attack by the –XH moiety[9a] of **E-1** on its activated and nearby –C═N– affording the intermediate **E-2** followed by (ii) elimination of ammonia to give the desired compound **4**.[9b] An attempt to isolate the intermediate **E-1** or **E-2** from the reaction of **3a** under the conditions employed however failed, perhaps due to its rapid participation in the next step leading to **4a**.

Some of the compounds synthesized were tested against PDE4B using an *in vitro* enzyme assay.[10] The compounds **4a** (**A** in Fig. 1 and 2), **4f**, **4g**, **4d** and **4n** showed 62, 53, 57, 48 and 85% inhibition, respectively, at 30 μM and **4n** (IC_{50} ~ 3 μM, Fig. 3) was comparable with rolipram (IC_{50} ~ 1 μM). Since COPD and asthma are the major health burden worldwide, the present class of compounds is of further interest.

In conclusion, a facile assembly of a benzimidazole or a benzoxazole ring with isoquinolinone has been achieved *via* a conceptually new and general strategy involving Amberlyst-15 mediated activation of a vinylic amino group leading to a diverse and unique class of small molecules as potential inhibitors of PDE4.

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8 Except **4c–e**, **4h**, **4i**, **4w** and **4x** other compounds do not require any chromatographic purification after isolation.
9 (*a*) The possibility of the –XH moiety to play the role of a leaving group (*cf.* ref. 6*a* where Br was used as a leaving group) was ruled out as the corresponding benzimidazo[1,2-*b*]isoquinolin-11-ones was not isolated in the case of **3v–y** instead of benzoxazolo[3,2-*b*]isoquinolin-11-ones **4v–y** (see Table 2). Indeed, the present role of –XH allowed us to introduce further diversity *i.e.* the R^3 group into the product **4**; (*b*) Alternatively, protonation of R^2 (*i.e.* ester, CN or amide) of **3** followed by intramolecular nucleophilic attack of XH on the –C═N– moiety could also lead to the formation of product **4**.
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