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COMMUNICATION

Construction of a six-membered fused *N*-heterocyclic ring *via* a new 3-component reaction: synthesis of (pyrazolo)pyrimidines/pyridines†

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A conceptually new three-component reaction was developed to construct a six-membered fused *N*-heterocyclic ring affording (pyrazolo)pyrimidines/pyridines as potential inhibitors of PDE4. The reaction is catalyzed by triflic acid in acetic acid in the presence of aerial oxygen.

The development of convergent, atom-economic, expedient and eco-friendly chemical methods is of utmost interest in modern synthetic chemistry. In particular, single-step or cascade reactions, such as multi-component reactions (MCRs),[1] often provide an inherently more efficient approach to chemical synthesis than conventional bimolecular reactions. Well known examples of MCR include the Strecker, Passerini, Ugi, Pauson–Khand, Biginelli and Mannich reactions. Since MCRs provide a powerful tool for the discovery of new chemical entities (NCEs) required by pharmaceutical and agrochemical industries,[2] the development and application of new MCRs have become a frontier area of research, both in academic and industrial organizations.

Over the last twenty years, the pyrazolo[1,5-*a*]pyrimidine framework has been a versatile scaffold for various pharmacological studies.[3] On the other hand, during the last ten years, the pharmaceutical industry has focused on developing novel anti-inflammatory agents that inhibit phosphodiesterase 4 (PDE-4) to treat chronic obstructive pulmonary disease (COPD) and asthma.[4] Recently, we have reported the usefulness of 7-(hetero)-aryl-substituted pyrazolopyrimidine **B** (Fig. 1) derived from Ibudilast **A** as a potential scaffold for the development of novel PDE4 inhibitors.[5] In further continuation of this research and our long standing interest in PDE4/TNF-α inhibitors,[4,6] we planned to generate a library of compounds based on **C** (Fig. 1). In this communication, we wish to present our preliminary work on the identification of potential PDE4 inhibitors, the synthesis of which was carried out using a conceptually new MCR.

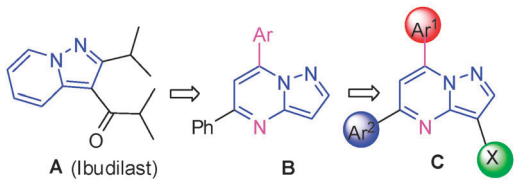
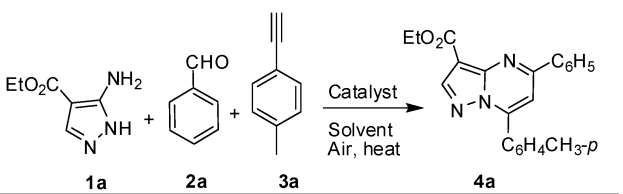


Fig. 1 Ibudilast and pyrazolo[1,5-*a*]pyrimidines as PDE4 inhibitors.

While numerous methods are known for the synthesis of pyrazolo[1,5-*a*]pyrimidines,[7] including the use of the Suzuki reaction or Pd-mediated coupling of an organometallic reagent, *e.g.* ArZnI,[8] most of these methods, however, are useful for the preparation of specific compounds. One of the major challenges and aims of the present work was therefore to develop a suitable methodology leading to heterocyclic structure **C**. We envisaged that the one-pot three-component synthesis of pyrazolo[1,5-*a*]pyrimidines from an aromatic aldehyde, terminal alkyne and a third reactant containing –C═C(NH$_2$)–NH– moiety could be handy in the present case. In order to maintain the pyrazole ring of **C** the 5-amino-1

Table 1 The effect of reaction conditions on MCR using ethyl 5-amino-1*H*-pyrazole-4-carboxylate (**1a**) with benzaldehyde (**2a**) and 1-ethynyl-4-methylbenzene[a] (**3a**)



Entry	Solvent	Catalyst	Time (h)	%Yield[b]
1	CH_3CN	CF_3CO_2H-AcOH (1 : 1)	15	74[c]
2	CH_3CO_2H	CF_3CO_2H	15	20[d]
3	CH_3CO_2H	CF_3SO_3H	2	82
4	CH_3CO_2H	No catalyst	36	56
5	CH_3CN	CF_3SO_3H	15	78[c]
6	CH_3CN	I_2	15	70[c]
7	CH_3CO_2H	$ZnBr_2$	15	10[d]

[a] All of the reactions were carried out using 5-amino-1*H*-pyrazole-4-carboxylate **1a** (1.0 mmol), benzaldehyde **2a** (1.0 mmol), 1-ethynyl-4-methylbenzene **3a** (1.0 mmol) and a catalyst (0.10 mmol) in a solvent (5 mL) at 100–110 °C in the presence of air. [b] Isolated yield. [c] The reaction was carried out at 80–85 °C. [d] A number of unknown side products formed.

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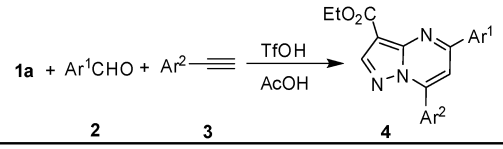
† Electronic supplementary information (ESI) available: Experimental procedures, spectral data for all new compounds, results of docking study. See DOI: 10.1039/c1cc16418j

Table 2 TfOH-mediated synthesis of 5,7-diaryl substituted pyrazolo[1,5-*a*]pyrimidines[a]



2 3 4

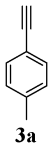
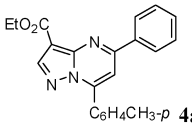
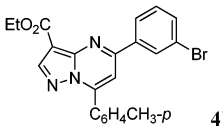
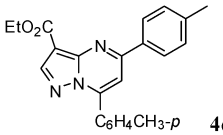
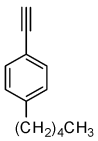
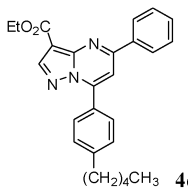
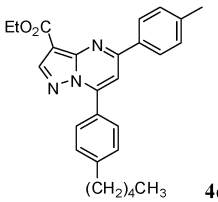
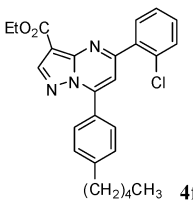
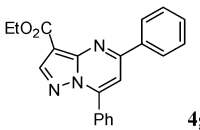
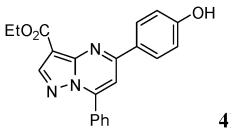
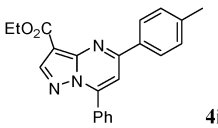
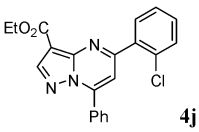
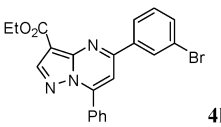
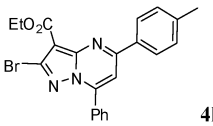
Entry	Aldehydes (**2**)	Alkynes (**3**)	Products (**4**)	Yield[b] (%)
1	PhCHO **2a**	 **3a**	 $C_6H_4CH_3$-*p* **4a**	82
2	*m*-BrC_6H_4CHO **2b**	**3a**	 $C_6H_4CH_3$-*p* **4b**	80
3	*p*-$CH_3C_6H_4CHO$ **2c**	**3a**	 $C_6H_4CH_3$-*p* **4c**	84
4	**2a**	 $(CH_2)_4CH_3$ **3b**	 $(CH_2)_4CH_3$ **4d**	84
5	**2c**	**3b**	 $(CH_2)_4CH_3$ **4e**	83
6	*o*-ClC_6H_4CHO **2d**	**3b**	 $(CH_2)_4CH_3$ **4f**	72
7	**2a**	 Ph **3c**	 Ph **4g**	85
8	*p*-HOC_6H_4CHO **2e**	**3c**	 Ph **4h**	76
9	**2c**	**3c**	 Ph **4i**	84

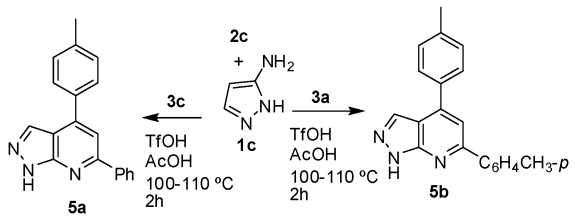
Table 2 (*continued*)

Entry	Aldehydes (**2**)	Alkynes (**3**)	Products (**4**)	Yield[b] (%)
10	**2d**	**3c**	 Ph **4j**	77
11	**2b**	**3c**	 Ph **4k**	80
12	**2c**	**3c**	 Ph **4l**	82[c]

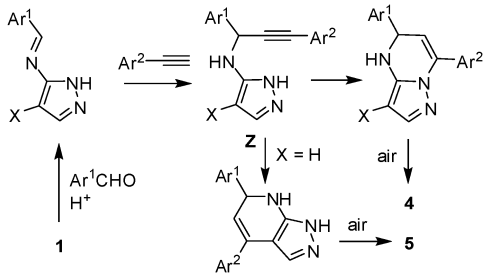
[a] All of the reactions were carried out using **1a** (1.0 mmol), aryl aldehyde **2** (1.0 mmol), terminal alkyne **3** (1.0 mmol) and TfOH (0.10 mmol) in acetic acid (5 mL) at 100–110 °C for 2 h in the presence of air. [b] Isolated yield. [c] Ethyl-3-amino-5-bromo-1*H*-pyrazole-4-carboxylate (**1b**) was used in place of **1a**.

H-pyrazole derivative appeared as an appropriate third component that would eventually allow the construction of the central pyrazolo[1,5-*a*]pyrimidine framework. To this end, we have observed that treatment of ethyl-5-amino-1*H*-pyrazole-4-carboxylate (**1a**) with benzaldehyde (**2a**) and 1-ethynyl-4-methylbenzene (**3a**) in the presence of a catalyst and air in a suitable solvent at an elevated temperature produced ethyl 5-phenyl-7-*p*-tolylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**4a**) as the only product (Table 1). Initially, the reaction was carried out using 1 : 1 trifluoroacetic acid (TFA)–acetic acid (AcOH) as the catalyst in acetonitrile for 15 h at 80–85 °C, when the desired product **4a** was isolated in 74% yield (entry 1, Table 1). The use of AcOH as a solvent increased the formation of impurities with a reduction in product yield (entry 2, Table 1). The use of trifluoromethanesulfonic acid (TfOH) in AcOH, however, significantly decreased the reaction time and increased the yield of **4a** (entry 3, Table 1). This reaction was carried out at 100–110 °C. The product yield dropped considerably in the absence of TfOH (entry 4, Table 1) indicating the key role played by the catalyst in the present 3-component reaction. Changing the solvent to acetonitrile did not affect the yield of **4a** (entry 5, Table 1). The use of other catalysts, *e.g.* iodine in acetonitrile, was found to be effective (entry 6, Table 1), whereas $ZnBr_2$ in AcOH was less efficient (entry 7, Table 1). Thus a combination of TfOH, AcOH and air was identified as the best reaction conditions for the preparation of **4a**.

With the optimized reaction conditions in hand, we then examined the generality and scope of the present MCR. We were pleased to find that the reaction proceeded well with a variety of aromatic aldehydes and terminal alkynes to give a range of 5,7-diaryl substituted derivatives (Table 2). The use of ethyl-3-amino-5-bromo-1*H*-pyrazole-4-carboxylate (**1b**) in place of **1a** provided the corresponding bromo compound (entry 12, Table 2), which was amenable to further structural elaboration *via* Suzuki, Heck or Sonogashira coupling.[9] Notably, isomeric pyrazolo[3,4-*b*]pyridine derivatives (**5a–b**) were obtained when



Scheme 1 The synthesis of pyrazolo[3,4-*b*]pyridine derivatives.



Scheme 2 The proposed reaction mechanism.

1*H*-pyrazol-5-amine possessing no substitution at C-4 was employed (Scheme 1). Compounds **5a–b** were characterized by the appearance of an NH signal in the region δ 11.2–11.3 in ^{1}H NMR and 3140–3145 cm^{-1} in the IR spectra, which was absent in case of **4**. In order to understand the mechanism of the reaction, a number of experiments were carried out. Accordingly, the reaction of **1a** with **2a** and **3a** was examined separately under the conditions presented previously (*cf.* entry 3, Table 1). The reaction proceed in the first case (but not in the second case) to give the corresponding imine. Based on these observations, a plausible mechanism is proposed (Scheme 2). The reaction seems to proceed through four steps, *e.g.* (i) *in situ* generation of imine *via* condensation of amine **1** and aldehyde **2**, (ii) subsequent nucleophilic addition of alkyne **3** to imine leading to the key propargyl amine **Z**, (iii) cycloisomerization of **Z** *via* intramolecular nucleophilic attack of pyrazole nitrogen (N-1) or carbon (C-4) in a 6-*endo-dig* fashion depending on the nature of X present and, finally, (iv) aerial oxidation of the resulting dihydropyrazolopyrimidine intermediate affording the product **3** or **4**. To gain further evidence, the reaction of **1a**, **2a** and **3a** (*cf.* entry 3, Table 1) was carried out strictly under an argon atmosphere when the corresponding dihydro derivative (*e.g.* ethyl-5-phenyl-7-*p*-tolyl-4,5-dihydropyrazolo[1,5-*a*]pyrimidine-3-carboxylate) was isolated instead of **4a**, confirming the role of air in the last step.

Some of the compounds synthesized were tested for their PDE4B inhibitory potential *in vitro* using PDE4B enzyme[10] and rolipram as a reference compound. Compounds **4h** and **4k** showed 67 and 33% inhibition of PDE4B at 30 μM, respectively. This was supported by the docking results (Fig. 2) of **4h** with PDE4B protein (binding energy −10.2 Kcal mol^{-1}), which showed H-bonding interactions between the –OH group of **4h** and THR345 residue of PDE4B. Additionally, π–π stacking interactions between the central pyrazolopyrimidine moiety of **4h** with the PHE414, PHE446 and TYR223 residues of PDE4B was also observed.

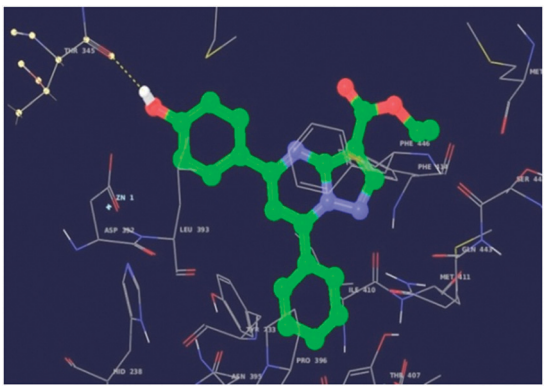


Fig. 2 Docking of **4h** at the active site of PDE4B.

In conclusion, a one-pot TfOH-mediated cascade reaction has been developed to construct a fused pyrimidine ring in the presence of aerial oxygen affording (pyrazolo) pyrimidines/pyridines as potential inhibitors of PDE4.

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Notes and references

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9 For example, reaction of **4l** with 3-carbamoylphenylboronic acid in the presence of $(PPh_3)_2PdCl_2$, PPh_3 in DMF at 100–110 °C for 2 h provided the corresponding Suzuki product (92%). Similarly, the Sonogashira product (75%) was obtained when **4l** was reacted with 1-ethynylcyclohexanol in the presence of $(PPh_3)_2PdCl_2$, CuI in DMF at 100–110 °C for 2 h (see ESI†).
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