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Unusual rearrangement of imidazo[1,5-*a*]imidazoles and imidazo[1,2-*b*]pyrazoles into imidazo[1,5-*a*]pyrimidines and pyrazolo[1,5-*a*]pyrimidines†

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A multicomponent reaction giving easy and cheap access to a variety of bicyclic 5,5-fused hetero-rings has been developed. Then, an usual rearrangement of imidazo[1,5-*a*]imidazoles or imidazo[1,2-*b*]pyrazoles leading to bi-heterocyclic imidazo- and pyrazolo[1,5-*a*]pyrimidines in the presence of a specific amount of I_2 in THF at room temperature has been achieved. This new method enables the hitherto unreported synthesis of functionalized imidazo- and pyrazolo[1,5-*a*]pyrimidines.

Introduction

Polynitrogenated heterocycles are specific candidates for the design and discovery of new compounds with a large spectrum of biological activities.[1–4] Widely known examples are those molecules containing imidazole or pyrazole as frameworks of high interest in medicinal chemistry, such as 5-(2-(3-((2,6-dichlorophenyl)amino)imidazo[1,2-*a*]pyrimidin-2-yl)-3,5-dimethoxyphenyl)-*N*-methyl-1,3,4-oxadiazol-2-amine (**A**) which is used as an SGLT2 inhibitor for type 2 diabetes,[5] *R*′-8-carbamoyl-4-(3-*R*-phenyl)-2-methyl-1,4-dihydroimidazo[1,5-*a*]pyrimidine-3-carboxylate (**B**) as a calcium antagonist,[6] 2,7-di(1*H*-indol-3-yl)pyrazolo[1,5-*a*]pyrimidine-6-carbonitrile (**C**) which has anti-oxidant activity[7] and 3-(((3-bromo-5-(2-fluorophenyl) pyrazolo[1,5-*a*]pyrimidin-7-yl)amino)methyl)pyridine 1-oxide (**D**) which exhibited inhibition of CDK2 (ref. 8) (Fig. 1).

Polycyclisation reaction has been steadily gaining importance in synthetic organic chemistry. It's an interesting way to access structural diversity and new privileged structures.[9] The multicomponent reactions (MCR), especially those based on isocyanide called Groebke–Blackburn–Bienaymé reactions,[10] are a method of choice to access complex heterocyclic molecules in a single step process from commercially available starting materials. Based on our expertise in the synthesis and functionalization of diverse polynitrogen-containing heterocycles,[11] we wish to describe herein the preparation of original imidazo- and pyrazolo-[1,5-*a*]pyrimidine derivatives from synthesized imidazo[1,5-*a*]imidazoles and imidazo[1,2-*b*]pyrazoles using MCR followed by iodine catalyzed intramolecular rearrangement.

Results and discussion

The imidazo-imidazole derivatives were prepared using MCR as described in the literature.[12] In this method, we treated 5-aminoimidazole-4-carbonitrile and *tert*-butyl isocyanide with various commercially available or readily prepared propargylic aldehydes **3a–j** (see ESI† for new aldehydes preparation) in the presence of perchloric acid as catalyst in methanol at room

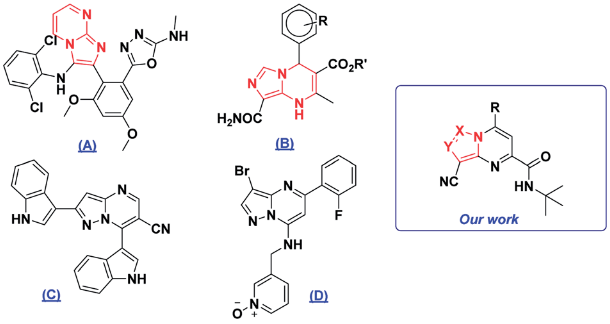

Fig. 1 Examples of active imidazolo and pyrazolo-pyrimidine derivatives.

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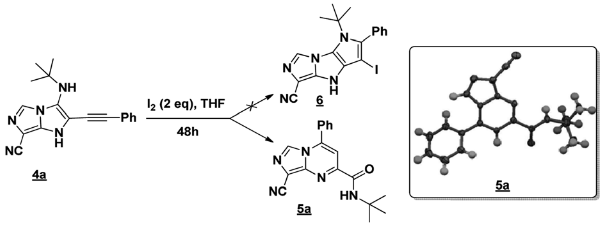
† Electronic supplementary information (ESI) available. CCDC 1900146. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ra04609g

temperature for 24 h. The imidazo[1,5-*a*]imidazole substrates **4a–j** were isolated in moderate to good yields. The use of either electron-donating or withdrawing groups on the aromatic ring of **3a–j** provided the desired products in acceptable yields (Table 1).

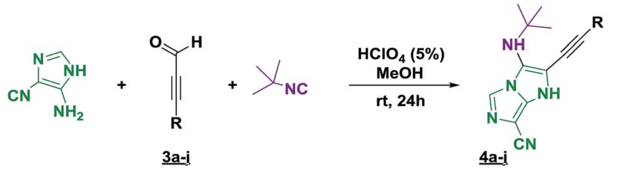
Firstly, the phenylpropargyl aldehyde was examined and the desired compound **4a** was isolated in 72% yield. The effect of substituents on the aromatic ring of benzaldehydes was then investigated. The 3-(*p*-tolyl)propiolaldehyde and 3-(*p*-methoxyphenyl)propiol-aldehyde, bearing electron-donor groups led to expect products **4b** and **4c** in 61 and 68% yields, respectively. These yields are slightly lower than those obtained using the electron withdrawing groups with both 3-(*p*-fluorophenyl)propiolaldehyde and 3-(*p*-(trifluoromethyl)phenyl) propiolaldehyde, the corresponding compounds **4d** and **4e** were isolated in 73 and 81% yields, respectively. Importantly, the use of the aliphatic aldehyde 2-octynal was also effective leading to compound **4j** in 75% yield. In contrast, we noticed a decrease in reaction yields when using aldehydes containing a methoxy group on the benzoic ring at either *ortho* or *meta*- positions. However, no significant decrease was observed when using fluorine group at either *ortho* or *meta*- positions on the aromatic ring. Once a variety of 3-(*tert*-butylamino)-2-(arylethynyl)-1*H*-imidazo[1,5-*a*]imidazoles has been synthesized, we decided to expand the utility of these scaffolds by using iodine polycyclisation reaction. According to our previous reports, the formation of tricyclic fused 3-iodo-pyrrolo[3′,2′:4,5]-imidazo[1,5-*a*]imidazoles could be easy obtained by an iodine intramolecular cyclisation of the multicomponent compounds in the presence of I_2 in DCM (Scheme 2).[13] So, we first investigated the general reaction conditions using 3-(*tert*-butylamino)-6-cyano-2-(phenylethynyl)-1*H*-imidazo[1,5-*a*]imidazole **4a** as model substrate in the presence of 2 equivalents of I_2 in DCM at room temperature. Under these reaction conditions, 60% of starting material was recovered (entry 1, Table 2). Surprisingly, the use of THF as solvent for the reaction gave access to imidazo[1,5-*a*]pyrimidine **5a** instead of tricyclic compound **6** (entry 2, Table 2). The structure of **5a** was confirmed by a single-crystal X-ray study (Scheme 1).



Scheme 1 Preparation of imidazo[1,5-*a*]pyrimidine **5a** by rearrangement of **4a**.

Encouraged by this preliminary result, other amounts of I_2 were also investigated. Adding 4 equiv. of I_2 instead of 2 equiv. increased the yield of **5a** to 54% with 31% of starting material recovered (entry 3, Table 2). To our delight, when using 6 equiv. of I_2, a complete conversion of the starting material into the rearranged product was achieved and **5a** was isolated in 71% yield (entry 4, Table 2). To further improve the reaction yield, 8 equiv. of I_2 were also examined, unfortunately, in this case only the degradation was observed (entry 5, Table 2). To gain more insight into the plausible mechanism of this rearrangement, oxygen free conditions were tested by trying the reaction under argon. However, only traces of product were isolated (entry 6, Table 2). Adding 6 equiv. of water into the reaction was associated by a complete degradation of the starting material (entry 7, Table 2). Next, we tried to extend our trials by changing the source of iodine. With iodine monochloride, unfortunately, no reaction occurred, only the starting material was recovered

Table 1 Synthesis of imidazo[1,5-*a*]imidazole derivatives *via* MCR



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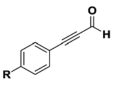
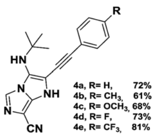
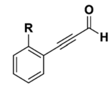
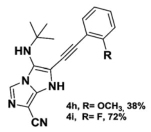
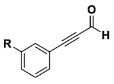
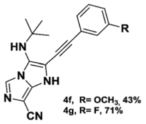
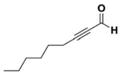
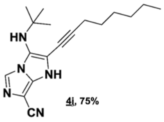
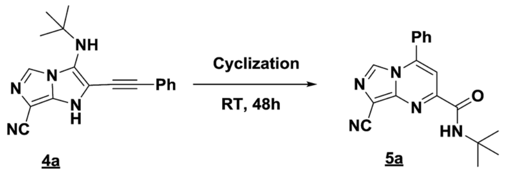
			
			

Table 2 Optimization study of the rearrangement of **4a**



Entry	Iodine source	Solvent	Yield (%)
1	I_2 (2 equiv.)	DCM	Traces(60)[a]
2	I_2 (2 equiv.)	THF	15(53)[a]
3	I_2 (4 equiv.)	THF	54(31)[a]
4	I_2 (6 equiv.)	THF	71
5	I_2 (8 equiv.)	THF	Traces
6	I_2 (6 equiv.)	THF	Traces[b]
7	I_2 (6 equiv.)	THF	0[c]
8	ICl (6 equiv.)	THF	0(90)[a]
9	NIS (6 equiv.)	THF	Traces(60)[a]
10	HI (6 equiv.)	THF	32(30)[a]

[a] Isolated starting material. [b] Reaction under argon. [c] 6 equiv. of water was added to the reaction : degradation.

(entry 8, Table 2). Even with *N*-iodosuccinimide or hydriodic acid, the desired product was isolated in traces and in low yields, respectively (entries 9 and 10, Table 2).

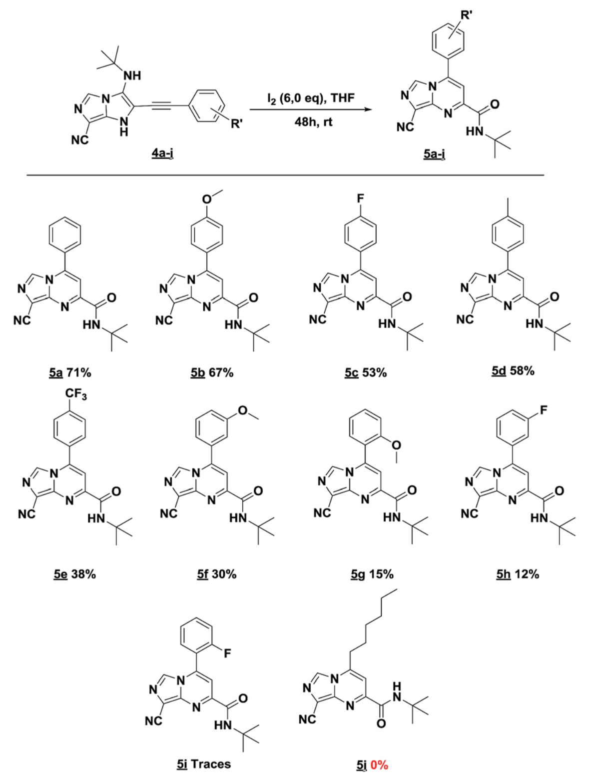
In an endeavor to expand the scope of this method, the reactivity of various 3-(*tert*-butylamino)-1*H*-imidazo[1,5-*a*]imidazole-7-carbonitriles **4b–4j** was investigated (Table 3).

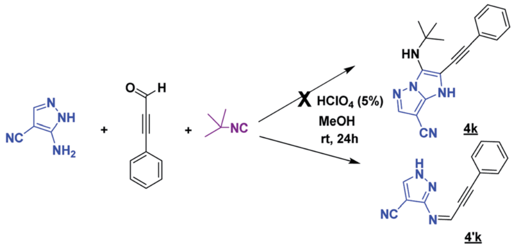
The reaction proceeded with electron-donating and electron withdrawing groups. Moderate yields were obtained with *para*-substituted substrates on the aromatic ring (Table 3, products **5b–e**) while lower yields were observed with *ortho* and -*meta*-substituted analogues (Table 3, products **5f–h**). Unluckily, for substrate containing fluorine group at *ortho* position, only traces of desired compound **5i** were obtained. Also, we investigated the rearrangement with an aliphatic aldehyde, but unfortunately, no reaction was observed.

After having successfully developed a chemical library of functionalized imidazo[1,5-*a*]pyrimidines in only two steps, we extended the methodology to prepare various pyrazolo[1,5-*a*]pyrimidines in which the pyrazole core is fused with a pyrimidine. For this aim, the 5-aminoimidazole-4-carbonitrile was replaced by 3-aminopyrazole-4-carbonitrile by using the reaction conditions of MCR (Scheme 2). This latter has been serving as a basic scaffold of some synthetic compounds identified for the treatment of several diseases such as inflammation,[14,15] tuberculosis[16] and cancer.[17]

Unfortunately, after 24 h of reaction, only the imine intermediate **4′k** was obtained. To prepare the desired compound **4k**, the optimization of the reaction conditions was needed. Indeed, we examined the following different conditions reported in the literature[18,19] (Table 4).

Table 3 Synthesis of imidazo[1,5-*a*]pyrimidine derivatives





Scheme 2 MCR of 3-aminopyrazole-4-carbonitrile.

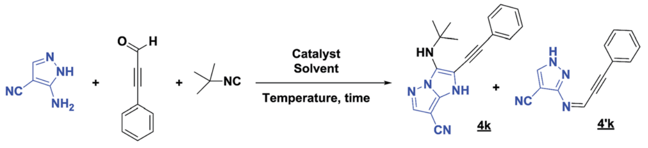
Based on the best reaction conditions obtained with 10% of zirconium tetrachloride and PEG-400, we extend this reaction with two different substituted aminopyrazoles (Table 5). Afterwards, the obtained imidazo[1,2-*b*]pyrazoles **4k–m** were involved in the rearrangement reaction to give the corresponding pyrazolo[1,5-*a*]pyrimidines **5k–m** as shown in Table 5.

With the nitrile group, the rearranged compound **5k** was obtained in an average yield of 35% while the starting materials containing phenyl or ester groups on the pyrazole ring gave the products **5l** and **5m** in good yields of 56 and 67%, respectively.

For a plausible mechanism, we think that, during the cyclization/aromatization, I_2 in the presence of O_2 (air) led to the formation of H_2O_2 (ref. 20) which may open the imidazo[1,5-*a*]imidazole **4a** and then by cyclisation resulting from the nucleophilic attack of the N1 of the imidazole on the benzylic position led to imidazo[1,5-*a*]pyrimidine **5a** (Scheme 3).

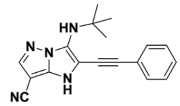
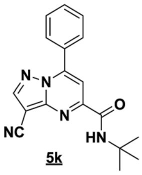
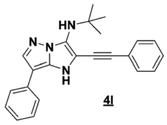
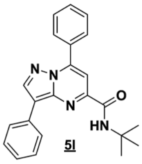
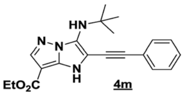
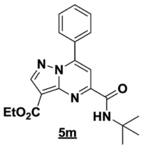
To support our hypothesis, we first carried out the reaction under the same conditions using the radical scavenger 1,4-cyclohexadiene (1,4-CHD), the results revealed the formation of the product which explained the non-radical reaction pathway. Next, we performed the reaction in the presence of hydrogen peroxide (3 equiv.) under argon, the result showed the formation of the iodinated product **6a** in 31% during 24 h (Scheme 3). Whereas, when the reaction was conducted without an oxidant

Table 4 Optimization of MCR with 3-aminopyrazole-4-carbonitrile



Entry	Catalyst	Solvent	*T* (°C)	*t* (h)	**4k** (%)	**4′k** (%)
1	$HClO_4$ (5%)	MeOH	r.t.	24	0	98
2	TFA (20%)	EtOH	r.t.	24	36	40
3	TFA (20%)	EtOH	50	24	35	42
4	$ZrCl_4$ (10%)	MeOH	r.t.	24	40	46
5	$ZrCl_4$ (10%)	MeOH	50	16	43	41
6	$ZrCl_4$ (10%)	PEG-400	50	2	54	0
7	$ZrCl_4$ (10%)	PEG-400	r.t.	1	76	0

Table 5 Generalization of MCR and synthesis of pyrazolo[1,5-*a*] pyrimidine derivatives

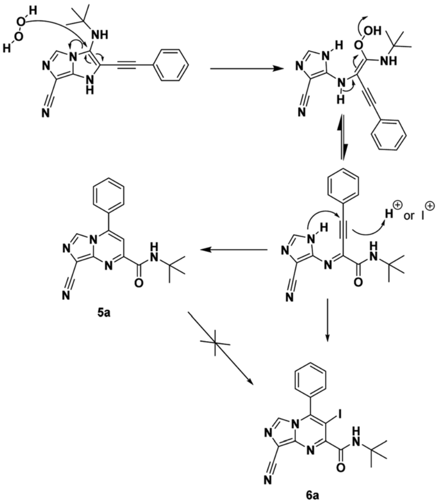
R	MCR product 4	Yield (%)	Product 5	Yield (%)
–CN	 **4k**	76	 **5k**	35
–Ph	 **4l**	37[a]	 **5l**	56
–CO_2Et	 **4m**	44	 **5m**	67

[a] Reaction time 0.5 h.

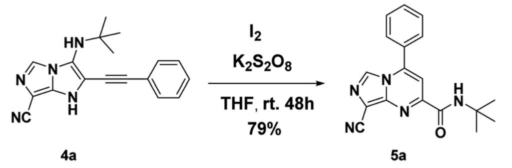
under argon no reaction occurred (see Table 2, entry 6). This shows the involvement of H_2O_2 in the reaction mechanism.

The formation of the product **6a** can be explained by an electrophilic addition of the iodinium cation I^+ during the cyclisation. To ensure this, no reaction took place when **5a** was treated under the same conditions (Scheme 3), which means that the product **6a** is not formed by iodination of **5a**. The iodination agent I^+ was produced *in situ* from the combination of I_2 and H_2O_2.[21]

The structure of this compound was elucidated by 1D and 2D NMR. In addition, the ^1H–^{13}C HMBC experiment indicated that the iodination occurs on the pyrimidine moiety rather than the imidazole moiety.



Scheme 3 Plausible mechanism and synthesis of **5a**.



Scheme 4 Synthesis of **5a** using $I_2/K_2S_2O_8$.

However, when another oxidant was added to the reaction mixture ($K_2S_2O_8$, 1.1 equiv.) under air, the reaction yield was improved to 79% (Scheme 4).

Conclusions

In summary, we have reported an exceptional rearrangement reaction starting from 3-(*tert*-butylamino)-2-(arylethynyl)-1*H*-imidazo[1,5-*a*]imidazoles or 3-(*tert*-butylamino)-2-(arylethynyl)-1*H*-imidazo[1,2-*b*]pyrazoles which were readily prepared by MCR reaction. This rearrangement reaction is unique and gives access rapidly and easily in two steps to a large diversity of functionalized imidazo- and pyrazolo-[1,5-*a*]pyrimidines, using mild reaction conditions in the presence of 6 equivalents of I_2 from available starting materials.

Author contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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