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New use of bis(benzotriazolyl)-1,2-(dialkylamino)ethanes for the synthesis of 2-*H*-3-dialkylamino imidazo[1,2-*a*]pyrazine derivatives

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ABSTRACT

First direct synthesis of 2-*H*-3-*N*-dialkyl-imidazo[1,2-*a*]pyrazines is described. This approach makes use of accessible substituted pyrazines and the assistance of benzotriazole. In such a manner we accomplished the introduction of cyclic amines at C-3 of the scaffold in a convenient formal cyclisation procedure. Detailed examples and utility of this approach are presented herein.

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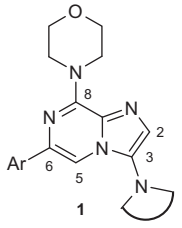
Imidazo[1,2-*a*]pyrazines are molecules with interesting biological activities. More specifically they have been reported for the treatment of degenerative, inflammatory,[1] type 2 diabetes diseases,[2] as well as antiulcer[3] and anticancer agents.[4]

6-Aryl/heteroaryl-8-morpholinyl-imidazo[1,2-*a*]pyrazines represent one of the most potent and drug-like chemical series of PI3K (phosphatidylinositol 3-kinases) inhibitors within our drug discovery project of new anticancer compounds.[5] In order to explore the SAR (structure–activity relationship) around the central imidazo[1,2-*a*]pyrazine core, we were very interested in the particular substitution of C-3 with secondary amines, **1**. However, we were limited by the poor reactivity of this position towards Buchwald type coupling of amines (Fig. 1).[6] Thus, the initial attempts to functionalise 3-Cl/Br/I-imidazo[1,2-*a*]pyrazines with piperidine using different catalysts ($Pd_2(dba)_3$ or $PdCl_2(dppf)$) and ligands (XanPhos, DavePhos or BINAP), yielded unreacted starting material together with the de-halogenated imidazo[1,2-*a*]pyrazine, and only traces of the desired compound.

Although this type of heterocycles have significance in drug discovery, there are few reported synthetic methods that enable the preparation of 2-*H*-imidazo[1,2-*a*]pyrazine bearing amine substitution at C-3. The literature describes mainly a variation of the Ugi reaction involving three-component coupling (3-CC) with isonitriles, aldehydes and the prerequisite 2-aminopyrazines, 2-aminopyrimidines or 2-aminopyridines.[7] Further developments of this procedure include microwave assisted protocols or polymer supported chemistry applications.[8,9] Among these reported methodologies, only a few examples were found that leave the 2-position unsubstituted. One method reported the nitration and subsequent zinc/acetic acid reduction of the nitro intermediate at C-3. Further reaction of the amino group, via reductive amination, afforded a variety of mainly secondary amines.[10] Following this synthetic approach, a few 3-dialkylamino-imidazo[1,2-*a*]pyrazines have been described recently.[11] A second method was based on the successful introduction of formaldehyde in the 3-CC reaction, via glyoxylic acid, that leaves 2-unsubstituted-3-amino-imidazoheterocycles.[12] Nevertheless, all of these synthetic approaches suffer either from poor diversity in the accessible amine synthons, or from the need of multi-step routes to build the secondary amines.



1

Figure 1. 6-Aryl/heteroaryl-8-morpholinyl-imidazo[1,2-*a*]pyrazines.

In 2003, Katritzky et al. developed an attractive methodology to prepare 3-dialkylamino-imidazopyridines and pyrimidines. This method relies on the preparation of 1,2-bis(benzotriazolyl)-1,2

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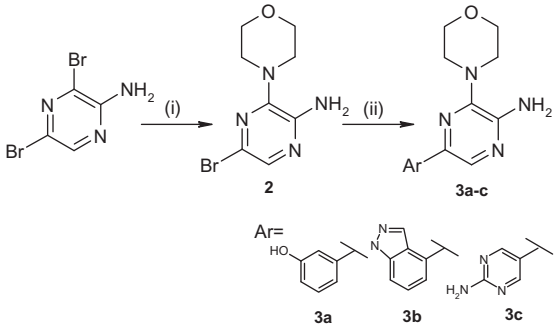
(dialkylamino)-ethanes that react with the required 2-aminopyridine or 2-aminopyrimidine in a formal cyclisation.[13]

In this communication we would like to report our work in the application of this approach to prepare 2-*H*-3-*N*-dialkylamino-imidazo[1,2-*a*]pyrazines. In order to facilitate a rapid exploration of C-3 with secondary amines, we fixed substituents at C-6 and C-8 in our target molecules, and therefore, in the key intermediates as well. Phenol, indazole and 2-aminopyrimidine were chosen for the C-6 aryl/heteroaryl substitution, and morpholine was selected at C-8.

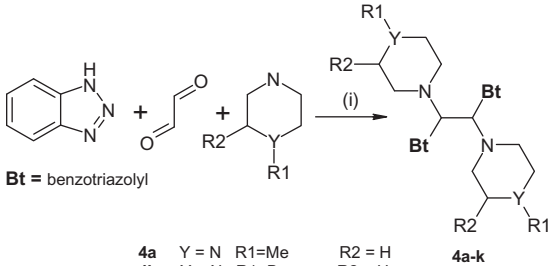
These fragments have been reported to provide key interactions in the ATP binding pocket of PI3-kinase,[14] and are introduced by a classical sequence of steps (Scheme 1, **3a–c**). On the other hand, the bis(benzotriazole) intermediates **4a–k** (Scheme 2) were readily prepared under mild conditions via condensation of glyoxal, benzotriazole and the corresponding amines in ethanol.[15,16]

The adducts **4a–k** were used directly into next step. Both pyrazinyl intermediates (**3a–c**) and amine adducts (**4a–k**) were reacted in a convergent manner through a formal cyclisation, by heating in 1,2-dichloroethane (DCE) to produce the corresponding 3-dialkylamino-imidazo[1,2-*a*]pyrazines (Table 1, **5a–o**).[17,18]

The cyclisation reaction proved to be highly regioselective, as reported previously by Katritzky et al. giving only C-3 substitution also in our imidazo[1,2,-*a*]pyrazine scaffold. This result was confirmed by NOE experiments for selected compounds **5a, 5d** and **5j**. Irradiation of H-5 in the pyrazine ring gave positive NOE effect with certain protons of piperazine and piperidine substituents, according to required substitution pattern.



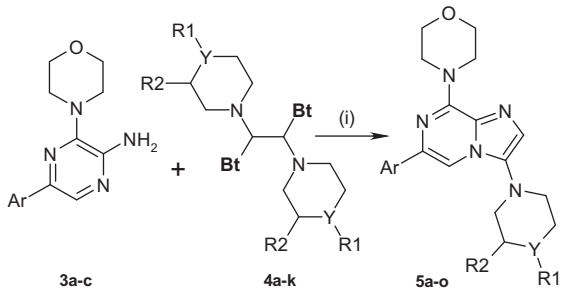
Scheme 1. Reagents and conditions: (i) morpholine, 120 °C, 48 h, 96%; (ii) arylboronic acid, K_2CO_3, $PdCl_2$(dppf), DME, MW, 130 °C, 10 min (**3a** 49%, **3b** 63%, **3c** 90%).



4a Y = N R1=Me R2 = H
4b Y = N R1=Boc R2 = H
4c Y = N R1= SO_2Me R2 = H
4d Y = C R1 = NHBoc R2 = H
4e Y = C R1 = H R2 = NHBoc
4f Y = C R1 = H R2 = H
4g Y = C R1 = SO_2Me R2 = H
4h Y = C R1 = Ph R2 = H
4i Y = C R1 = H R2 = Ph
4j Y = C R1=Me R2= H
4k Y = C R1 = CH_2Ph R2 = H

Scheme 2. Reagent and condition: (i) EtOH, rt, 18 h.

Table 1
Synthesis of 2-unsubstituted-3-*N*-cyclic-amine-imidazo[1,2-*a*]pyrazines



Compound number	Ar/Het	Y	R1	R2	Yield[a] (%)
5a	3-Phenol	N	Me	H	40
5b	1*H*-Indazol-4-yl	N	Me	H	24
5c	3-Phenol	N	SO_2Me	H	15
5d	3-Phenol	N	H	H	15[b]
5e	1*H*-Indazol-4-yl	N	SO_2Me	H	23
5f	1*H*-Indazol-4-yl	N	H	H	15[b]
5g	1*H*-Indazol-4-yl	C	NH_2	H	30[b,c]
5h	1*H*-Indazol-4-yl	C	H	NH_2	15[b,c]
5i	2-Aminopyrimidinyl	N	SO_2Me	H	18
5j	1*H*-Indazol-4-yl	C	H	H	48[c]
5k	1*H*-Indazol-4-yl	C	SO_2Me	H	30[c]
5l	1*H*-Indazol-4-yl	C	Phenyl	H	34[c]
5m	1*H*-Indazol-4-yl	C	H	Phenyl	68[c]
5n	1*H*-Indazol-4-yl	C	Me	H	27[c]
5o	1*H*-Indazol-4-yl	C	CH_2Ph	H	23[c]

[a] Isolated compounds with purity ⩾95%.
[b] Yield after Boc-group deprotection.
[c] Racemic mixture of regioisomers.

Despite the moderate yields obtained with this synthetic route, (results summarised in Table 1), the short number of steps and the readily available starting building blocks (secondary amines), allowed us an immediate access to these specific imidazo[1,2-*a*]pyrazine derivatives. Such a straightforward and rapid synthetic approach is very valuable in medicinal chemistry SAR explorations in comparison with multi-step and more elaborate pathways.

In conclusion, we have demonstrated the application of the methodology reported by Katritzky et al. to the first straightforward synthesis of complex 2-*H*-3-dialkylamino-6-aryl/heteroaryl-8-morpholinyl imidazo[1,2-*a*]pyrazines. Further applications for the preparation of bioactive compounds are in progress in our medicinal chemistry projects.[16]

Acknowledgment

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17. General procedure A. *Preparation of Bis(benzotriazolyl) products* (**4b**, **4c**, **4f**, **4g**, **4h**, **4i**, **4j**, **4k**): A mixture of benzotriazole (300 mg, 2.43 mmol), the appropriate piperidine or piperazine (2.43 mmol) in EtOH (20 mL) was stirred for 20 min. Glyoxal (0.160 mL of a 40% w solution in water, 1.2 mmol) was added, and the resultant mixture was stirred for 16 h. The white solid formed was filtered off, washing with EtOH and diethylether to yield required products that were used in the next reaction step without further purification. General procedure B. *Preparation of Bis(benzotriazolyl) products* (**4a**, **4d**, **4e**): A mixture of benzotriazole (300 mg, 2.43 mmol), the appropriate piperidine or piperazine (2.43 mmol) in EtOH (20 mL) was stirred for 20 min. Glyoxal (0.160 mL of a 40% w solution in water, 1.2 mmol) was added, and the resultant mixture was stirred for 16 h. The solution was concentrated under high vacuum leaving an oily residue. The cream/white solid formed by the addition of diethyl ether was filtered off, rinsing with diethyl ether and dried in vacuo. The product was used in the next reaction step.
18. General procedure C. *Synthesis of 3-substituted-imidazo[1,2-a]pyridazines*. (**5a**–**k**): Required bis(benzotriazolyl) (0.44 mmol) and 5-aryl-3-morpholinopyrazin-2-amine (0.44 mmol) were dissolved in DCE (7 ml) and refluxed until reaction was completed as determined by LC–MS analysis (5–48 h). The reaction mixture was cooled down to rt and then KOH (powder, 250 mg) was added. The mixture was stirred for 20 min at rt, filtered off and washed with DCM. Filtrate was concentrated and the residue obtained was purified by Biotage flash column chromatography eluting with the adequate required solvent system.