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# Metal-free protocol for the synthesis of novel 6-(het)aryl-5-aryl-5*H*-imidazo[4,5-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazines

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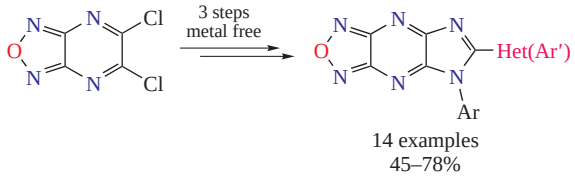
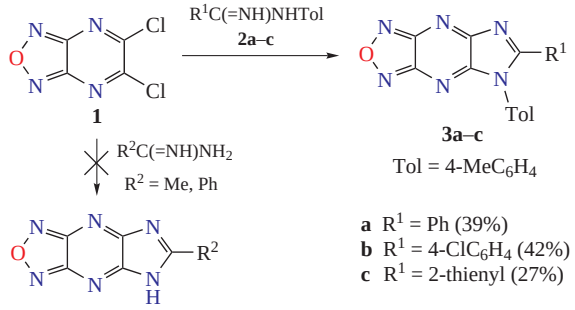
**New 5-aryl-5*H*-imidazo[4,5-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazines with the 6-positioned electron-rich (het)aryl substituents have been obtained from 5,6-diamino[1,2,5]oxadiazolo[3,4-*b*]-pyrazines through the effective two-step strategy: the starting diamino compounds were treated with triethyl orthoformate, followed by the reaction with a π-excessive arene in the presence of trifluoroacetic acid. The structures of target products were for the first time confirmed by X-ray diffraction analysis.**




During the last decade, imidazoles fused with heteroaromatic rings have gained interest as compounds for advanced materials, and molecules of medicinal interest. In particular, imidazopyrazine derivatives are used as inhibitors of casein and serin/threonin protein kinases.[1–3] The fusing of imidazoles with electron-withdrawing pyrazine ring makes these heterocyclic systems to acquire π-conjugated push-pull properties, which is of importance for organic dyes suitable as optoelectronic components, especially organic light-emitting diodes.[4–10] From this point of view, azolo annulated imidazopyrazines, *e.g.*, 5*H*-imidazo[4,5-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazines, can also be promising building units to obtain prospective materials for optoelectronics.

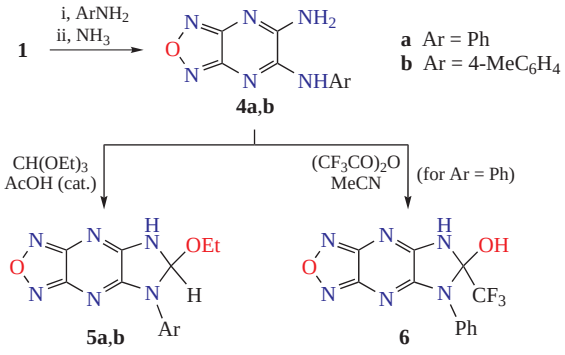
This structural core can be obtained either by condensation of diaminopyrazines with ortho esters, carbonyl compounds or some other electrophiles, or through cyclization of azoxy compounds.[11–15] Another approach to build this heterocyclic system includes the displacement of good leaving groups, such as Cl or Br,[16,17] or a combination of the first two methods.[18] The third method is based on a metal-catalyzed coupling of amides or amidines with aromatic halides. It has been reported that the synthesis of imidazopyrazines can be accomplished *via* the C–N coupling of amides with 2-amino-3-halopyrazines followed by the ring closure.[9,19–21] In spite of achievements in the field of C–N coupling of amines with aromatic halides, there are only few reports on C–N couplings of 2-amino-3-halopyrazines with amine derivatives. Another significant drawback of this method is the application of catalytic systems containing Pd or Cu. Due to annulation of electron-withdrawing furazane ring to the pyrazine framework, an electrophilic character of the fused heterocyclic furazano[3,4-*b*]pyrazine system becomes an extremely high, which makes nucleophilic substitution of a halogen in the pyrazine ring to be a very favorable process.

In this communication, we report on the synthesis of new series of 6-(het)aryl-5-aryl-5*H*-imidazo[4,5-*b*][1,2,5]oxadiazolo-[3,4-*e*]pyrazines, and also several synthetic ways for their modifications. We began our studies with interaction of amidines with 5,6-dichloro[1,2,5]oxadiazolo[3,4-b]pyrazine **1** (Scheme 1). Amidines **2a–c** were obtained using a known procedure.[22] All attempts to react dichloro compound **1** with benzamidine or acetamidine were unsuccessful, and brought about complex mixtures. Meanwhile, the use of disubstituted amidines **2a–c** gave the expected products **3a–c** in moderate yields.




**Scheme 1**

To increase yields of the target compounds, we developed a counter-synthesis strategy. First, non-asymmetric diamino derivatives of furazano[3,4-*b*]pyrazines were synthesized using a successive substitution of halogen atoms in the pyrazine ring in compound **1** (Scheme 2). The resulting diamines **4a**,**b** were tested in condensation with various electrophiles. However, their reaction




**Scheme 2**

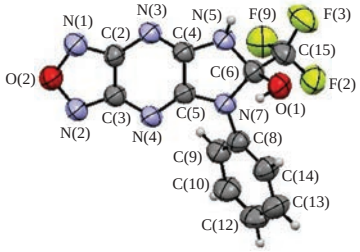
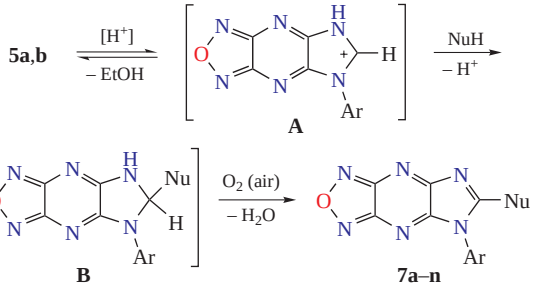



**Figure 1** X-ray crystal structure of compound **6**. Ellipsoids are drawn at 50% probability level.

with acid chlorides, aldehydes or propionic anhydride did not give the expected products. Moving to application of triethyl orthoformate under acidic conditions or trifluoroacetic anhydride afforded unexpected dihydro derivatives of 5-aryl-5*H*-imidazo-[4,5-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazines **5a**,**b** and **6**. Attempts to eliminate EtOH or $H_2O$ from these O-adducts to access aromatic compounds failed. The structures of all products were proved on the basis of $^1H$ and $^{13}C$ NMR spectroscopy data, as well as X-ray crystallography analysis for compound **6** (Figure 1).

We assumed that under acidic conditions the adducts **5a**,**b** could undergo dissociation to form the corresponding carbocation **A** capable of trapping some nucleophiles (Scheme 3). The reaction apparently begins with protonation at ethoxy group. The next elimination of alcohol leads to carbocations **A**, followed by addition of nucleophiles to give $\sigma^H$-adducts **B** whose air-promoted aromatization results in final products **7**. The aromatization proved to occur readily in air, so the intermediate $\sigma^H$-adducts **A** could not be isolated (see Scheme 3). The structures of all products were proved by $^1H$ and $^{13}C$ NMR spectroscopy, as well as X-ray crystallography analysis performed for 2,6-di-*tert*-butyl-6-(5-phenyl-5*H*-imidazo[4,5-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazin-6-yl)phenol **7a** (Figure 2).




| | Ar | Nu | Yield of **7** (%) |
|---|---|---|---|
| **a** | Ph | 3,5-$Bu^t_2$-4-$HOC_6H_2$ | 69 |
| **b** | Ph | 3,5-$Bu^t_2$-2-$HOC_6H_2$ | 61 |
| **c** | Ph | 2,4,6-$(MeO)_3C_6H_2$ | 52 |
| **d** | Ph | 2-methoxy-1-naphthyl | 62 |
| **e** | Ph | 4-$Ph_2NC_6H_4$ | 62 |
| **f** | Ph | 5-phenylpyrrol-2-yl | 76 |
| **g** | Ph | 1-ethyl-3-indolyl | 64 |
| **h** | 4-$MeC_6H_4$ | 3,5-$Bu^t_2$-4-$HOC_6H_2$ | 57 |
| **i** | 4-$MeC_6H_4$ | 3,5-$Bu^t_2$-2-$HOC_6H_2$ | 56 |
| **j** | 4-$MeC_6H_4$ | 2,4,6-$(MeO)_3C_6H_2$ | 45 |
| **k** | 4-$MeC_6H_4$ | 2-methoxy-1-naphthyl | 53 |
| **l** | 4-$MeC_6H_4$ | 4-$Ph_2NC_6H_4$ | 60 |
| **m** | 4-$MeC_6H_4$ | 5-phenylpyrrol-2-yl | 78 |
| **n** | 4-$MeC_6H_4$ | 1-ethyl-3-indolyl | 69 |

**Scheme 3**

Attempts to replace the ethoxy group in the $\sigma^H$-adduct **5a** with aliphatic or aromatic amines caused the imidazole ring opening to give formamidines **8** and **9** (Scheme 4). Based on

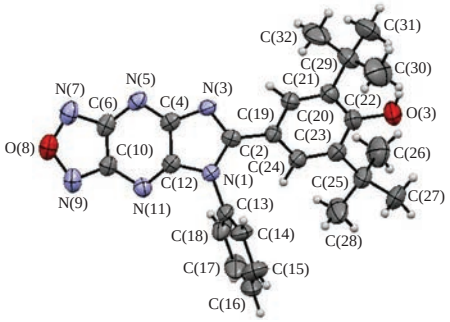
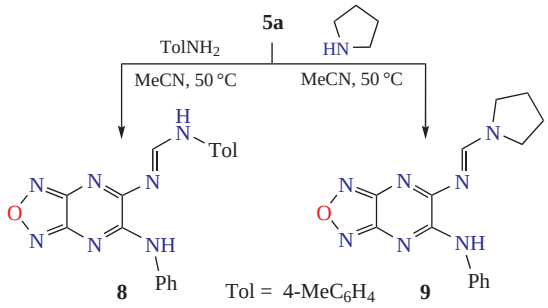



**Figure 2** X-ray crystal structure of compound **7a**. Ellipsoids are drawn at 50% probability level.




**Scheme 4**

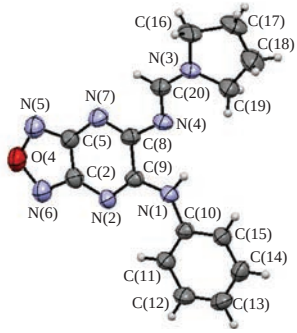



**Figure 3** X-ray crystal structure of compound **9**. Ellipsoids are drawn at 50% probability level.

X-ray crystallography analysis, the structure of compound **9** was established to have the *E*-configuration (Figure 3).

The UV absorption spectra of compounds **7e** and **7l** bearing triphenylamine moiety show a long-wave absorption maxima band at 504 nm for **7e** and 503 nm for **7l**, their extinction coefficients being 43 840 and 44844 $dm^3\ mol^{-1}\ cm^{-1}$, respectively (see Online Supplementary Materials).

In conclusion, we have developed an efficient and general method for the synthesis and functionalization of novel 6-(het)-aryl-5-aryl-5*H*-imidazo[4,5-*b*][1,2,5]oxadiazolo[3,4-*e*]pyrazines from 5,6-dichloro[1,2,5]oxadiazolo[3,4-*b*]pyrazine using the three-step synthetic protocol. This procedure provides a rapid and efficient access to a number of π-conjugated compounds of the imidazopyrazine family. The reactions appear to be extremely simple to carry out and do not require the use of metal-based catalytic systems.

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*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.09.002.

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