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New regio/chemoselective synthesis of hydrogenated imidazo[1,5-*b*]pyridazines

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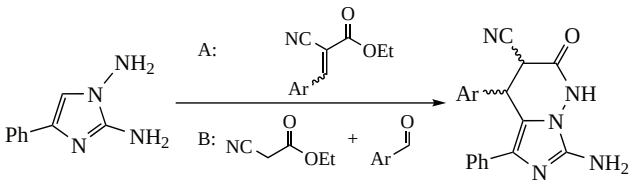
The cascade heterocyclization of 1,2-diamino-4-phenylimidazole with ethyl 2-arylidene-2-cyanoacetates affords 1,2,3,4-tetrahydroimidazo[1,5-*b*]pyridazine-3-carbonitrile derivatives as mixtures of diastereomers. The experimental data and quantum chemical calculations were used to propose the mechanism and account for the regio/chemoselectivity of processes. The three-component processing with above-mentioned diamine, ethyl cyanoacetate and aromatic aldehydes leads to the same products in generally lower yields.



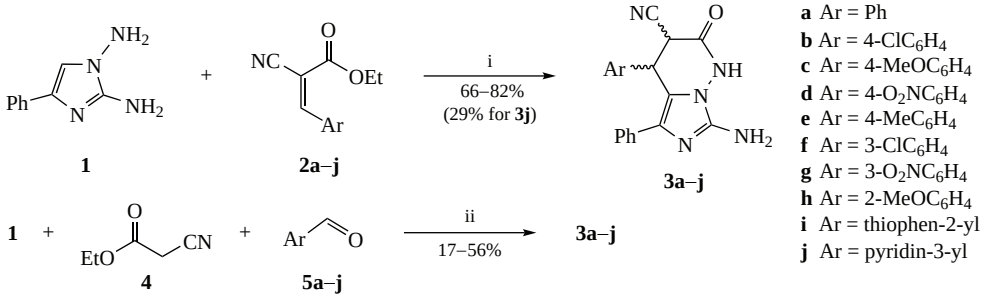
Keywords: 1,2-diamino-4-phenylimidazole, imidazo[1,5-*b*]pyridazines, arylidenecyanoacetates, diastereomers, regioselectivity, quantum chemical calculations, cascade processes.

Fused heterocycles with saturated fragments are among the promising scaffolds.[1–4] Natural products and drugs that have higher saturation and, therefore, a greater number of chiral centres possess higher conformational lability,[4–7] which determines their higher cell permeability and solubility compared to fully aromatized analogues.[8–10] In general, this also has a positive effect on their comparative overall physiological activity. Thus, the creation of new combinatorial heterocyclic compounds libraries with hydrogenated fragments containing chiral centres is an important and promising field in the search for new drugs.

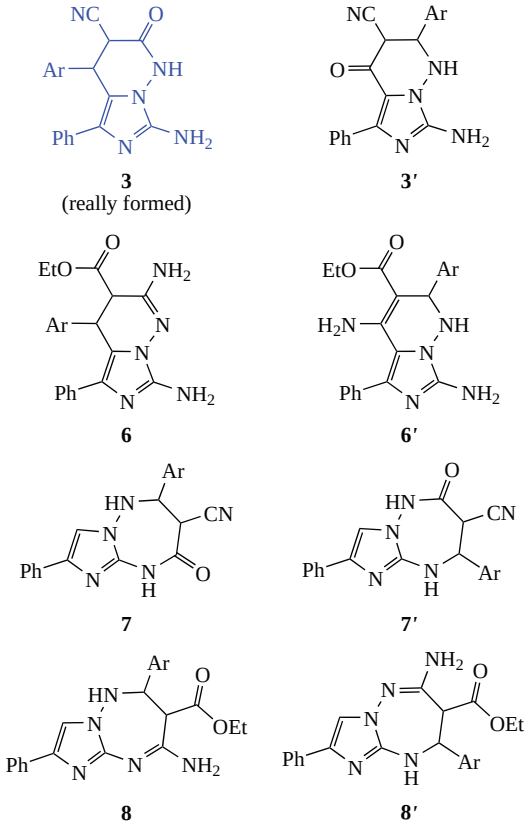
Imidazo[1,2-*b*]- and imidazo[1,5-*b*]pyridazine fused systems are of particular interest due to their diverse biological activity.[11–18] Despite a significant number of studies many promising areas remain undiscovered in the chemistry of these compounds.[19–21] In particular, regio- and chemoselectivity is one of the key problems in their synthesis. Partially hydrogenated imidazo[1,5-*b*]pyridazines can be obtained by cascade re-cyclization of unsaturated dicarboxylic acids cyclic imides[20,21] or by the reaction of Meldrum's acid derivatives[19] with 1,2-diamino-4-phenylimidazole. However, the selectivity in these processes is not always satisfactory.

In this work, we have studied the selectivity in two- or three component heterocyclization of 1,2-diamino-4-phenylimidazole with polyelectrophilic cyanoacetate reactants in both synthetic and computational aspects. The choice of optimal conditions is based on the results of the previous works[18–20,22–29] dealing with close transformations. Refluxing the reactants in various solvents such as protic alkanols and/or aprotic acetonitrile, 1,4-dioxane or DMF was tested. In all cases, acetic acid was used as the catalyst. Initially, we have studied the two-component reaction of 1,2-diaminoimidazole **1** with ethyl 2-arylidene-2-cyanoacetates **2a**–**j** (Scheme 1). The highest yields of products **3a**–**j** were achieved by refluxing in 1,4-dioxane.

The C,N- or N,N-polynucleophilicity of 1,2-diamino-4-phenylimidazole **1** and the multifunctional C,C-electrophilicity of 2-arylidene-2-cyanoacetates **2a**–**j** would suggest different reaction pathways for their interaction. Alternative imidazopyridazines **3′**,**6**,**6′** or imidazotriazepines **7** and **7′** may be in principle formed, due to the difference in the regioselectivity of



Scheme 1 *Reagents and conditions*: i, **1**/**2a**–**j** (1 : 1 mol/mol), AcOH (5 mol%), 1,4-dioxane, reflux, 6 h; ii, **1**/**4**/**5a**–**j** (1 : 1 : 1 mol/mol/mol), AcOH (5 mol%), 1,4-dioxane, reflux, 7–8 h (for details, see Online Supplementary Materials).



initial Michael addition of diaminoimidazole **1** by CH- or N(1)–NH_2-groups to the activated double bond of reactant **2** and subsequent chemoselective intramolecular condensation at the ester fragment. In turn, the possible formation of imidazopyridazines **7**,**7′** or imidazotriazepines **8**,**8′** can be explained by the participation of the nitrile group of arylidenecyanoacetates **2** in the second cyclization stage. Mechanistically, the initial C-Michael addition is the most obvious.

Spectral data of the obtained substances excluded the formation of diaminoimidazopyridazines **6′**,**6**, as well as imidazotriazepines **8**,**8′**. The IR spectra showed band of the nitrile group in the region 2200–2240 cm^{-1} and an intense band around 1670 cm^{-1} characteristic of formal δ-lactam fragments (the 'amide I' band). The absence of signals for ethoxycarbonyl group in the ^1H NMR spectra is the evidence for the chemoselectivity at the second stage involving the ester group.

The resonance of the amide NH proton in the ^1H NMR spectra at 12.4–12.6 ppm and the presence of two broad singlets for the NH_2 group in the region 6.8–7.1 ppm ruled out the structures from **6** to **8′**. Finally, the signals in the ^{13}C NMR spectra at 161–163 ppm which can only correspond to the C-atom of the amide carbonyl group[21,30–32] excluded the structure of imidazopyridazines **3′** with the cyclic keto group.

Apparently, imidazopyridazines **3** are formed as a result of the regio/chemoselective cascade reaction of diaminoimidazole **1** and 2-arylidene-2-cyanoacetates **2** with the participation of the ester group of the latter. On the other hand, this heterocyclization leads to diastereomeric mixtures of imidazopyridazines **3** having

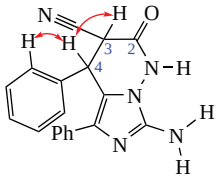


Figure 1 Key interactions of protons in the ^1H–^1H NOESY experiment for compound **3a**.

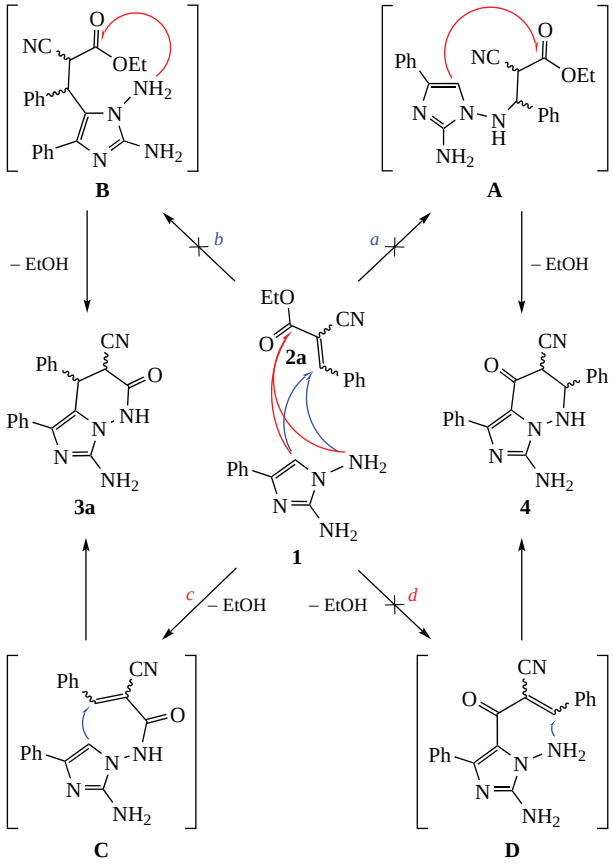


Figure 2 Possible mechanism of the reaction between 1,2-diaminoimidazole **1** and ethyl 2-benzylidene-2-cyanoacetate **2a**.

two chiral centres. Their ^1H NMR spectra contain two sets of methine doublets of the pyridazine cycle. For the one of diastereomers, **3a**, double cross peaks were found in the ^1H–^1H NOESY experiment for the CH–Ph proton at 4.95 ppm, both with the CH–CN signal at 3.77 ppm and with the protons of the benzene ring (Figure 1). For the second diastereomer, the corresponding correlations were observed for the signals at 4.89 ppm and 4.54 ppm (CH^3). The formation of diastereomeric mixtures was also confirmed by the presence of two signals of lactam C-atoms at 161–163 ppm in the ^{13}C NMR spectra. Also, two peaks with equal molecular ion masses were detected in HPLC–HRMS data.

Based on the experimental and calculation data (for details, see Online Supplementary Materials), we proposed the following sequence of the diamine **1** cascade reaction with arylidenecyanoacetate **2a** as an example (Figure 2). First, the addition of 1,2-diamino-4-phenylimidazole **1** as N- or C-nucleophile to activated C=C bond of Michael acceptor **2** may result in intermediates **A** or **B**. Another initial step can be nucleophilic attack at the carbonyl carbon atom followed by the elimination of ethanol molecule and the formation of intermediates **C** or **D**, respectively. Earlier works[29,33,34] generally stated that such cascade reactions proceeded following pathways *a* and *b* (see Figure 2). We assume that in our case the reaction can proceed along routes *b* or *c*, however, direction *c* is predominant because of charge control (pathway *c*), with the formation of amidation intermediate **C**. In addition, this route is also preferable, since the resulting intermediate **C** is more sterically stable than **B**.

We also found that imidazopyridazines **3a**–**j** can be obtained by a three-component procedure ii (see Scheme 1) using ethyl cyanoacetate **4** and aldehydes **5a**–**j** under the same conditions as in two-component variant (*cf.* procedure i). It should be noted that the yields of **3a**–**j** in the multicomponent process were

significantly lower, which is probably due to the side formation of Schiff bases.

In summary, we have developed a new approach to tetrahydroimidazo[1,5-*b*]pyridazines in two- or three-component variants. Cascade two-component heterocyclization proceeded *via* initial regioselective Michael addition of 1,2-diamino-4-phenylimidazole as C-nucleophile to activated C=C bond of 2-arylidene-2-cyanoacetates. Intramolecular cyclization as the second step proceeded chemoselectively for the ester group. The selectivity and sequence of the reactions were also confirmed by the results of quantum chemical calculations.

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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.2022.09.023.

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