Mendeleev Communications

Mendeleev Commun., 2025, **35**, 24–26

A new method for constructing pyrido[3′,2′:4,5]imidazo[1,2-*b*]pyridazine system and preparation of its derivatives

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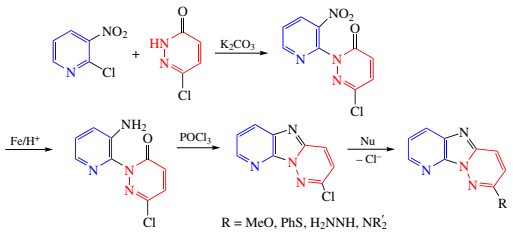
DOI: 10.71267/mencom.7457

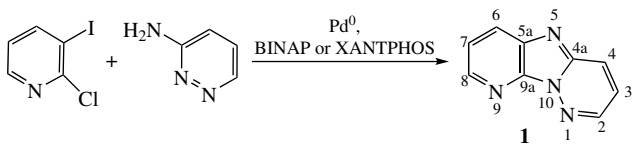
A new method for the construction of the pyrido[3′,2′:4,5]-imidazo[1,2-*b*]pyridazine system involves the use of 2-chloro-3-nitropyridine and 6-chloropyridazin-3(2*H*)-one as the starting reactants. The key step is the $POCl_3$-promoted cyclization of the intermediate 2-(3-aminopyridin-2-yl)-6-chloropyridazin-3(2*H*)-one. The 2-positioned chlorine atom in the thus obtained 2-chloropyrido[3′,2′:4,5]imidazo[1,2-*b*]-pyridazine can be replaced by a variety of nucleophiles.



Keywords: 2-(3-aminopyridin-2-yl)-6-chloropyridazin-3(2*H*)-one, cyclization, pyridazines, pyrido[3′,2′:4,5]imidazo[1,2-*b*]pyridazine, phosphorus oxychloride, quantum chemical calculations, nucleophilic substitution.

The pyridazine ring that is a bioisoster of the most important six-membered aromatic heterocyclic systems[1] is a structural part of many drugs.[2] The examples of such drugs are described.[3–7] Tricyclic fused systems involving pyridazine part are usually obtained from various mono- or bicyclic precursors by annulation of the missing bi- or monocyclic part.[8–12] Alternatively, they can be synthesized from linear polyfunctional precursors (see review[13]). The parent pyrido[3′,2′:4,5]imidazo[1,2-*b*]pyridazine **1** is one of their most interesting representatives since it comprises, in addition to pyridazine, pyridine and imidazole that are even more important pharmacological heterocycles.[14] The imidazo[1,2-*b*]pyridazine bicyclic subsystem is also very interesting in this respect (see reviews[15–17]).

However, the biological activity of pyrido[3′,2′:4,5]-imidazo[1,2-*b*]pyridazines is difficult to predict based on general considerations, except for their ability to block DNA replication by intercalation or to form covalent bonds with DNA in the form of Pt^{II} complexes, like in the case of other platinum complexes, in particular, 1,10-phenanthroline[18] and phenanthridine[19] ones. However, experimental investigations of bioactivity are strongly hampered by the fact that only one member of this series, unsubstituted tricycle **1** itself, has been reported to date. It was obtained by tandem hetarylation of 3-aminopyridazines with 3-iodo-2-chloropyridines in the presence of expensive $Pd(OAc)_2$/BINAP(XANTPHOS) catalysts, and this is the only currently known synthetic approach to obtain the pyrido-[3′,2′: 4,5]imidazo[1,2-*b*]pyridazine system (Scheme 1).[20]

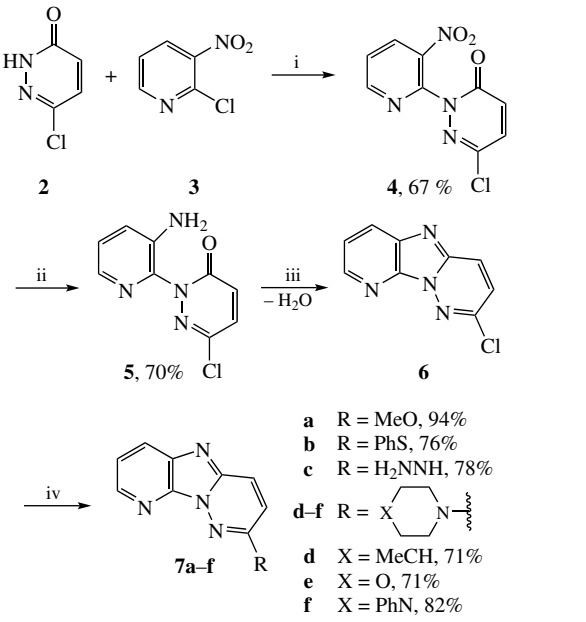


Scheme 1

The alternative options for the synthesis of pyrido[3′,2′:4,5]-imidazo[1,2-*b*]pyridazines from pyridazines, by analogy with techniques used for [1,2-*b*]-annulation of just one imidazole ring,[21] or methods to obtain other similar tricyclic imidazo-[1,2-*b*]pyridazines,[22–25] have different chances of success. The first option seems unrealistic due to the poor availability, instability, or even unknown nature of necessary pyridine analogs of linear imidazole-annulating agents such as, for example, short-living 2,3-dehydropyridines. The second approach is more promising, particularly in comparison with the synthesis of pyrido[3′,2′:4,5]imidazo[1,2-*b*]pyridazines from imidazoles. It requires two separate annulation processes, first of a pyridazine ring, for example by the reported method,[26] and then of a pyridine ring, or *vice versa*.

The present work reports a new method for building tricyclic system **1** starting from pyridazin-3-ones through their *N*-het-arylation with 2-halo-3-nitropyridines, reduction of the resulting *N*-(nitropyridyl)pyridazinones to the corresponding amino derivatives, and cyclization of the latter with closure of the imidazole ring (Scheme 2). The method is not based on the analogies described above and does not require a catalyst. The efficiency of this synthetic method was demonstrated by the synthesis of the first derivative of pyridoimidazopyridazine **1** with a chlorine atom at the 2-position from available 6-chloropyridazin-3-one **2** and 3-nitro-2-chloropyridine **3**. The reaction conditions are easy to perform, and the yields of intermediate products **4**,**5** and final chloro derivative **6** are generally good (see Scheme 2).

The ^1H, ^{13}C and ^{15}N–^1H HMBC NMR spectra of chloro derivative **6** demonstrate the presence of five protons, nine carbon and four nitrogen atoms in the molecule. In the ^1H spectrum, five single-proton signals are observed: two doublets at δ 7.71 (H^3), 8.36 (H^4) and three doublets of doublets at δ 7.66 (H^7), 8.39 (H^6) and 8.65 (H^8). The ^{13}C NMR spectrum



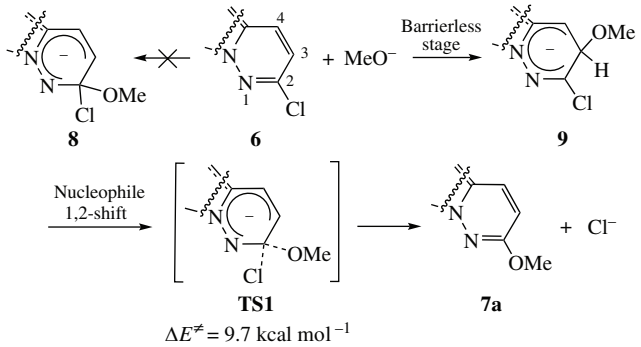
Scheme 2 *Reagents and conditions*: i, K_2CO_3, 60 °C, 3 h; ii, Fe, HCl, reflux, 2 h; iii, $POCl_3$, reflux, 40 min; iv, for **7a**: MeONa, reflux, 1 h, for **7b**: PhSNa, EtOH, reflux, 10 min, for **7c**: $N_2H_4 \cdot H_2O$, EtOH, reflux, 1 h, for **7d**: 4-methylpiperidine, $MeO(CH_2)_2OH$, reflux, 4 h, for **7e**: morpholine, $MeO(CH_2)_2OH$, reflux, 1,5 h, for **7f**: 4-phenylpiperazine, tetramethylurea, reflux, 4 h.

was interpreted using ^{13}C–^{1}H HSQC and HMBC two-dimensional experiments showing signals with chemical shifts of δ 122.75 (C^7), 126.17 (C^3), 129.33 (C^6), 129.64 (C^4), 135.79 (C^{5a}), 141.91 (C^{9a}), 142.19 (C^{4a}), 145.59 (C^8), 146.34 (C^2). The ^{15}N–^{1}H HMBC NMR spectrum shows the presence of a family of cross-peaks allowing, among others, the determination of chemical shifts of nitrogen nuclei: δ 215 (N^{10}), 223 (N^5), 275 (N^9) and 299 (N^1). The mass spectrum (ESI) of compound **6** contains a peak of the $[M+H]^+$ ion.

Chloro derivative **6** readily undergoes nucleophilic substitution reactions with typical O-, N- and S-nucleophiles. These reactions allow one to obtain various 2-R-pyrido-[3′,2′:4,5]imidazo[1,2-*b*]pyridazines, such as **7a–c** (R = MeO, PhS, NH_2NH). 2-Amino derivatives **7d–f** were synthesized as free bases (see Scheme 2), however the analytically pure samples as salts were then accessed upon treatment with mineral acids (see Online Supplementary Materials).

Quantum chemical DFT calculations (B3LYP/6-311++G**) showed the following. (*1*) The molecules of pyrido[3′,2′:4,5]-imidazo[1,2-*b*]pyridazines **1**, **6** and their *N*-protonated forms are planar. The most stable cationic forms of compounds **1**, **6** are their 5H-forms. The 9H-forms that have E^{tot} energies by 1.1 and 0.2 kcal mol^{-1} higher, respectively, are slightly less stable, while the 1H-forms are rather strongly destabilized compared to the 5H-forms: by 16.4 and 17.7 kcal mol^{-1}, respectively. (*2*) Nucleophilic displacement of chlorine in the chloro derivative **6** with methoxide ion can occur by an unusual indirect mechanism. Like in the classical mechanism, the reaction occurs through the formation of a σ-Meisenheimer complex. In contrast to the intramolecular variant of the attack of the hetero-ring by the C-anionic center in ionized 1-(2-benzylthiophenyl)-3,4-dihydroisoquinoline that we recently reported,[27] this is a barrier-free process. In addition, a Meisenheimer-type transition state (TS) is also formed in the reaction, like in the case of concerted nucleophilic aromatic substitution.[28–30]

These specific features of the reactions, which seem mutually exclusive at first glance, are due to the unusual nucleophilic attack of the substrate that occurs not at the substitution position, but at the neighboring unsubstituted position 3. Accordingly,



Scheme 3

instead of the usual σ-complex **8**, its 3-isomer **9** acts as the intermediate in this reaction (Scheme 3). The reason for this attack is the dominant orbital control factor associated with a significantly higher electron density on the LUMO of C^3 atom than of the C^2 atom. The charge effect factor (calculated APT charges on the C^2 and C^3 atoms are +0.630 and –0.214, respectively, see Online Supplementary Materials, Figure S2), which orients the nucleophile in the normal way, is of secondary importance in this case.

The subsequent conversion of σ-complex **9** into the substitution products is induced by the displacement of the nucleophile toward the C^2 atom, which results in its tetrahedrization to give not the usual σ-complex **8**, as might be expected, but a low-barrier ($\Delta E^{\neq} = 9.7$ kcal mol^{-1}) Meisenheimer-type transition state, **TS1**. It is the latter that directly binds the complex **9** with the products of nucleophilic substitution, like in the case of concerted substitution (Figure 1). This transition state is characterized by an essential structural feature that its nucleophilic center (O atom) is located at approximately equal distances from the C^2 and C^3 atoms. As a result, all these three atoms form an almost isosceles triangle (see Figure 1). Note that a certain possibility of experimental confirmation of such a substitution mechanism may involve the detection of isomeric σ-complexes by some methods. It should be noted that we failed to find any examples of such indirect substitution in the literature, although orbital-controlled

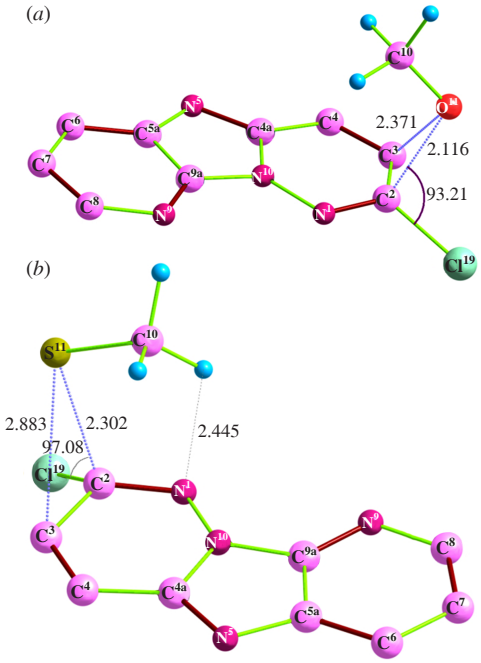


Figure 1 Optimized structures of transition state (*a*) **TS1** for the nucleophilic substitution in compound **6** with MeO^- anion and (*b*) **TS2** for similar reaction with MeS^-. Some hydrogen atoms are not shown.

substitution *via* the conventional σ-Meisenheimer complexes has been known for quite a long time.[31]

Reactions of compound **6** with nucleophiles of other types may occur differently, for example, substitution with participation of the MeS^- ion as a nucleophile. Probably, due to the much lower energy of the C–S bond compared to the C–O bond,[32] the formation of neither 3- nor 2-σ-complexes is possible in the **6**–MeS^- reaction system. Hence, both the indirect and usual substitution mechanisms are impossible, and under these conditions the reaction occurs by a concerted mechanism through the low-barrier ($\Delta E^{\neq}$ = 8.2 kcal mol^{-1}) transition state **TS2** (see Figure 1).

In summary, a new non-catalytic method for building the tricyclic pyrido[3′,2′:4,5]imidazo[1,2-*b*]pyridazine system has been suggested and the first derivatives of this system have been obtained. Quantum chemical calculations showed that the nucleophilic substitution of the 2-positioned chlorine atom can occur both by an unusual mechanism with nucleophile attack at the unsubstituted position 3 and by the concerted mechanism.

Preparation of the article, synthesis of compounds **7a–c**, discussion of the structure of all the compounds obtained and spectroscopic studies were performed at the Institute of Physical and Organic Chemistry, Southern Federal University with financial support of the Ministry of Science and Higher Education of the Russian Federation (project FENW-2023-0031). Synthesis of compounds **4–6** and **7d–f** was carried out at the North Caucasian Zonal Veterinary Institute with financial support of the Ministry of Science and Higher Education of the Russian Federation (project FZFZ-2022-0007). The equipment of the Center for Collective Use of the Southern Federal University 'Molecular Spectroscopy' was used for spectroscopic studies. The mass spectrometer used was the SKFU Center of Collective Use, which operates with the support of the Ministry of Science and Higher Education of the Russian Federation (RF-2296.61321X0029, no. 075-15-2021-687).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7457.

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Received: 11th April 2024; Com. 24/7457