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Efficient synthesis of tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridines based on the recyclization of *N*-arylitaconimides with aminopyrazoles

Yana Yu. Shmoylova,*[a] Yuri A. Kovygin,[a] Evgeniya A. Kosheleva,[a] Khidmet S. Shikhaliev,[a] Irina V. Ledenyova[a] and Mikhail A. Prezent[b]

[a] *Voronezh State University, 394018 Voronezh, Russian Federation. E-mail: shmoylovay@gmail.com*
[b] *N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 119991 Moscow, Russian Federation*

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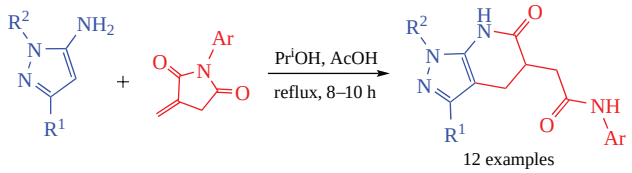
New polyfunctional hydrogenated pyrazolo[3,4-*b*]pyridines were obtained by the chemoselective reaction between *N*-aryl-itaconimides and 5-aminopyrazoles. The transformation is the cascade reaction including Michael addition at the active double bond of the itaconimide followed by the intramolecular transamidation and recyclization.



Keywords: pyrazolo[3,4-*b*]pyridines, itaconimides, 5-aminopyrazoles, recyclization, chemoselectivity, heterocyclization.

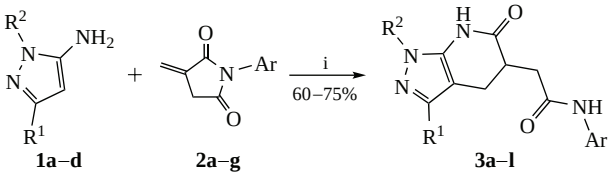
A special group of biologically active compounds belongs to pyrazolopyridine heterocyclic family. Pyrazolo[3,4-*b*]pyridine derivatives include antagonists of the adenosine A1[1] receptor and inhibitors of glycogen synthase kinase-3 (GSK3),[2,3] which accounts for their antitumor,[2,4–6] antiviral,[7] and anti-inflammatory[8] activity. Such compounds are also used in the treatment of HIV,[7] Alzheimer's disease,[3(a)] drug addiction and infertility.[3(b)]

Although pyrazolo[3,4-*b*]pyridines have been studied for a long time, the focus has mostly been on compounds with plane aromatic rings,[2–6] while hydrogenated non-planar analogues remain largely ignored. Indeed, most of the modern synthetic drugs contain plane heteroaromatic rings,[9,10] whereas natural biologically active compounds are often saturated and occur as three-dimensional molecules.[11,12] Apparently, three-dimensional fragments being more complex than their flat counterparts should exhibit some other activity.[13,14] The use of non-planar fragments may have certain advantages with regard to the binding of the pharmacophore and lipid solubility, which in turn can enhance the properties of potential medicinal drugs.[10,12,15]

Two main methodologies for the synthesis of pyrazolo[3,4-*b*]-pyridines comprise annulation of the pyridine ring to pyrazole and annulation of the pyrazole cycle to pyridine. The most common method is based on the condensation of aminopyrazole with α,β-unsaturated reagents. Thus, pyrazolo[3,4-*b*]pyridines are formed in the reaction between 5-amino-1-phenylpyrazole and 3-dimethylamino-1-phenylprop-2-ene-1-one.[16] Substituted pyrazolo[3,4-*b*]pyridines are also formed in the course of cyclization of aminopyrazoles with arylidenepyrotartaric acids,[17] benzylidene derivatives of malonodinitrile,[17] or methoxy-methylene[18(a)] and benzylidene derivatives of Meldrum's acid.[18(b),(c)] This bicyclic system can also be formed as a result of a multicomponent one-pot reaction between 5-amino-1-phenyl-3-(pyridin-3-yl)-1*H*-pyrazole, aromatic aldehydes and para-substituted benzoylacetonitriles in acetic acid.[19] A cascade reaction between arylglyoxal monohydrate, 5-aminopyrazole and primary aromatic amines also gives pyrazolo[3,4-*b*]pyridine derivatives.[20] The annulation of the pyrazolic cycle to pyridine occurs, for instance, in the course of the reaction between hydrazine and 3-acetyl-,[21] 3-carboxy-[22] or 3-cyanopyridines[23] containing 2-positioned leaving group. Another popular method deals with the reaction between 2-chloro-3-cyanopyridines and hydrazine.[23,24]

Surprisingly, documented syntheses of hydrogenated pyrazolo[3,4-*b*]pyridines are scarce. For instance, dihydro-pyrazolo[3,4-*b*]pyridin-6-one derivatives were obtained in a three-component reaction between aldehyde, Meldrum's acid, and 5-aminopyrazole,[18] as well as by treatment of 2-methoxy-6-oxo-1,4,5,6-tetrahydropyridine-3-carbonitriles with hydrazines.[25] Obviously, one of the major problems when constructing hydrogenated pyrazolo[3,4-*b*]pyridines is the choice of an available reactant with high reactivity.

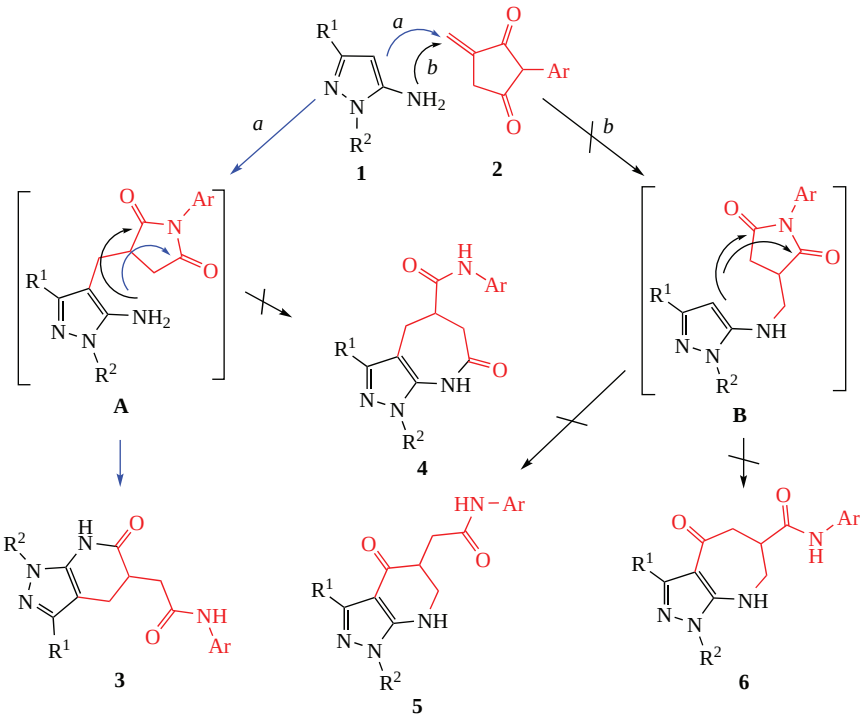
N-Arylitaconimides are promising sources for C3-synthons previously used to synthesize polysubstituted hydrogenated heterocyclic matrices[26–28] containing an acetanilide fragment. The presence of this fragment often makes compounds more



1a–d **2a–g** **3a–l**

3a R^1 = Me, R^2 = Ph, Ar = 3-Cl-4-FC_6H_3
3b R^1 = Me, R^2 = Ph, Ar = 2-Me-3-ClC_6H_3
3c R^1 = Me, R^2 = Ph, Ar = 4-FC_6H_4
3d R^1 = Me, R^2 = Ph, Ar = 4-ClC_6H_4
3e R^1 = R^2 = Ph, Ar = 2-Me-3-ClC_6H_3
3f R^1 = R^2 = Ph, Ar = 3-Cl-4-FC_6H_3
3g R^1 = R^2 = Ar = Ph
3h R^1 = Ph, R^2 = Me, Ar = 4-$MeOC_6H_4$
3i R^1 = 4-MeC_6H_4, R^2 = Ph, Ar = 3-Cl-4-FC_6H_3
3j R^1 = 4-MeC_6H_4, R^2 = Ph, Ar = Ph
3k R^1 = 4-MeC_6H_4, R^2 = Ph, Ar = 4-$O_2NC_6H_4$
3l R^1 = Me, R^2 = Ar = Ph

Scheme 1 *Reagents and conditions*: i, PriOH/AcOH (10 : 1), reflux, 8–10 h.



Scheme 2

cytotoxically, antibacterially, and antivirally active,[29] which makes it possible to use them, for example, for the treatment of human immunodeficiency virus (HIV-1).[30,31]

To develop an efficient and simple general method for synthesizing new polyfunctional derivatives of hydrogenated pyrazolo[3,4-*b*]pyridines, we studied herein the recyclization of *N*-arylitaconimides **2a**–**g** with readily available 1,3-disubstituted 5-amino-1*H*-pyrazoles **1a**–**d** (Scheme 1). Earlier studies demonstrated that the most preferable medium for the recyclization of itaconimides with various N,N- or C,N-dinucleophiles (1,2-diamino azole derivatives[26,27] or 3-aminocyclohexan-2-ones,[28] respectively) were the mixtures of polar solvents with acetic acid or pure acetic acid. Acetic acid was also reported[26] to hinder the isomerization of itaconimide to citraconimide.

In this study, the optimization was performed on the model reaction between 5-amino-3-methyl-1-phenylpyrazole **1a** and *N*-phenylitaconimide **2e** affording product **3l** when isopropyl alcohol, toluene, methanol, 1,4-dioxane and DMF were tested as the solvents, the reaction time having been 10 h (for details, see Online Supplementary Materials, Table S1). In fact, the use of pure solvents resulted either in low conversion or in the formation of complex inseparable mixtures. The use of these solvents with the addition of 10% glacial acetic acid proved to be more effective. The highest yield of product **3l** was achieved with the application of 10 : 1 Pr^{i}OH/AcOH mixture.

Our preparative experiments demonstrated that the maximal yields of other products **3a**–**l** were also obtained in the reactions between *N*-arylitaconimides **2a**–**f** and 5-aminopyrazoles **1a**–**d** (see Scheme 1) in refluxing isopropanol in the presence of acetic acid for 10 h.[†]

As for the reaction mechanism (Scheme 2), two pathways for the transformation are possible. In the pathway *a*, C-nucleophilic Michael addition occurs across the activated double bond of itaconimide with the formation of the intermediate linear compound **A**. In the pathway *b*, similar interaction with the participation of the *endo*-nitrogen atom results in the formation of intermediate **B**. After this, each adduct can undergo re-cyclization to a C-3 or C-4 reagent leading to the corresponding pyrazolo[3,4-*b*]pyridines **3**, **5** or pyrazolo[3,4-*b*]azepines **4**, **6**.

The analysis of the spectra of the products unambiguously indicates that the transformation proceeds according to pathway *a* with the formation of *N*-aryl-2-(6-oxo-1-R^1-3-R^2-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)acetamides **3a–l**. The structures were confirmed by ^{1}H and ^{13}C NMR and two-dimensional NMR, as well as by high performance liquid chromatography in combination with high-resolution mass spectrometry (electrospray ionization, HPLC-HRMS-ESI). In the ^{1}H NMR spectra of compounds **3a**–**l**, the proton signals of two methylene groups and a tertiary proton are important for determining the regiochemistry of the process. The assignment of the signals of diastereotopic methylene protons is based on the correlations observed in the ^{1}H–^{1}H NOESY and ^{1}H–^{13}C HMBC spectra for compound **3d**.

In the ^{1}H–^{13}C HMBC spectrum of compound **3d**, the cross peaks of *endo*-methylene protons with C3a carbon (100.35 ppm) are the most informative, which indicates the proximity of the interacting groups (Figure 1). This should not occur in structures **5** and **6**. Furthermore, there are clear cross peaks of *exo*-methylene protons at 2.5 and 2.9 ppm with an *exo*-carbonyl carbon atom. This allows us to exclude structures **6** and **4** as they contain both *endo*-methylene groups in the conformationally nonrigid seven-atomic cycle. In the latter case, the situation would be different: equal interactions between both methylene groups and the carbonyl carbon atom should be observed.

Two-dimensional ^{1}H–^{1}H NOESY spectrum revealed the interaction between the protons of the CH_2 groups. Due to the conformational rigidity of the structure of the 5 + 6 bicycle, only geminal interactions were detected. Thus, we observed cross peaks between two multiplets of protons for the *exo*-methylene group and between two multiplets of protons of the *endo*-methylene group. There were no prominent vicinal interactions

[†] *Synthesis of 2-(6-oxo-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-*N*-arylacetamides* **3a**–**k**. A solution of *N*-arylitaconimide **2a**–**f** (5 mmol) and 5-aminopyrazole **1a**–**d** (5 mmol) was refluxed in isopropanol (5 ml) in the presence of catalytic amounts of acetic acid for 8–15 h. The precipitate formed was filtered off and recrystallized from a 2 : 1 MeOH/DMF mixture.

between protons, and the absence of cross peaks indicating the interaction between the methine proton and the endocyclic methylene group is obviously accounted for by the conformational effect. It is important to note that there were no cross peaks with NH proton of the piperidine cycle observed for the protons of the *endo*-methylene group, which were present in alternative structures **5** and **6**.

In conclusion, we have demonstrated that 5-aminopyrazole chemoselectively reacted with *N*-arylitaconimides. The alleged path of the cascade reaction includes a C-nucleophilic Michael addition across the activated multiple bond of the itaconimide followed by the intramolecular transamination of the intermediate alongside with the recyclization and formation of final *N*-aryl-2-(6-oxo-1-R^1-3-R^2-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*b*]-pyridin-5-yl)acetamides.

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The authors declare no conflict of interest.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.09.041.

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