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Synthesis of new tetrahydropyrido[1,2-*a*]benzimidazoles based on recyclization of *N*-arylitaconimides with 2-cyanomethylbenzimidazole

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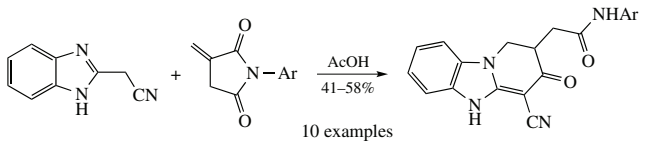
A convenient preparative synthesis of *N*-aryl-2-(4-cyano-3-oxo-1,2,3,5-tetrahydropyrido[1,2-*a*]benzimidazol-2-yl)-acetamides is based on the reflux of *N*-arylitaconimides with 2-cyanomethylbenzimidazole in acetic acid.



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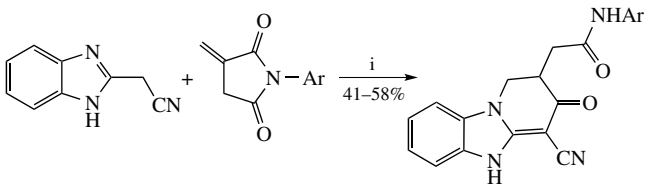
Compounds of pyridobenzimidazole family exhibit a wide spectrum of biological activity,[1–3] and some of them are used as drugs.[4] The antagonists of A-GABA receptors[5] and inhibitors of protein kinases AGC6 have been found among pyrido[1,2-*a*]-benzimidazole derivatives. Such compounds are used in the therapy of cancer,[6,7] insulin resistance, diabetes, autoimmune diseases,[8] neurological and neurodegenerative disorders.[9] In addition, they demonstrate fluorescent[10] and semiconducting properties[11] and are used in organic electronics and photovoltaics.[12–14] Among their regioisomers, the most common are pyrido[1,2-*a*]benzimidazoles multiply prepared previously.[7,15–17]

On the other hand, itaconic acid imides are known to undergo recyclization when reacting with various heterocyclic N,N- and N,C-binucleophiles, in particular, with the derivatives of 1,2-diaminoimidazole.[18,19] Such transformations afford poly-substituted hydrogenated heterocyclic systems containing acetanilide moiety. The presence of such a fragment in the molecules often provides additional cytotoxic, antibacterial and antiviral activities,[20] which makes it possible to use these compounds in the therapy of the immunodeficiency virus type HIV-1.[21,22]

The present work is devoted to searching for a new access to polyfunctional pyrido[1,2-*a*]benzimidazole derivatives and expanding the synthetic potential of 2-cyanomethylbenzimidazole **1** being a reactive C,N-binucleophile.[23–25] For this purpose, we studied the reaction of compound **1** with *N*-arylitaconimides **2a–j**. Earlier it was shown that acetic acid was the optimal solvent for the reactions of itaconimides with binucleophilic reagents,[19,26] so we chose it as a medium for our experiments. Importantly, acetic acid does not promote isomerization of itaconimide to citraconimide,[18] and usually is a good solvent for binucleophiles while the reaction products would possess limited solubility in it. In this regard, the heterocyclization of 2-cyanomethylbenzimidazole **1** with itaconimides **2a–j** was carried out by refluxing equimolar amounts of reactants in acetic acid for 1–2 h (Scheme 1). In this way, the side reactions were minimized and *N*-aryl-2-(4-cyano-3-oxo-1,2,3,5-tetrahydropyrido[1,2-*a*]-benzimidazol-2-yl)acetamides **3a–j** were formed in reasonable yields.†

Taking into account the polyfunctionality of the reactants **1** and **2a–j**, one may suppose different routes for their reaction, both at the initial steps and in the course of the further transformations (Scheme 2). The starting 2-cyanomethylbenzimidazole **1** is known to readily tautomerize into 2-(cyanomethylidene)benzimidazoline form **1′**, in particular in acidic media.[27–29] According to the literature data, the Michael addition is usually the first stage of the reaction of activated enamines (amino enones, enamino nitriles, *etc*.) with α,β-unsaturated carbonyl compounds. The reaction between **1** and **2** with the participation of the N-nucleophilic centre of the reactant (either in **1** or **1′** form) would lead to intermediate **A** (see Scheme 2, pathway *a*). Its further recyclization as a result of intramolecular trans-amidation affords tetrahydropyrido[1,2-*a*]benzimidazole

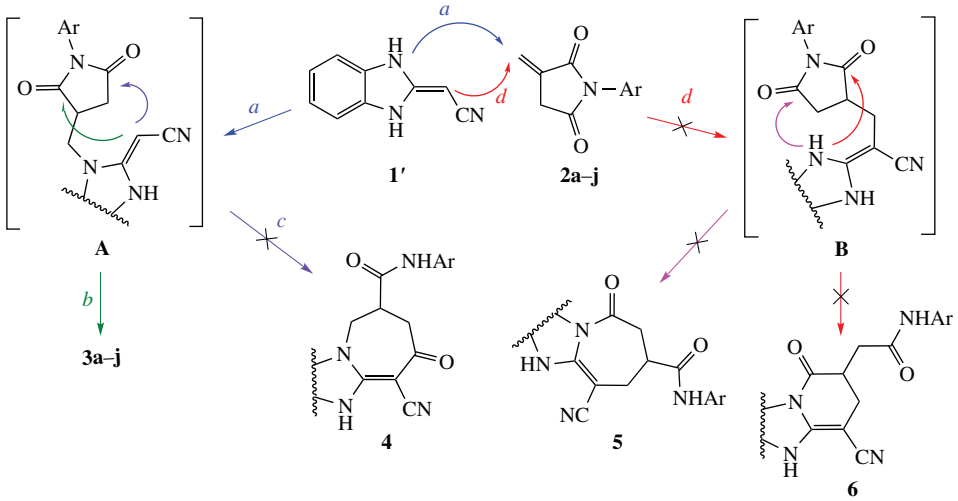


1 **2a–j** **3a–j**

a Ar = 4-MeC_6H_4
b Ar = 4-$O_2NC_6H_4$
c Ar = 3-Cl-4-FC_6H_3
d Ar = 4-EtC_6H_4
e Ar = 3-ClC_6H_4
f Ar = 3-Cl-4-MeC_6H_3
g Ar = 2,3-$Cl_2C_6H_3$
h Ar = 3,4-$Cl_2C_6H_3$
i Ar = Ph
j Ar = 4-ClC_6H_4

Scheme 1 *Reagents and conditions*: i, AcOH, reflux, 1–2 h.

† *Synthesis of* N-*aryl-2-(4-cyano-3-oxo-1,2,3,5-tetrahydropyrido[1,2-*a*]-benzimidazol-2-yl)acetamides* **3a–j** *(general procedure).* A solution of substituted itaconimide **2a–j** (0.005 mol) and 2-cyanomethylbenzimidazole **1** (0.005 mol) in acetic acid (5 ml) was refluxed for 1–2 h. The crystals formed were filtered off and dried. For the characteristics of the products, see Online Supplementary Materials.



Scheme 2

system **3** (pathway *b*). An alternative way *c* for the recyclization of species **A** into 6-cyano-7-oxo-7,8,9,10-tetrahydro-5*H*-azepino[1,2-*a*]benzimidazole-9-carboxamides **4** incorporating less favourable seven-membered heterocycle does not take place. Other possible isomers of type **5** or **6** are not formed either. Apparently, for their formation C-attack of tautomer **1′** onto olefin **2** (pathway *d*) is required while the fraction of this tautomer can be insufficient.

The structures of the obtained products **3a–j** were established by ^{1}H and ^{13}C NMR data and high performance liquid chromatography combined with high resolution mass spectrometry. In the ^{1}H NMR spectra of compounds **3a–j**, the singlet for the heterocyclic NH-proton is significantly shifted downfield (~13.00 ppm) in comparison with unsubstituted benzimidazole,[30] which is apparently associated with the presence of a strong electron-withdrawing group. The signals for the *endo*-methylene protons (4.57 and 3.99 ppm) also undergo a downfield shift, which indicates their proximity to the electronegative atom. Alternative structures **5** and **6** contain two amide groups, while the ^{13}C NMR spectra of the obtained products manifest a strong downfield carbonyl signal (~186 ppm) typical of unsaturated ketones.

The product structure was ultimately derived from two-dimensional correlation ^{1}H–^{13}C NMR HMBC experiment for the representative **3b** (Figure 1). In this spectrum, intensive

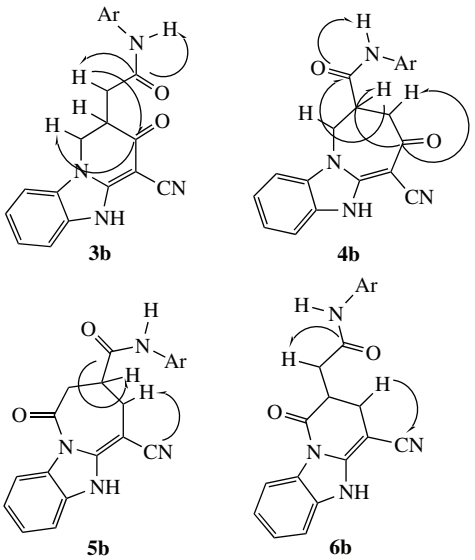


Figure 1 The most significant interactions in the ^{1}H–^{13}C NMR HMBC spectra of compound **3b** (experiment) and possible alternative products **4b**, **5b** and **6b** (supposed).

cross-peaks for the carbon atom at 170.0 ppm and the *exo*-amide proton at 10.68 ppm are observed, which makes it possible to assign them to the *exo*-amide group. Cross-peaks from *exo*-methylene protons are detected for both carbonyl atoms, which is indicative of the formation of a six-membered ring. In alternative azepine structures **4b** and **5b**, carbonyl carbon atoms should correlate with methine protons. The spectra of alternative bis-amides **5b** and **6b** should contain cross-peaks between nitrile carbon (117.9 ppm) and protons of the vicinal methylene unit (64.4 ppm). However, such correlations are not observed.

In summary, we have developed a new access to 1,2,3,5-tetrahydropyrido[1,2-*a*]benzimidazole derivatives containing 2-positioned acetanilide fragment based on regioselective recyclization of *N*-arylitaconimides with 2-cyanomethylbenzimidazole. The sequence of transformations in this cascade process includes aza-attachment of the N-nucleophilic center to the activated multiple bond of the electrophile by a Michael-type reaction and subsequent recyclization of the intermediate species.

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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.2021.03.037.

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