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Mendeleev Commun., 2021, **31**, 259–261

Mendeleev Communications

An efficient synthesis of new polyfunctional hexahydro pyrido[1,2-*a*]pyrazin-1-ones

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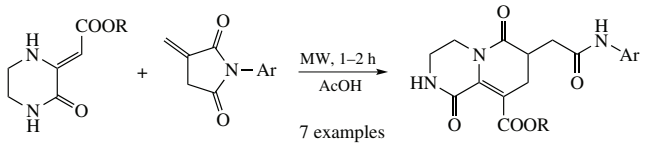
DOI: 10.1016/j.mencom.2021.03.039

New polyfunctional hydrogenated pyrido[1,2-*a*]pyrazin-1-ones were obtained by regioselective recyclization of *N*-arylitaconimides with alkyl (3-oxopiperazin-2-ylidene)-acetates. The supposed cascade reaction pathway involves the Michael addition of the nucleophile to an activated double bond and subsequent intramolecular transamidation of the intermediate with simultaneous recycling.



Keywords: pyrido[1,2-*a*]pyrazin-1-ones, *N*-arylitaconimides, alkyl (3-oxopiperazin-2-ylidene)acetates, recyclization, microwave irradiation.

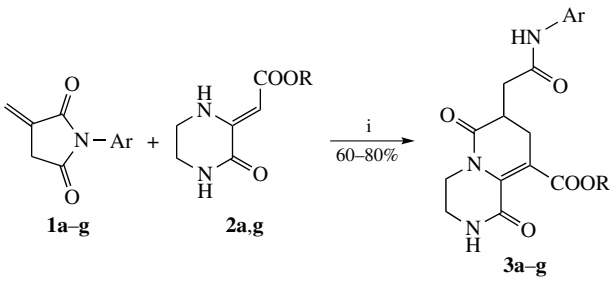
Pyrido[1,2-*a*]pyrazin-1-one fragment is a structural motif of numerous natural compounds[1–4] including alkaloids (for instance, markfortine B[5]). Therefore, it may be considered as a promising framework for the medicinal chemistry. Hydrogenated derivatives of pyrido[1,2-*a*]pyrazin-1-one are also of great interest as they have already been used in the treatment and prevention of helminthic diseases,[2,6,7] neurological disorders,[8,9] and infections caused by the human immunodeficiency virus.[10–12]

It was surprising that the methods for the synthesis of hydrogenated pyrido[1,2-*a*]pyrazinones were documented only in a few papers[9,10,13] devoted to the preparation of substituted 3,4-dihydropyrido[1,2-*a*]pyrazine-1,8-diones by the amidation of dihydropyridine-2-carboxylic acids with 2-amino alcohols followed by intramolecular cyclo-condensation.[9,10] The cascade reaction of 2-bromo-*N*-propargylacetamide derivative and 3-chloropropylamine resulted in tetrahydropyrido[1,2-*a*]pyrazin-3-one.[13] Obviously, one of the key problems in the design of this bicyclic system is the choice of an available substrate with large preparative capabilities.

N-Arylitaconimides are promising sources as C_3-synthons in the creation of various hydrogenated heterocyclic systems[14–16] containing the pharmacophore acetanilide group. The presence of the latter fragment in the molecule often provides the compounds with additional cytotoxic, antibacterial, and antiviral activity,[17] which makes their application more effective, for instance, in the treatment of immunodeficiency virus (HIV-1) type.[18,19]

In order to develop an effective, simple and general method for synthesizing new polyfunctional derivatives of hydrogenated pyrido[1,2-*a*]pyrazin-1-ones, we investigated the recyclization of *N*-arylitaconimides **1a**–**g** under the action of readily available alkyl (3-oxopiperazin-2-ylidene)acetates **2a**,**g** (Scheme 1) being the reactive C,N-binucleophiles.[20–24] Previously,[14–16] it was noted that the preferred media for recyclization of itaconimides with various heterocyclic N,N- and C,N-binucleophiles, in particular 1,2-diaminoimidazole[14,15] and 3-aminocyclohexen-2-ones,[16] were acetic acid or its mixtures with high-polar solvents. It has also been reported[14] that the use of acetic acid prevents isomerization of itaconimide to citraconimide.

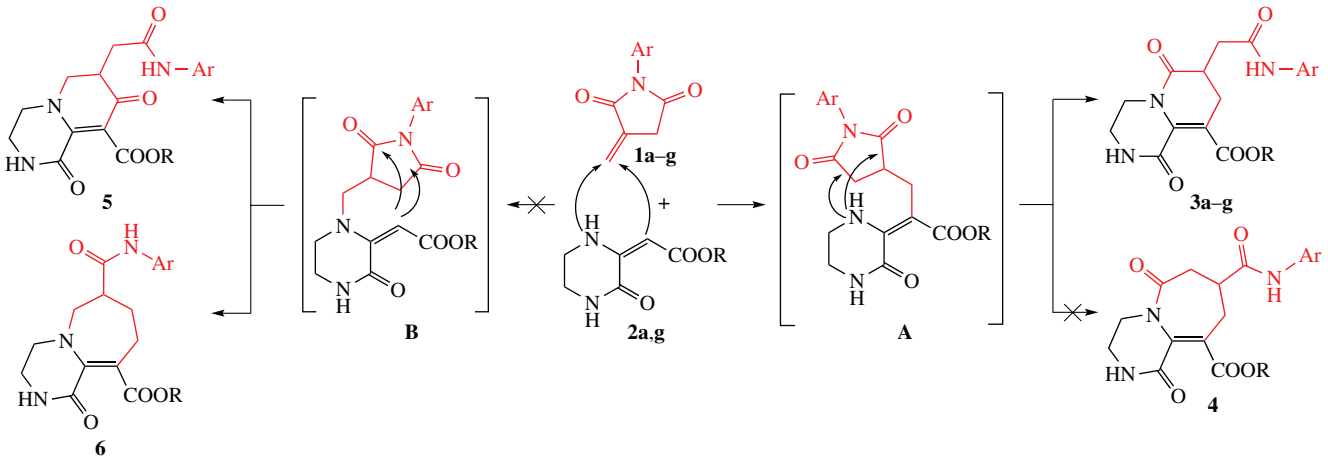
We found that the reaction of *N*-arylitaconimides **1a**–**g** and alkyl (3-oxopiperazin-2-ylidene)acetates **2a**,**g**, regardless of the reaction conditions (when boiling in solvents consisting of acetic acid and propan-2-ol, a mixture of methanol, xylene or DMF in various ratios or pure acetic acid), proceeded with extremely low conversion of reactants or led to complex inseparable mixtures of unidentified compounds. An increase in the reaction rate with minimizing the formation of side compounds was achieved by conducting the process in acetic acid under microwave irradiation for 1–2 h. The main products, alkyl 7-(2-arylamino-2-oxoethyl)-1,6-dioxo-1,3,4,6,7,8-hexahydro-2*H*-pyrido[1,2-*a*]pyrazine-9-



1a–g **2a,g** **3a–g**

a R = Me, Ar = 2-Me-3-ClC_6H_3
b R = Me, Ar = 3-Cl-4-FC_6H_3
c R = Me, Ar = 2,4-$Me_2C_6H_3$
d R = Me, Ar = 2,3-$Cl_2C_6H_3$
e R = Me, Ar = 4-MeOC_6H_4
f R = Me, Ar = 4-MeC_6H_4
g R = Et, Ar = 4-EtC_6H_4

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



Scheme 2 The possible routes of polyfunctional precursors **1** and **2**.

carboxylates **3a–g**, were isolated in 60–80% yields (see Scheme 1).†

In theory, the first stage of reaction of polyfunctional precursors **1** and **2** can proceed along two routes: either C-nucleophilic attack at the activated Michael multiple bond of itaconimide **1** to form an intermediate linear compound **A**, or a similar reaction involving the *endo*-nitrogen atom, leading to intermediate **B** (Scheme 2). Further, each of the intermediate adducts can be recyclized as a C_3 or C_4 synthon to form pyrido[1,2-*a*]pyrazines **3**, **5** or pyrazino[1,2-*a*]azepines **4**, **6**, respectively.

However, the ^{1}H NMR, ^{13}C NMR and 2D NMR spectroscopy data, as well as high performance liquid chromatography (HPLC) in combination with high-resolution mass spectrometry [electrospray ionization, HRMS (ESI)] analysis of the isolated reaction products unambiguously confirm the course of the process through intermediate **A** with the formation of 2*H*-pyrido[1,2-*a*]pyrazines **3a–g**.

The signals of two methylene and one methine protons in the ^{1}H NMR spectra of compounds **3a–g** are significant for establishing the regiochemistry of the process, because the analysis of their interactions with the related groups allows one to make a choice between the alternative structures. The unambiguous assignment of the diastereotropic methylene proton signals was performed in accordance with the observed correlations in the NOESY ^{1}H–^{1}H and HMBC ^{1}H–^{13}C spectra for compound **3f** (Figure 1).

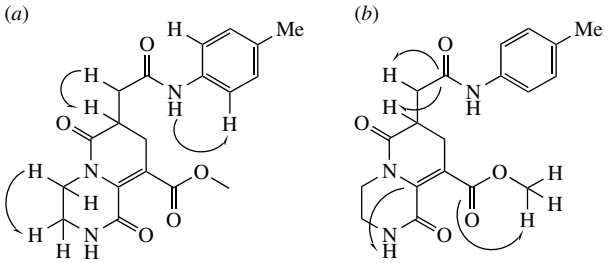


Figure 1 The most significant interactions in the (*a*) NOESY and (*b*) HMBC spectra of compound **3f**.

† *7-(2-Arylamino-2-oxoethyl)-1,6-dioxo-1,3,4,6,7,8-hexahydro-2*H*-pyrido[1,2-a]pyrazine-9-carboxylates* **3a–g** *(general procedure).* A solution of substituted itaconimide **1a–g** (5 mmol) and the corresponding alkyl (3-oxopiperazin-2-ylidene)acetate **2a**,**g** (5 mmol) in acetic acid (5 ml) was refluxed under microwave irradiation (300 W) in an open flask for 1–2 h. The formed precipitate was filtered off and recrystallized from a 2 : 1 mixture of dioxane and DMF.

For characteristics of compounds obtained, see Online Supplementary Materials.

Only one correlation was observed in the 2D NOESY ^{1}H–^{1}H spectrum between the signal of a methine proton (2.98 ppm) and the doublet of one of the protons of the *exo*-methylene group (2.44 ppm). The absence of cross-peaks with the protons of *endo*-methylene groups allows us to exclude the formation of structures **4–6**. In the HMBC spectrum of compound **3f**, the cross-peaks of methine (2.98 ppm) and *exo*-methylene protons (2.44 and 2.84 ppm) with an *exo*-carbonyl carbon atom (168.62 ppm) are detected, which agrees with the data of the 2D NOESY ^{1}H–^{1}H spectrum.

In conclusion, a new synthetic route to 7-(2-arylamino-2-oxoethyl)-1,6-dioxo-1,3,4,6,7,8-hexahydro-2*H*-pyrido-[1,2-*a*]pyrazine-9-carboxylates based on the regioselective recyclization of *N*-arylitaconimides under the action of alkyl (3-oxopiperazin-2-ylidene)acetates was herein developed. The proposed cascade reaction pathway involves the Michael addition of the nucleophile to an activated multiple bond and subsequent intramolecular transamidation of the intermediate with simultaneous recycling.

This research was supported by the Russian Science Foundation (grant no. 18-74-10097).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2021.03.039.

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Received: 15th December 2020; Com. 20/6397