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A convenient synthesis of dihydropyridinone dicarboxylic derivatives by the recyclization of *N*-arylitaconimides with 3-aminocrotonates

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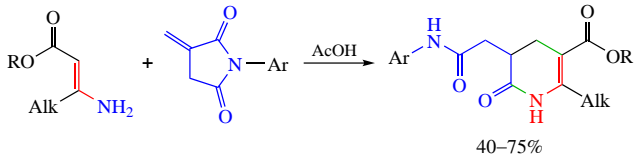
***N*-Arylitaconimides undergo smooth recyclization with 3-aminocrotonic esters to afford 6-alkyl-3-(2-anilino-2-oxoethyl)-2-oxo-3,4-dihydro-1*H*-pyridine-5-carboxylates when heated in acetic acid. The product structure has been established by NMR, which allows one to rule out the formation of other alternative heterocyclic derivatives.**



Keywords: itaconimides, enamines, aminoalkenoates, pyridones, hetarylacetanilides, recyclization, domino reaction.

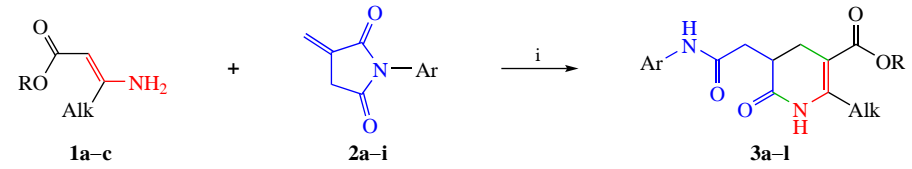
The design of multitarget ligands is one of the trends in modern medicinal chemistry. Hybrid molecules could revolutionize the treatment of multifactorial pathologies, such as cardiovascular diseases,[1] diabetes,[2] cancer,[3] inflammatory processes,[4] requiring action on multiple receptors or signaling pathways. A significant advantage of multi-target drugs over combination drugs is a decrease in the effective concentration and, in the long term, a decrease in the toxic effect on the body.[5] Combining functional groups in one molecule can significantly improve the pharmacokinetics of drugs due to better binding to specific receptors and is of undoubted interest for the design of new multi-target drugs.[6] Acetanilides are widely used in medicine as antipyretics,[7] and a number of derivatives also exhibit antibacterial and cytotoxic[8] activity. Acetanilide fragment is included in antiviral drugs.[9,10] It has been shown that replacing the oxyethyl bridge with an amide one improves the binding of the antiviral drug to the target.[11] At the same time, the dihydropyridin-2-one structure is a popular scaffold for important classes of compounds exhibiting diverse biological activities: antibacterial,[12] antiviral[13] and antitumor.[14] Inhibition of a number of kinases[15,16] and reductases[17] by dihydropyridinone derivatives has been reported, which implies a search for promising cardiac drugs among pyridone derivatives.

Several synthetic approaches to the preparation of polysubstituted pyridin-2-ones are known, the [3 + 3] cycloaddition being the leading strategy.[18] Assembly of dihydropyridin-2-one from an amide and an *in situ* generated enone is possible,[19] the oxidative coupling of an unsaturated aldehyde and an enamine are also documented.[20] The most commonly used precursor in these cases is aminocrotonate while the second component of these cascade transformations can be unsaturated ester,[21] acid chloride,[22] or α-bromo enal.[23] There is evidence that this kind of syntheses can be carried out in a multicomponent version.[24,25] An approach involving the recyclization of lactone[26] and itaconic anhydride with an aminoalkenoic ester is also promising.[27] The last synthetic solution brings us close to the synthesis of 2-(pyridin-2-one)acetanilides by recyclization of *N*-arylitaconimides with 3-aminocrotonate.

We have previously shown that the transformation of itaconimides into hetarylacetanilides containing a pyridine ring could be easily carried out by employing such C,N-binucleophiles as β-aminocyclohexen-2-ones,[28] cyanomethylenebenzimidazole,[29] or aminouracils.[30] This work proposes an effective one-step synthesis of various 6-alkyl-3-(2-arylamino-2-oxoethyl)-2-oxo-3,4-dihydro-1*H*-pyridine-5-carboxylates by recyclization between aminoalkenoic esters **1a–c** and *N*-arylitaconimides **2a–i** (Scheme 1).

As noted in previous works,[28–30] the recyclization of itaconimides by carbo- and heterocyclic C,N-binucleophiles proceeded smoothly when the reagents were boiled in acetic acid. In this work we have found that the optimal medium for the reaction of *N*-arylitaconimides **2a–i** with aminoalkenoates **1a–c** was also acetic acid. Carrying out the reaction in alcohols, dioxane, and acetone did not cause the recyclization.

Several routes are theoretically possible for the reaction in question (Scheme 2). The first step may be the *aza*-addition of the aminoalkenoate **1a–c** at the conjugated double bond of the imide **2a–i** with the formation of the *aza*-Michael adduct **A**. The products of its recyclization may be tetrahydroazepin-4-ones **4a–l** or dihydropyridin-4-ones **5a–l**. A similar direction of recyclization is realized for itaconimides and cyanomethylenebenzimidazole.[29] An alternative route should begin with the Michael addition of the C-nucleophilic center of the aminoalkenoate **1a–c** to form adduct **B**. Options for its recyclization could be dihydropyridin-2-ones **3a–l** or tetrahydroazepin-2-ones **6a–l**. We previously implemented such a route for the reaction between itaconimides and 3-aminocyclohex-2-enones.[28] The structural similarity of amino esters **1a–c** and 3-aminocyclohex-2-enones suggests that this direction is most likely in our case. The structure of 6-alkyl-3-(2-arylamino-2-oxoethyl)-2-oxo-3,4-dihydro-1*H*-pyridine-5-carboxylates **3a–l** was determined using NMR spectroscopy. The choice between



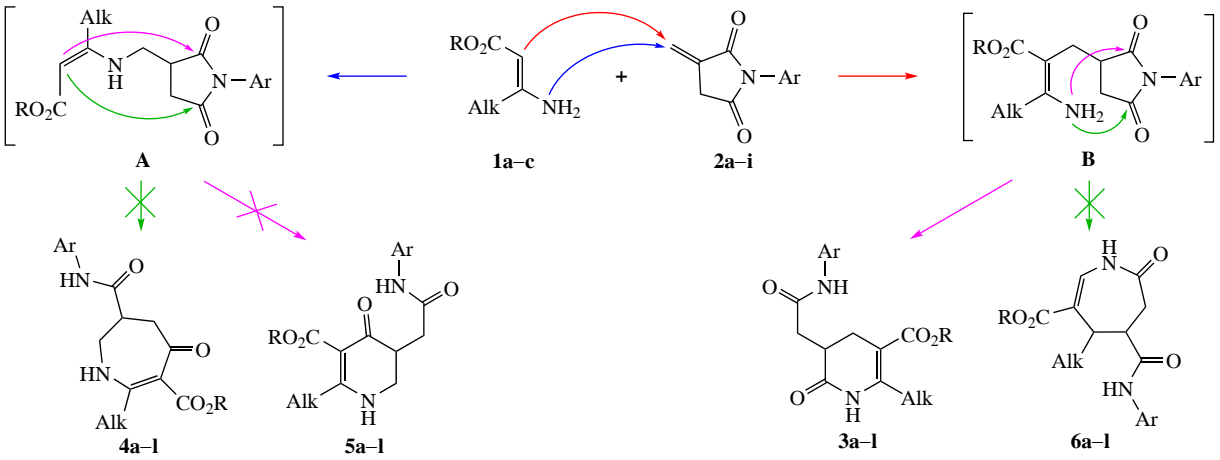
1a–c **2a–i** **3a–l**

a R = Et, Alk = Me
b R = Alk = Me
c R = Me, Alk = Pr^i

a Ar = Ph
b Ar = 4-MeC$_6$H$_4$
c Ar = 4-EtC$_6$H$_4$
d Ar = 4-AllOC$_6$H$_4$
e Ar = 4-ClC$_6$H$_4$
f Ar = 3-ClC$_6$H$_4$
g Ar = 3,4-Cl$_2$C$_6$H$_3$
h Ar = 3,4-Me$_2$C$_6$H$_3$
i Ar = 2-Me-3-ClC$_6$H$_3$

a R = Et, Alk = Me, Ar = Ph
b R = Et, Alk = Me, Ar = 4-MeC$_6$H$_4$
c R = Et, Alk = Me, Ar = 4-ClC$_6$H$_4$
d R = Et, Alk = Me, Ar = 3-ClC$_6$H$_4$
e R = Alk = Me, Ar = Ph
f R = Alk = Me, Ar = 4-MeC$_6$H$_4$
g R = Alk = Me, Ar = 3,4-Me$_2$C$_6$H$_3$
h R = Alk = Me, Ar = 4-AllOC$_6$H$_4$
i R = Alk = Me, Ar = 3,4-Cl$_2$C$_6$H$_3$
j R = Alk = Me, Ar = 2-Me-3-ClC$_6$H$_3$
k R = Me, Alk = Pr^i, Ar = 4-EtC$_6$H$_4$
l R = Me, Alk = Pr^i, Ar = 4-ClC$_6$H$_4$

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



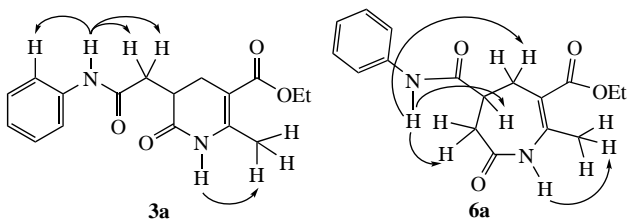
A **1a–c** **2a–i** **B**
4a–l **5a–l** **3a–l** **6a–l**

Scheme 2

alternative structures is made based on the position of the NH proton signals. The spectra of the products contain two one-proton singlets in the region of 9.7–10.3 ppm, corresponding to amide groups, which convincingly indicates the implementation of route **B** leading to structures either **3a–l** or **6a–l**, both containing amide and lactam NH groups. In structures **4a–l** and **5a–l**, corresponding to *aza* intermediate **A**, one of the nitrogen atoms belongs to enamine fragment whose proton should resonate in a lower field.[29]

For the final identification of the obtained compounds, two-dimensional NMR spectroscopy data were analyzed. The ^{1}H–^{1}H NOESY spectrum shows clear cross-peaks of the amide proton at 9.97 ppm with the diastereotopic protons of the *exo*-methylene group at 2.38 and 2.41 ppm (Figure 1). This clearly indicates the structure of dihydropyridin-2-one **3**, since in the spectrum of tetrahydroazepin-2-one **6** the correlation patterns should be different. The amide NH would give a pronounced cross peak with the methine proton at position 4 of the ring and, perhaps less pronounced, with the protons at the methylene groups of positions 3 and 5.

In conclusion, we have developed a new synthesis of 6-alkyl-3-(2-arylamino-2-oxoethyl)-2-oxo-3,4-dihydro-1*H*-pyridine-5-carboxylates based on the regioselective recyclization of *N*-arylitaconimides upon their reaction with 3-aminoalk-2-enoic acid esters. The proposed cascade reaction route involves Michael addition of the C-center of the aminoalkenoate at the activated multiple bond of the electrophile and subsequent intramolecular transamidation of the intermediate with simultaneous recyclization.



3a **6a**

Figure 1 The most significant correlations in the ^{1}H–^{1}H NOESY spectrum of ethyl 3-(2-anilino-2-oxoethyl)-6-methyl-2-oxo-3,4-dihydro-1*H*-pyridine-5-carboxylate **3a** and alternative ethyl 7-methyl-2-oxo-4-(phenylcarbamoyl)-1,3,4,5-tetrahydroazepine-6-carboxylate **6a**.

Mass spectra were recorded at the research base of the Center for Collective Use of Scientific Equipment of Voronezh State University.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7794.

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