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# Recyclization of *N*-arylitaconimides with hydrazines as a new effective synthesis of 2-(3-oxopyrazolidin-4-yl)acetanilides

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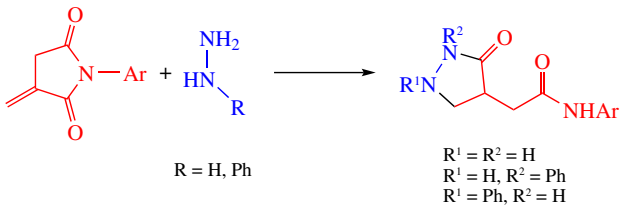
**Recyclization of *N*-arylitaconimides with hydrazine in dioxane at room temperature selectively leads to 2-(3-oxopyrazolidin-4-yl)acetanilide derivatives in moderate to good yields. The similar reaction with phenylhydrazine proceeds with the simultaneous formation of isomeric 3- and 5-oxo-1-phenylpyrazolidine-containing acetanilides.**




*Keywords*: itaconimides, hydrazine, phenylhydrazine, pyrazolidinones, acetanilides, recyclization.

Natural compounds containing a pyrazole ring were discovered relatively recently,[1] although synthetic pyrazole derivatives are widely used as pharmaceuticals. The simplest pyrazoles are known as hypoglycemic[2] and analgesic agents.[3,4] Modification of the scaffold with various pharmacophores makes it possible to supplement its basic biological activity[5,6] with bacteriostatic, antipyretic, cytostatic[7] and other impacts to create multi-targeted drugs. A significant number of antibacterial,[8] antifungal[8,9] and antiviral[10,11] drugs have been based on pyrazole. Pyrazole derivatives inhibit some enzymes such as Janus kinases,[12] acetyltransferases,[13] demethylases,[14,15] lipoxygenases[16] and cyclooxygenases.[17]

Replacing an aromatic heterocycle with a hydrogenated one[18] is widely used in pharmaceutical design. The nonplanar pyrazolidine system interacts effectively with a large number of targets. This contributes to both enhancing the physiological effect,[19] and expanding its spectrum.[20] Among pyrazolidine derivatives, hetero analogues of prostaglandins[21] and kainic acid[22] are of interest. The use of pyrazolidines as organocatalysts[23,24] has also been reported.

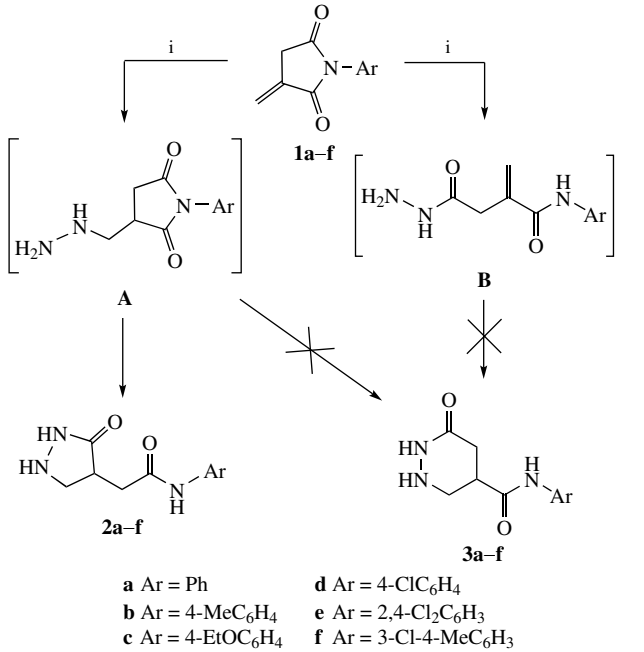
Despite the growing interest in hydrogenated pyrazole derivatives, methods for their synthesis are not diverse.[25] Pyrazolidine-3,5-diones are formed in the course of acylation of hydrazine with malonic ester derivatives[26,27] or intramolecular cyclization of hetarylacetic ester with semicarbazide.[28] Pyrazolidin-3-ones are obtained by cyclization of hydrazines with 3-haloalkanoic[21] or 3-hydroxyalkanoic acid esters.[25,29] Synthesis of pyrazolines by the condensation of hydrazine with unsaturated carbonyl compounds such as acrylates[30,31] or 2-bromoalkenals,[32] and by cyclization of oxo acetylenes with hydrazides[33] has been reported. Domino reactions also represent a very promising means for the synthesis of pyrazole derivatives. The formation of 4-carboxaminopyrazol-3-ones in the reaction of hydrazine with 4-alkylideneoxazol-5-ones,[34] and the re-cyclization of 3-arylidenefuran-2-ones with hydrazine into 5-arylpyrazolidin-3-ones[35,36] are documented.

The purpose of this work was to study the recyclization of *N*-arylitaconimides with hydrazine and phenylhydrazine under various conditions as a promising access to substituted 2-(oxopyrazolidin-4-yl)acetanilides. We previously reported on cyclic itaconic acid imides as the promising substrates for recyclization. Preparatively available *N*-arylitaconimides are easily customized and suitable for the formation of combinatorial libraries. Their reactions with various 1,3-*N*,*N*-binucleophiles, such as carboximidoamides,[37] aminotriazoles[38] as well as diaminoimidazole[39] and diaminobenzimidazole[40] led to formation of a tetrahydropyridine cycle.

In this study, *N*-arylitaconimides were reacted with anhydrous hydrazine under various conditions. Attempts to extend the conditions tested previously for 1,3-binucleophiles[37–40] were unsuccessful, namely, boiling the reactants in methanol, propan-2-ol, dioxane, acetonitrile, DMF or acetic acid caused hydrazinolysis of itaconimides. However, mixing them without boiling turned out to be more suitable for recyclization. In fact, the reactions of *N*-arylitaconimides **1a–f** and anhydrous hydrazine at 20–40 °C in methanol, dioxane or acetonitrile produced 2-(3-oxopyrazolidin-4-yl)acetanilides **2a–f** in reasonable yields (Scheme 1, for optimization details see Online Supplementary Materials, Table S1). The option was the stirring the solutions of reactants at 30–35 °C in dioxane in which the reaction products are poorly soluble and would precipitate as formed. When other solvents are used, the purification of products **2a–f** becomes more difficult.

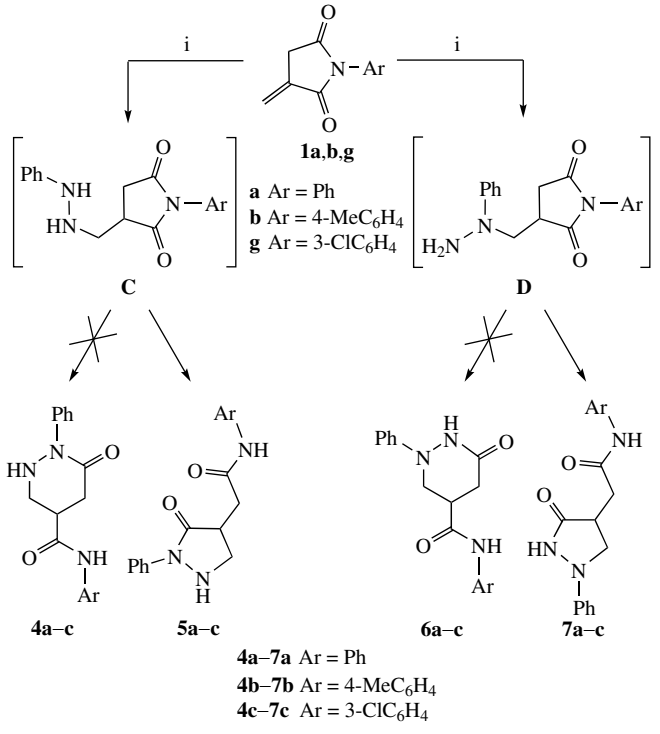
Two routes are theoretically possible for the reaction of hydrazine with *N*-arylitaconimides **1a–f** (see Scheme 1). The first stage can be aza-Michael addition leading to adduct **A**, or transamidation with ring opening into acyclic amide hydrazide **B**. Intermediate **A** can be further recyclized into 3-oxopyrazolidine **2a–f** and 6-oxohexahydropyridazine **3a–f**. For intermediate **B**, transformation is only possible into a six-membered derivative **3a–f**. Apparently, the formation of the aza-Michael adducts is the preferred route. Also, we have previously shown[37] that **B**-type adducts are not prone to further cyclization, thus we can exclude this intermediate from consideration.

$^{1}$H and $^{13}$C NMR spectroscopy data allow us to state the formation of cyclic system judging by the nature for the NH proton signals. The presence of two low-field singlets at 9.2 and 10.2 ppm indicates the transformation of the imide ring into an amide fragment and the formation of a lactam. The broadened one-proton singlet in the 5.4 ppm area apparently corresponds to




**Scheme 1** *Reagents and conditions*: i, $N_2H_4$, dioxane, 25–35 °C.

hydrazine NH proton of the ring. However, for an unambiguous choice in favor of one of the alternative structures, one-dimensional spectroscopy data is not enough. Study of the two-dimensional NOESY spectrum of the obtained compounds confirms the 2-(3-oxopyrazolidin-4-yl)acetanilide structure **2**. The amide NH singlet at 10.08 ppm correlates with doublets for the *exo*-methylene group at 2.67 and 2.27 ppm. In addition, the interaction of protons of the *exo*-methylene group with the *ortho*-protons of the aromatic ring is observed. For possible 3-oxo-hexahydropyridazine-5-carboxanilides **3**, a single cross-peak of the amide NH with the methine CH multiplet at 2.72–2.85 ppm should have been observed. Also, due to free rotation of acetanilide fragment, an equivalent interaction of *ortho*-protons with both methylene groups might be observed.




**Scheme 2** *Reagents and conditions*: i, $PhNHNH_2$, MeOH, reflux.

**Table 1** Ratios of regioisomeric phenylpyrazolones **5** and **7** formed in the reaction.

| Entry | Solvent | Conditions | **5**/**7** ratio | |
|---|---|---|---|---|
| | | | LC/MS | Isolated[a] |
| 1 | MeOH | reflux | 3:5 | 15:45 |
| 2 | MeOH | ~20 °C | 1:2 | 15:45 |
| 3 | EtOH | reflux | 2:5 | 5:35 |
| 4 | EtOH | ~20 °C | 1:1 | 10:15 |
| 5 | $Pr^iOH$ | reflux | 3:5 | 15:40 |
| 6 | $Pr^iOH$ | ~20 °C | 2:1 | 15:10 |
| 7 | Dioxane | reflux | 1:2 | 10:30 |
| 8 | Dioxane | ~20 °C | 1:6 | 5:25 |
| 9 | DMF[b] | reflux | 2:3 | – |
| 10 | DMF[b] | ~20 °C | 1:1 | – |
| 11 | PhH[c] | reflux | – | – |
| 12 | PhH[c] | ~20 °C | – | – |

[a] Ratios of isolated yields in percent. [b] Destruction of itaconimide occurred. [c] Low conversion of the reactants.

Recyclization of *N*-arylitaconimides **1a**,**b**,**g** with phenylhydrazine turned out more complicated (Scheme 2). The initially formed alternative aza-Michael adducts **C** and **D** can theoretically be recyclized to regioisomeric oxohexahydropyridazines **4a–c** and **6a–c** or oxopyrazolidines **5a–c** and **7a–c**. The study of the reaction mixtures by LC/MS showed that they contained two isomeric adducts of itaconimides and phenylhydrazine whose ratios were found to be dependent on the solvent and temperature (Table 1). Methanol was recognized as the optimal reaction medium providing high yields of the products. Luckily, these adducts were separable by column chromatography. In addition, isomers **7a–c** precipitated from methanol upon cooling, which facilitated full separation of the components.

Employing $^1H$, $^{13}C$ NMR spectroscopy and two-dimensional NOESY, HSQC and HMBC experiments, we were able to unambiguously establish structures **5** and **7**. $^1H$ NMR spectroscopy data allow us to preliminarily assign regioisomeric heterocycles to series **C** and **D** (see Scheme 2). Alternative products **4a–c** and **5a–c** should manifest single low-field singlet corresponding to the amide proton while the spectra of regioisomers **6a–c** and **7a–c** should contain two singlets for amide and lactam NH protons in the region of 9–10 ppm.

The choice between the five- and six-membered cycles was made based on data from the two-dimensional NOESY and HMBC experiment. Characteristic correlations for structures **5** and **7** are the interactions of the amide NH protons with the protons for the *exo*-methylene group and the absence of a cross-peak of the amide proton with the *endo*-methine one. For the pyridazine system in **4** and **6**, the spectral pattern should be opposite: a pronounced cross-peak of the amide proton with the methine one with weak or no correlations with the signals of methylene protons.

It is also indicative that there is a correlation between the carbon signals of the *endo*-carbonyl group and the proton signals of all methylene and methine groups. This confirms the formation of five-membered structures of 2-(5-oxo-1-phenylpyrazolidin-4-yl)acetanilides **5a–c** and 2-(3-oxo-1-phenylpyrazolidin-4-yl)acetanilides **7a–c** with methylene groups equidistant from *exo*-carbonyl carbon. In alternative six-membered products, protons of the 6-positioned methylene group are distanced from carbonyl carbon by four bonds, which should not give cross-peaks in the HMBC spectrum.

To conclude, itaconimides act as $C_3$ reagents with hydrazines to produce exclusively oxopyrazolidine derivatives. The proposed reaction route involves the aza-Michael addition of

a nucleophile to the activated double bond of *N*-arylitaconimide, followed by the recyclization of the primary adduct. The ultimate products are 2-(oxopyrazolidin-4-yl)acetanilide derivatives promising for targeted design of multipurpose drugs of the pyrazolidine series.

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

*Online Supplementary Materials*

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2024.02.040.

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