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A highly efficient and stereoselective cycloaddition of nitrones to *N*-arylitaconimides

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ABSTRACT

The 1,3-dipolar cycloaddition of keto- and aldonitrones with *N*-arylitaconimides proceeds regioselectively giving only 5-spiroisoxazolidines. In the case of aldonitrones the reaction proceeds with high diastereoselectivity. A range of the obtained adducts were subjected to reductive cleavage of the N—O bond using zinc powder in acetic acid to give the corresponding spirolactones and 1,3-amino alcohols.

Introduction

The isoxazolidine ring is an important structural part of a wide range of heterocyclic systems possessing valuable pharmacological properties [1], including antiviral [2], antibacterial [3] and antitumor [4] activities. 5-Spiroisoxazolidines have attracted particular interest in recent years [5]. This structural fragment is also found in alkaloids extracted from plants [6]. Highly effective and selective 1,3-dipolar cycloadditions of nitrones with exocyclic double bonds were employed for the synthesis of complex heterocyclic scaffolds containing the spiroisoxazolidine moiety. Many of these products were shown to possess valuable biological properties [7] An undoubted advantage of 1,3-dipolar cycloaddition is the ability to selectively generate up to three new stereocenters in one step without the use of catalysts [8], that makes it indispensable in the synthesis of natural products and their analogues [9].

At the same time, alkylidene succinimides are promising building blocks for the synthesis of complex spiroheterocyclic scaffolds containing the pyrrolidine-2,5-dione fragment. It was shown that their reactions with various 1,3-dipoles: azomethine ylides [10], azomethine imines [11] and nitrile oxides [12] allow construction of the corresponding spirocyclic molecules with high efficiency and diastereoselectivity. However, the regioselectivity of these reactions can be unpredictable and depends on both steric and electronic effects [10–12]. Recently these reactions have attracted interest due to the promising antibacterial [10a,f], including antimycobacterial [10b,f], and antifungal [10f] activities of the products. Nevertheless, the reactions of these dipolarophiles with nitrones have not been previously studied.

A distinct advantage of isoxazolidines is the possibility of using them as precursors of biologically valuable 1,3-amino alcohols [13], β-lactams [14] and β-amino acids [15]. For example, one of the most universal, simple and inexpensive methods for the reduction of isoxazolidines is the use of zinc powder in acetic acid [16]. In the presence of certain sensitive functional groups or structural fragments, the amino alcohol intermediates can undergo further transformations under the reaction conditions [2d,17].

The aim of this work was to investigate the regio- and stereoselectivity of the 1,3-dipolar cycloaddition of keto- and aldonitrones with *N*-arylitaconimides and transformations of the obtained spiroisoxazolidines under reductive (Zn, acetic acid) conditions.

Results and discussion

Initially, we investigated the regioselectivity of the 1,3-dipolar cycloaddition of *N*-arylitaconimides **1a-d** with *N*-aryl-*C,C*-bis (methoxycarbonyl)nitrones **2a-d**. The reactions were carried out in dichloromethane at room temperature for three days. It was found that the reactions proceeds regioselectively giving only 5-spiroisoxazolidines **3a-i** in good yields (Table 1).

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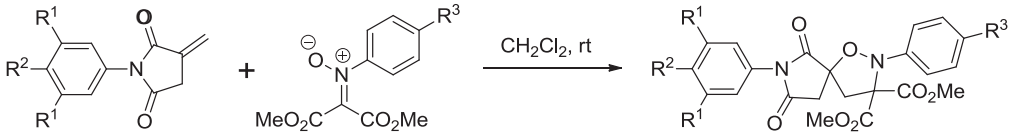
Table 1
1,3-Dipolar cycloaddition of *N*-arylitaconimides **1a-d** with *N*-aryl-*C*,*C*-bis(methoxycarbonyl)nitrones **2a-d**.



1a-d **2a-d** **3a-i**

Entry	Itaconimide	R^1	R^2	Nitrone	R^3	Product	Isolated yield (%)
1	**1a**	H	H	**2a**	H	**3a**	74
2	**1a**	H	H	**2b**	Me	**3b**	66
3	**1a**	H	H	**2c**	Br	**3c**	80
4	**1b**	H	Br	**2a**	H	**3d**	89
5	**1b**	H	Br	**2b**	Me	**3e**	81
6	**1b**	H	Br	**2c**	Br	**3f**	92
7	**1b**	H	Br	**2d**	OMe	**3g**	76
8	**1c**	H	OMe	**2c**	Br	**3h**	63
9	**1d**	Cl	H	**2c**	Br	**3i**	64

The ^{1}H NMR spectra of the crude reaction mixtures did not show the signals of any other products. The structures of the adducts were confirmed by spectroscopic methods and additionally proved by X-ray diffraction analysis for compound **3a** (Fig. 1) [18].

Next, the regio- and diastereoselectivities of the cycloaddition of aldonitrones were investigated. The reactions of highly reactive *N*-aryl-*C*-carbamoylnitrones **4a-d** were carried out under the previously mentioned conditions (r.t., 3 days). It was shown, that the 1,3-dipolar cycloaddition of these nitrones also proceeds regioselectively yielding a mixture of diastereomeric 5-spiroisoxazolidines **5** and **5′**. The isomers with *cis* relative configuration of the substituent at the C^3 position of isoxazolidine ring and the methylene group of the pyrrolidine ring are predominant in all cases (Table 2). NOESY NMR spectra and X-ray diffraction analysis data for compound **5d** [19] (Fig. 2) were used to determine the relative configuration of the cycloadducts.

In most cases, in the ^{1}H NMR spectra of the crude reaction mixtures only signals for major isomer **5** were observed. However, in the cases of imide **1a** and nitrones **4b** and **4c** the formation of minor diastereomers **5′b** and **5′c**, respectively, was also observed. The obtained isomers were purified by column chromatography on silica.

The reactions of itaconimide **1a** with *C*,*N*-diarylnitrones **6a**, **b** containing no electron-withdrawing groups were also investigated. Nitrones **6a**, **b** demonstrated diminished reactivity in the reactions with itaconimide **1a**. Only low conversion of the starting compounds was observed after three days in dichloromethane at room temperature; therefore the reactions were carried out in toluene at 110 °C for 3 h. Under these conditions the reactions also proceeded regioselectively giving only 5-spiroisoxazolidines **7** and **7′**. The stereoselectivity was lower for **6a**, **b** compared with nitrones **4a-d** (Table 3). Column chromatography on silica gel was used for purification of the isomers. The diastereomeric adducts **7a** and **7′a** were difficult to separate completely. However, a moderate amount of **7a** was obtained in pure form, crystallized and used for X-ray diffraction analysis [20], which established its relative configuration.

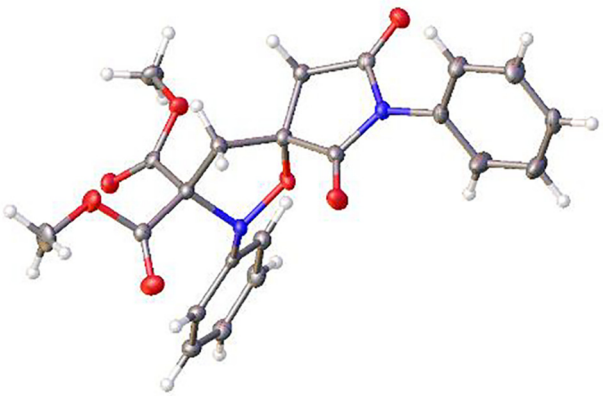


Fig. 1. Single crystal X-ray structure of **3a**.

In order to explain the regioselectivity, we carried out quantum chemical calculations at the DFT level of theory (B3LYP/6-31G*, geometry optimization in dichloromethane solution, for details see Computational details section) of global electrophilicity and nucleophilicity indices and Fukui functions [21] for the model structures of dipolarophiles **1a** and **1b** and dipoles **2a**, **4a**, **6a** (Table S1, see ESI). From the analysis of global electrophilicity and nucleophilicity indices and the energies of the frontier orbitals, it can be concluded that different FMO of the dipolarophiles and dipoles can interact depending on the substituents in the nitrones. In the case of nitrone **2a** bearing two electron withdrawing groups, the dipole acts as an electrophile (inverse electron demand cycloaddition). At the same time nitrone **6a** acts as a nucleophile in the reactions with itaconimides. For nitrone **4a** both types of interactions are possible. However, analysis of the Fukui functions does not allow us to rationalize the reasons of the observed regioselectivity. Therefore, it can be assumed that the regioselectivity is determined by steric factors.

Moreover, our results are consistent with previously reported data for the cycloaddition of *C*,*N*-diphenylnitrone and 3,4-dihydro-*2H*-pyrrole 1-oxide with *exo*-methylene heterocyclic compounds (3-methylene-5,5-dimethyl-2-pyrrolidinone, 3-methylene-5,5-dimethyl-2-pyrrolidinethione, α-methylene-δ-butyrolactone), where the observed regio- and stereoselectivity appeared to be controlled by steric effects in the transition states (Scheme S1, see ESI) [7h–m].

The presence of functional groups in isoxazolidines **3** and **5** make them promising substrates for further transformations. In this work the N—O bond of the isoxazolidine rings were reduced by employing zinc in acetic acid. First, isoxazolidines **3**, containing two ester groups at the C^3 position of the isoxazolidine ring were reduced. The reactions were carried out in THF at 60 °C and mix-

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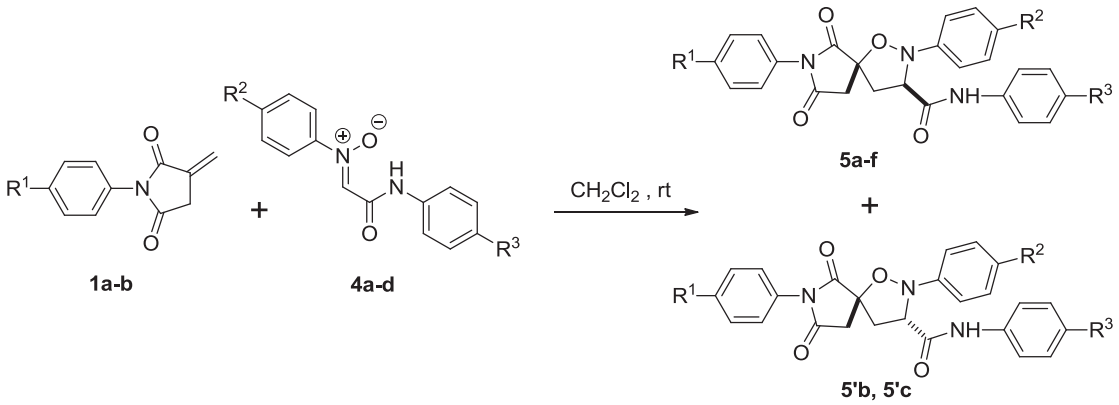
Table 2
1,3-Dipolar cycloaddition of *N*-arylitaconimides **1a-b** with *N*-aryl-*C*-carbamoylnitrones **4a-d**.



Entry	Itaconimide	R^1	Nitrone	R^2	R^3	Products	Ratio **5**:**5′**[a]	Isolated yield (%)	
								5	**5′**
1	**1a**	H	**4a**	H	H	**5a**	–	80	–
2	**1a**	H	**4b**	Me	Cl	**5b, 5′b**	9:1	60	4
3	**1a**	H	**4c**	Me	Me	**5c, 5′c**	10:1	69	9 (**5c** + **5′c**)[b]
4	**1b**	Br	**4a**	H	H	**5d**	–	88	–
6	**1b**	Br	**4b**	Me	Cl	**5e**	–	88	–
5	**1b**	Br	**4d**	Me	H	**5f**	–	84	–

[a] From ^{1}H NMR spectra of the crude reaction mixture.
[b] Mixture of diastereomers. Ratio **5**:**5′** – 1:1.4.

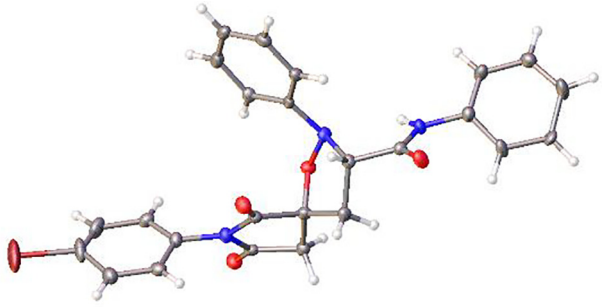
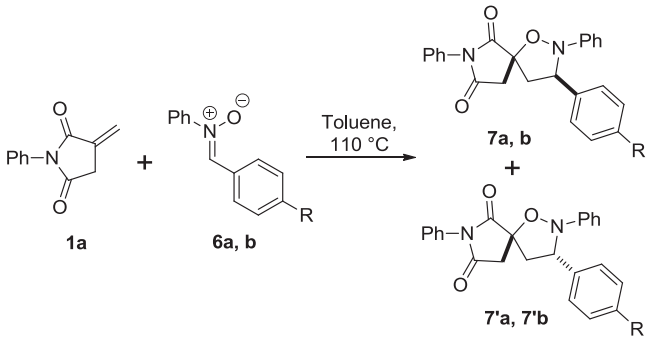


Fig. 2. Single crystal X-ray structure of **5d**.

tures of diastereomeric aminolactones **9** were obtained (Table 4). Attempts to carry out this reaction at room temperature were unsuccessful and no conversion was observed. For compounds **3e** and **3f** full conversion was achieved after 4 h. However, in the case of **3d**, the starting compound was detected in the reaction mixture after 4 h (Table 4, entry 1), so the reaction time was increased to 8 h. To investigate the possibility of the isomerization of **9′a**, the isomer was heated under the standard reaction conditions. Formation of **9a** was not detected (TLC control). After 4 h **9′a** decomposed giving an unidentifiable mixture of products. As a result, full conversion was observed and only major isomer **9a** was obtained. The ^{1}H NMR spectra of the crude reaction mixtures did not show signals of any other products. NOESY NMR spectra and X-ray

Table 3
1,3-Dipolar cycloaddition of *N*-arylitaconimide **1a** with *N*-aryl-*C*-carbamoylnitrones **6a, b**.



Entry	Nitrone	R	Products	Ratio **7**:**7′**[a]	Isolated yield (%)
1	**6a**	H	**7a**, **7′a**	4.7:1	83 (**7a** + **7′a**)
2	**6b**	Cl	**7b**, **7′b**	3.5:1	52 (**7b**), 11 (**7b** + **7′b**)[b]

[a] From ^{1}H NMR spectra of the crude reaction mixture.
[b] Mixture of diastereomers. Ratio **7b**:**7b'** – 1:5.7.

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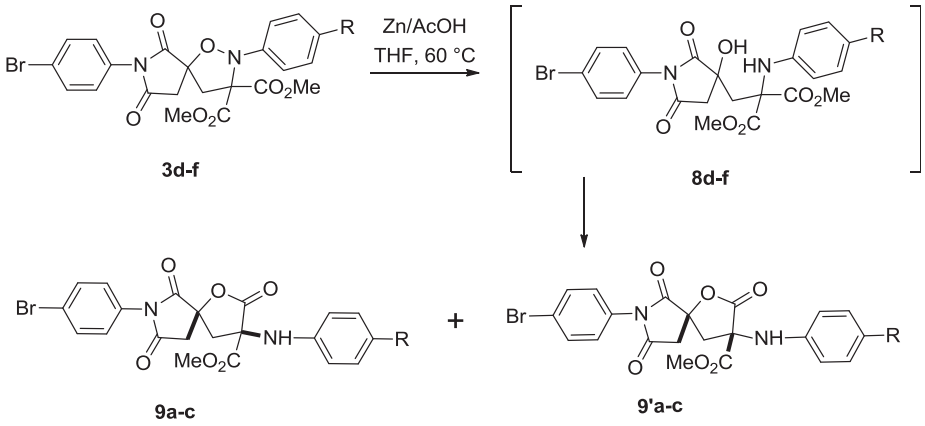
Table 4
Reduction of isoxazolidines **3d**-**f**.



Entry	3	R	Time h	Products	Ratio 9:9′[a]	Isolated yield (%)	
						9	9′
1	**3d**	H	4	**9a**, **9′a**	5.5:1	18	23[b]
2	**3d**	H	8	**9a**	–	37	–
3	**3e**	Br	4	**9b**, **9′b**	1.9:1	34	18
4	**3f**	Me	4	**9c**, **9′c**	1.9:1	37	22

[a] From ^{1}H NMR spectra of the crude reaction mixture.
[b] Mixture of **9′a**:**3d** – 1:1.6.

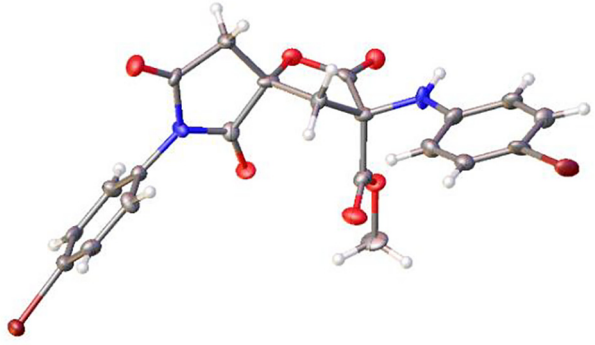


Fig. 3. Single crystal X-ray structure of **9b**.

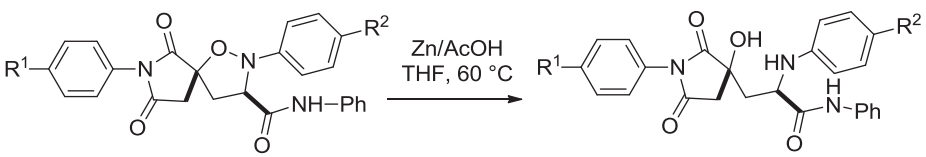
diffraction analysis data for compound **9b** [22] (Fig. 3) were used to determine the relative configuration of the lactones.

Clearly, aminolactones **9** are formed from 1,3-amino alcohol intermediate **8**, *via* the reaction of the hydroxyl group with one of the ester groups. Although 5-spirolactones are a promising substance class due to their pharmacological properties [23], strategies based on reductive cleavage of the isoxazolidine ring have not been previously employed for their synthesis.

Three of the isoxazolidines **5** were also reduced under the same conditions. The reactions were carried out for 4 h to complete the conversion of starting isoxazolidines. As a result the corresponding 1,3-amino alcohols **10a-c** were obtained in 50–60% yield (Scheme 1).

Conclusion

In summary, we have demonstrated that the reactions between the *N*-arylitaconimides and keto- and aldonitrones proceed regioselectively and in high yields to give 5-spiroisoxazolidines. The regioselectivity is assumed to be determined by steric factors. The reactions with aldonitrones proceed with high diastereoselectivity in most cases. A number of the obtained adducts were reduced under Zn/AcOH conditions. It was demonstrated that this strategy can lead not only to 1,3-amino alcohols, but also to aminolactones from adducts containing two ester groups. Thus a new synthesis of this promising substance class was developed.



5a: R^1=R^2=H;
5d: R^1=Br; R^2=H;
5e: R^1=Br; R^2=Me;

10a: R^1=R^2=H, 53%;
10b: R^1=Br; R^2=H, 50%;
10c: R^1=Br; R^2=Me, 60%

Scheme 1. Reduction of the isoxazolidines **5a**, **d**, **e**.

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Acknowledgments

NMR, HRMS and XRD studies were performed at the Saint Petersburg State University Center for Magnetic Resonance, Center for Chemical analysis and materials research and X-Ray Diffraction Center, respectively.

Appendix A. Supplementary data

^{1}H, ^{13}C NMR spectra of new compounds and computational details. Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.tetlet.2019.151063.

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