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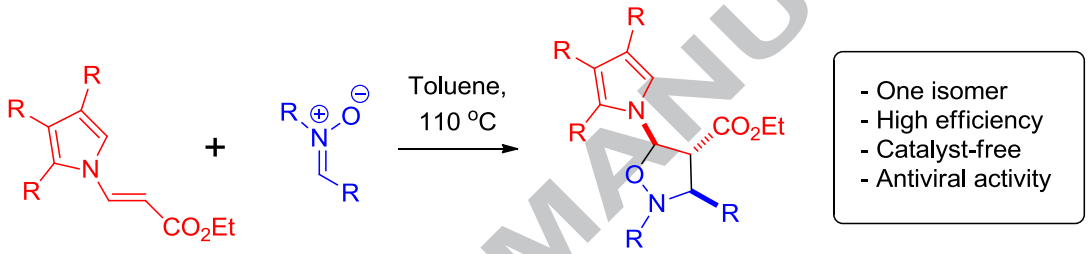

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ABSTRACT

The reactions of various nitrones with indolyl- and pyrrolylacrylates proceeds regioselectively with high diastereoselectivity in the case of aldonitrones, and represents an effective method for obtaining new indolyl- and pyrrolyl-substituted isoxazolidine carboxylates stabilized by weak (C–H···O) and moderate (N–H···N) strength intramolecular hydrogen bonding. The resulting cycloadducts exhibit promising in vitro anti-influenza activities.

1. Introduction

The isoxazolidine ring is an important structural fragment of natural compounds and biologically active substances.[1] Isoxazolidine derivatives exhibit a wide range of pharmacological properties, in particular antiviral,[2] antibacterial[3] and antitumor[4] activities. It should be noted that the formation of intramolecular hydrogen bonds has a pronounced effect on the binding ability of these compounds with enzymes or receptors and also their membrane permeability, water solubility, and lipophilicity.[5] Isoxazolidines are valuable intermediates because the N-O bond can be easily cleaved under mild reducing conditions to afford 1,3-aminoalcohols, which themselves are highly valuable synthetic building blocks in the synthesis of analogues of natural compounds: e.g. alkaloids and β-lactam antibiotics.[6a] One of the most convenient and widely studied methods for the synthesis of substituted isoxazolidines is the 1,3-dipolar cycloaddition of nitrones to the C=C double bond.[6] The undoubted advantage of this method is the possibility of selectively obtaining a molecule containing several stereocenters.

In addition, indole and pyrrole derivatives can react with dipoles giving a wide range of products depending on the structures of the reagents and the reaction conditions. Indole and pyrrole fragments, due to their high nucleophilicity, directly react with 1,3-dipoles giving products of alkylation[7] or cycloaddition[8] as well as activating conjugated multiple bonds for 1,3-dipolar cycloaddition. Recently, we investigated the reactions of *N*-vinylpyrroles and indoles with 1,3-dipoles (nitrones, nitrile oxides, azomethine imines). It has been shown that in the absence of a catalyst, the reaction proceeds to give the corresponding (3+2)-cycloadducts in good yields *via* reaction of the vinyl double bond.[9] However, in the case of nitrones and azomethine imines in the presence of Lewis acids, a change of reaction path was observed and polycyclic products of formal (3+3)-cycloaddition were obtained instead of adducts of 1,3-dipolar cycloaddition.[10] It should be noted that these reactions are not only an effective method for the construction of heterocyclic systems including the pyrrole ring, but they are also of interest for theoretical investigations of the details of the 1,3-dipolar cycloaddition mechanism.[11] Previously, we investigated only *N*-vinylpyrroles and indoles without any substituents on the vinyl double bond[9] or *N*-propadienyl heterocycles.[12] The only known example of the reaction of indolylacrylate with 1,3-dipoles is a catalytic reaction with an azomethine imine.[13] It is known that both steric and electronic factors are important to the regio-selectivity of the 1,3-dipolar cycloaddition of unsymmetrical dipolarophiles. Aldonitrones add to variously substituted acrylates to give 4- or 5-isoxazolidinecarboxylates[14]. Also, the presence of an ethoxycarbonyl group raises the diversity of the synthesized products.

The aim of this work is the detailed experimental study of the reactions of indolyl- and pyrrolylacrylates with nitrones as a highly efficient way to synthesise indolyl- and pyrrolyl-substituted isoxazolidinecarboxylates. The study is supported by

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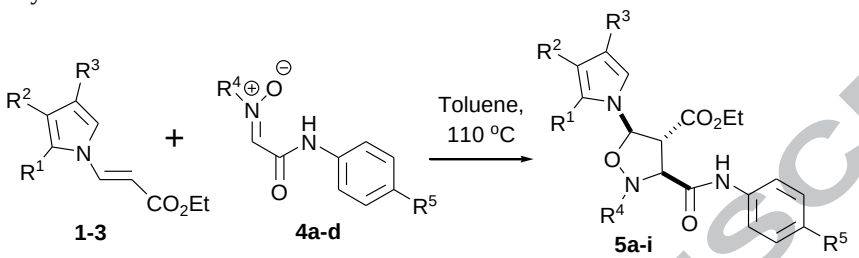
theoretical investigations of the nature and energies of intramolecular hydrogen bonding (N–H···N and C–H···O) which is responsible for the conformation of the resulting compounds and the testing of their antiviral activity.

2. Results and Discussion

Our study began with an investigation of the reactions of indolyl- and pyrrolylacrylates **1-3** with highly reactive *C*-carbamoylnitrones **4a-d**. The reactions were carried out at 110 °C in toluene for 20-100 hours. The reactions proceeded regio- and diastereoselectively resulting in good to excellent yields of 5-indolyl- or pyrrolyl-substituted isoxazolidinecarboxylates as single diastereomers in all cases (Table 1). The ^{1}H NMR spectra of the crude reaction mixtures did not contain signals of any other regio- or diastereoisomers. The structure of all adducts were established on the basis of spectroscopic data, and the relative configuration of adduct **5a** was confirmed using single crystal X-ray diffraction analysis (Fig. 1).[15]

Table 1. Reactions of acrylates **1-3** with nitrones **4a-d**.



No	Acrylate	Nitrone	R^1	R^2	R^3	R^4	R^5	Product	Time (h)	Isolated yield (%)
1	**1**	**4a**	-$(CH)_4$-		H	Ph	H	**5a**	30	98
2	**1**	**4b**	-$(CH)_4$-		H	*p*-Tol	H	**5b**	20	92
4	**1**	**4c**	-$(CH)_4$-		H	*p*-Tol	OMe	**5c**	60	76
3	**1**	**4d**	-$(CH)_4$-		H	Me	H	**5d**	100	62
5	**2**	**4a**	-$(CH)_4$-		Me	Ph	H	**5e**	30	86
6	**2**	**4b**	-$(CH)_4$-		Me	*p*-Tol	H	**5f**	30	67
7	**2**	**4c**	-$(CH)_4$-		Me	*p*-Tol	OMe	**5g**	60	78
8	**3**	**4a**	*p*-Cl-C_6H_4	H	H	Ph	H	**5h**	30	60
9	**3**	**4b**	*p*-Cl-C_6H_4	H	H	*p*-Tol	H	**5i**	30	75

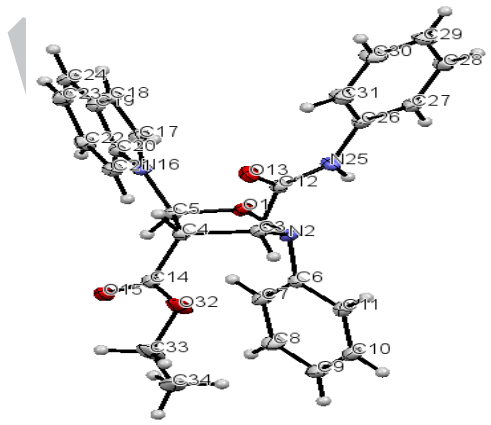


Figure 1. X-ray crystal structure of **5a**.

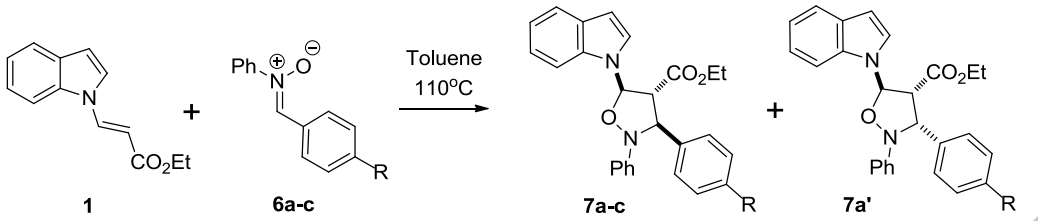
Inspection of the crystallographic data suggests the presence of intramolecular hydrogen bonding (N–H···N and C–H···O) which is responsible for the conformation of **5a** in the solid state, *viz*. N(25)–H···N(2), C(17)–H···O(13), and C(31)–H···O(13). Indeed, the observed distances H···N (2.187 Å) and H···O (2.304 and 2.621 Å) are shorter than the sum of Bondi's[16] vdW radii for the appropriate atoms (2.75 and 2.72 Å, respectively). Taking into account the significance of such weak contacts,[5] additional structural analysis through a computational study was desirable.

In order to confirm or deny the existence of these weak contacts and quantify their energies from a theoretical point of view, we carried out DFT calculations and performed a topological analysis of the electron density distribution within the framework of Bader's theory (QTAIM method)[17] for model structure **5a** (see ESI for details; this methodology has already been successfully used by us previously).[18]

The QTAIM analysis demonstrates the presence of appropriate bond critical points (BCP's) (3, –1) for intramolecular hydrogen bonding N–H···N and C–H···O in the optimized equilibrium structure of **5a** (Table S1, Fig. S1, ESI). The energies for these contacts were defined according to the procedures proposed by Espinosa and co-workers[19] and Vener and co-workers[20] (Table S1, ESI), and one can state that these non-covalent interactions can be classified as weak (C–H···O, 2.2–4.1 kcal/mol) and moderate (N–H···N, 5.6–5.7 kcal/mol) strength hydrogen bonding mainly due to electrostatics following the classification of Jeffrey[21] ("weak": <4 kcal/mol, "moderate": 15–4 kcal/mol, "strong": 40–15 kcal/mol).

Next, we investigated the reaction of acrylate **1** with other aldonitrones – *C*,*N*-diarylnitrones **6a-c**. These nitrones were less reactive towards indolylacrylate **1** (Table 2). The reaction required prolonged heating and gave only moderate yields of the 5-indolyl-substituted isoxazolidine carboxylates. In the case of nitrone **6a**, 3% of the minor diastereomer **7a'** was isolated from the reaction mixture as well as the main product **7a**. The relative configuration of adducts **7a** and **7a'** were additionally confirmed

Table 2. Reactions of acrylate **1** with nitrones **6a-c**.



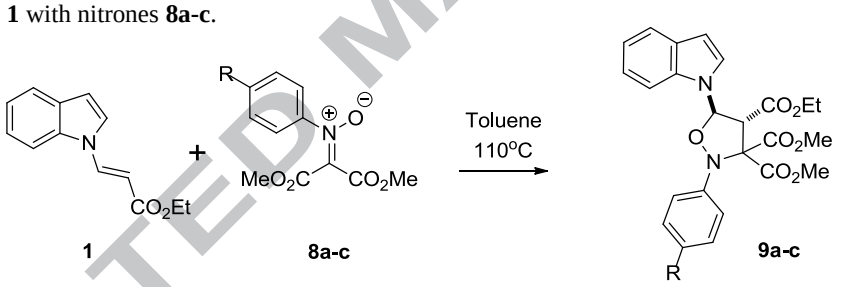
1 **6a-c** **7a-c** **7a'**

Entry	Nitrone	R	Products	Time (h)	Isolated yield (%)
1	**6a**	H	**7a**, **7a'**	100	30 (**7a**), 3 (**7a'**)
2	**6b**	Cl	**7b**	100	50
3	**6c**	OMe	**7c**	80	25

using their ^{1}H–^{1}H NOESY spectra in which a cross-peak for the protons in the C^{3}- and C^{5}-positions of the isoxazolidine ring in structure **7a** was observed.

An alteration of the reaction path in the presence of Lewis acids had been shown in our previous work for the reaction of *C*,*N*-diarylnitrones and *N*-vinylpyrroles.[10] An attempt was made to use nickel(II) perchlorate in the reaction of pyrrolylacrylate **3** with nitrone **6c**. However, in this case, only decomposition of the starting nitrone occurred and the formation of any type of cycloadducts was not observed.

Table 3. Reactions of acrylate **1** with nitrones **8a-c**.



1 **8a-c** **9a-c**

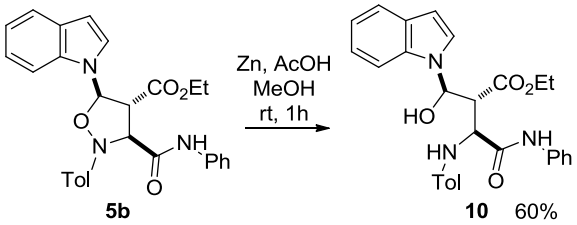
Entry	Nitrone	R	Product	Time (h)	Isolated yield (%)
1	**8a**	H	**9a**	40	68
2	**8b**	Cl	**9b**	40	82
3	**8c**	Me	**9c**	40	77

It is known that the selectivity of cycloaddition with ketonitrones may differ from aldonitrones due to increased steric hindrance.[12, 22] We investigated the cycloaddition of acrylate **1** with *N*-aryl-*C*,*C*-bis(methoxycarbonyl)nitrones **8a-c**. The reaction proceeded well, giving good yields of 5-indolyl-substituted isoxazolidinecarboxylates **9a-c**.

Thereby, it has been established that the cycloaddition reactions of indolyl- and pyrrolylacrylates with different types of nitrones proceeds regioselectively giving 5-indolyl- or pyrrolyl-substituted isoxazolidinecarboxylates. To achieve complete conversion of the starting nitrone, much longer heating was required than for reactions with *N*-vinylindoles and pyrroles. In the case of aldonitrones, the reaction proceeds stereoselectively.[9a-c] Moreover, when using nitrones containing electron-withdrawing substituents at the carbon atom, the reaction proceeds faster, giving higher yields of cycloadducts.

Cleavage of the N–O bond of isoxazolidines using a variety of reducing agents is a powerful tool in organic synthesis.

Depending on the structure of the isoxazolidine these methods allow a wide range of both cyclic and open-chain products to be obtained.[9a, 23] To investigate the synthetic utility of the obtained adducts, two of them were subjected to treatment with Zn/AcOH. Cycloadduct **5b** underwent isoxazolidine ring opening giving aminoalcohol **10** (Scheme 1).



5b

Scheme 1. Reduction of isoxazolidine **5b**.

The structure of aminoalcohol **10** was confirmed using single crystal X-ray diffraction analysis (Fig. 2).[24]

Under the action of Zn/AcOH at room temperature, product **9b** containing two ester groups at the C^{3}-atom of the isoxazolidine ring underwent isoxazolidine ring opening to form diastereomeric lactones **11** and **11'** (Scheme 2).

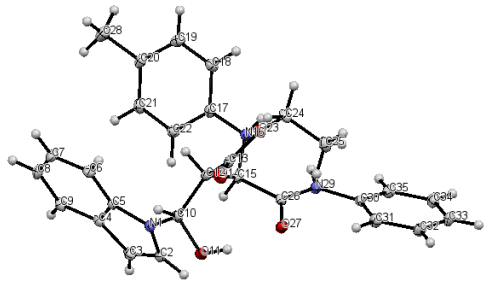
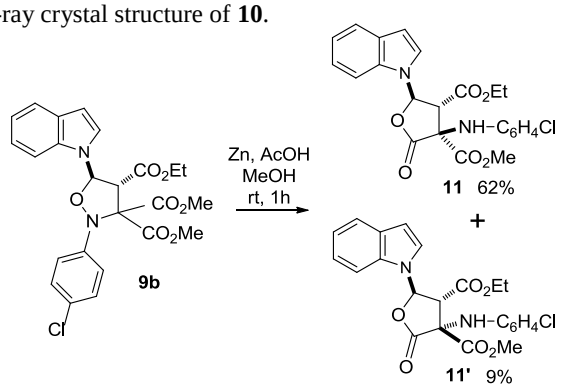


Figure 2. X-ray crystal structure of **10**.



Scheme 2. Reduction of isoxazolidine **9b**.

The relative configurations of lactones **11** and **11'** were determined by $^{1}H–^{1}H$ NOESY spectra. The spectrum of compound **11'** contains a cross-peak for the proton of the amino group and the proton at the C^{5}-atom of the lactone (see ESI).

Compounds **5a-c** and **5e-g** were tested for their cytotoxicity with respect to the MDCK cell line and their inhibition activity against influenza virus A/Puerto Rico/8/34 (H1N1) (Table 4).

Table 4. Cytotoxicity and virus-inhibiting properties of indolyl- and pyrrolyl-substituted isoxazolidine carboxylates against the influenza virus A/Puerto Rico/8/34 (H1N1) in MDCK cells.

Substance	CC_{50} (μM) [a]	IC_{50} (μM) [b]	SI [c]
5a	658±31	20±3	32
5b	>638	83±9	8
5c	600±51	600±69	1
5e	638±35	183±21	3
5f	620±42	620±71	1
5g	584±39	49±6	12
Rimantadine	264±21	39±6	7

[a] 50% Cytotoxicity Concentration (μM).

[b] 50% Inhibiting Concentration (μM).

[c] Selectivity Index (CC_{50}/IC_{50})

All compounds tested displayed comparatively low toxicity; their CC_{50} values were in the range of hundreds of micromoles or higher. Their virus-inhibiting activity varied from completely inactive (**5c**, **5e**, **5f**) to moderately high (**5a**, IC_{50}=20 μM, SI=32). Thus, two of the six compounds tested demonstrated SI higher than 10, indicating that they could undergo further optimization and development as potential anti-influenza drugs.

It should be also noted that the virus A/Puerto Rico/8/34 (H1N1) used for screening is resistant to adamantane-based antivirals, amantadine and rimantadine. These compounds block viral replication by inhibiting the activity of virus-specific proton channel M2 thus preventing dissociation of a viral genome within the cytoplasm. The reference drug rimantadine was inactive against this virus (Table 4) while compound **5a** demonstrated high anti-viral potential. This suggests that it utilizes a target other than M2 and therefore may represent a novel class of anti-viral compounds with alternative target(s) and mode of action.

3. Conclusion

The reaction of indolyl- and pyrrolylacrylates with various nitrones proceeds regio- and stereoselectively *via* 1,3-dipolar cycloaddition, and represents an efficient way to synthesise 5-indolyl- or pyrrolyl-substituted isoxazolidinecarboxylates exhibiting promising *in vitro* anti-influenza activity. The resulting cycloadducts are stabilized by weak (C–H···O) and moderate (N–H···N) strength intramolecular hydrogen bonding and can be reduced using Zn/AcOH to give 1,3-aminoalcohols or lactones containing amino- and carboxyl functionality.

Acknowledgments

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24. Suitable crystals were obtained from ethanol. Crystallographic data for compound **10** have been deposited at the Cambridge Crystallographic Data Centre (Deposition No. CCDC 1585812) and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

Supplementary Material

Experimental procedures, characterization data, ^{1}H, ^{13}C NMR spectra of new compounds; results of QTAIM analysis (Table S1); Cartesian atomic coordinates for the optimized equilibrium geometry of **5a** (Table S2). Supplementary data associated with this article can be found in the online version, at doi:

- Aldo- and ketonitrones add to indolyl- and pyrrolylacrylates with high regioselectivity
- In case of aldonitrones the addition proceeds with high diastereoselectivity
- 1,3-cycloaddition is an efficient method synthesise isoxazolidinecarboxylates
- Isoxazolidinecarboxylates reduce by Zn/AcOH to 1,3-aminoalcohols or lactones