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Highly efficient and stereoselective cycloaddition of nitrones to indolyl- and pyrrolylacrylates

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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.

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

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factors are important to the regioselectivity 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 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.

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 h. It has been shown that 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]

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

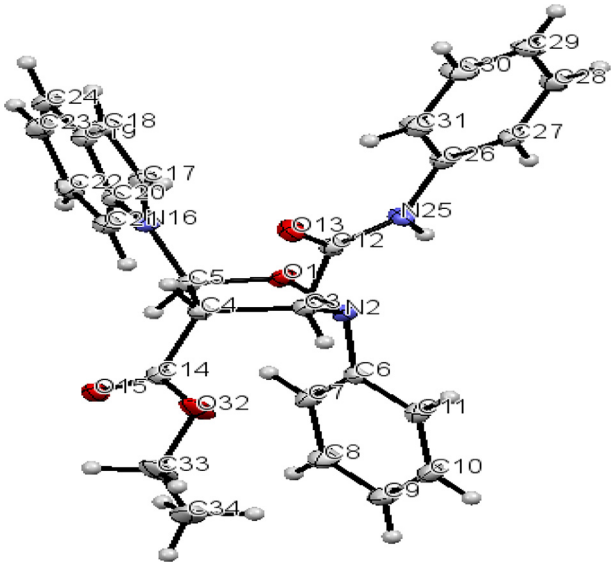


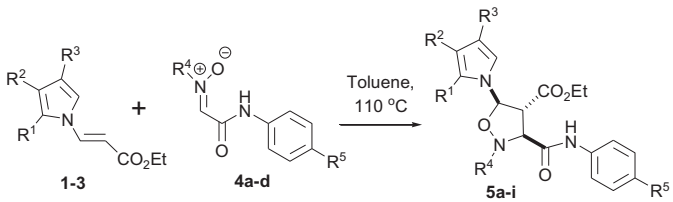
Fig. 1. X-ray crystal structure of **5a**.

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

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$_6$H$_4$	H	H	Ph	H	**5h**	30	60
9	**3**	**4b**	*p*-Cl-C$_6$H$_4$	H	H	*p*-Tol	H	**5i**	30	75