Formation of 3-Aminofuran-2-(5*H*)-ones and 3-Amino-1*H*-pyrrole-2,5-diones by Rearrangement of Isoxazolidines

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Dedicated to Prof. Alberto Brandi on the occasion of his 60th birthday

Abstract: A novel rearrangement pathway of 3-alkoxycarbonyl-4-carbamoylisoxazolidines, leading to 1*H*-pyrrole-2,5-diones by treatment with TBAF, is reported. DFT quantum chemical calculations support the reaction route, controlled by ring strain, which proceeds through the opening of a bicyclic intermediate, with aldehyde extrusion.

Key words: 1,3-dipolar cycloaddition, isoxazolidines, furan-2(5*H*)-ones, 1*H*-pyrrole-2,5-diones, density function calculations

Diketo acids (DKA) have been described as effective inhibitors of human retroviruses: in 2007, the FDA approved for the first time a DKA analogue, raltegravir (Figure 1), for the treatment of human immunodeficiency virus (HIV-1) infection in combination with other antiretroviral agents.[1] Some DKA analogues have also been shown to inhibit the hepatitis C virus (HCV) replication by the block of NS5B polymerase.[2]

In this context, we have synthesized a series of 3-aminofuran-2(5*H*)-ones **1** containing a carbonyl group at the C_4 position; these derivatives may be regarded as DKA cyclic analogues where the 1,3-diketone functionality is replaced by the 1-keto-3-imino group, enolized into the corresponding 1-keto-enamino functionality, while the acid moiety is masked in the furanose structure. In particular, *N*-phenyl carboxamide **2**, featured by a 3-aminofuran-2(5*H*)-one skeleton, recently emerged as a good HCV inhibitor, with EC_{50} = 19 μM in the replicon assay.[3]

Compounds **1** have been prepared by exploiting the basic rearrangement of 3-carboxyalkyl isoxazolidines **3** using a mild base such as tetrabutylammonium fluoride (TBAF).[4,5] Recently, we have reported that the nature of the substituents at C_4 and C_5 of the isoxazolidine nucleus determines two different rearrangement routes, which may lead to 3-aminofuran-2(5*H*)-ones **4** (Scheme 1, path A) or β-enaminones **5** (Scheme 1, path B). Two alternative mechanisms (lactonization and retroaldolization) have been rationalized by DFT quantum chemical methods and the relative importance of two reaction channels may be predicted by considering the electronic and steric features of substituents on the isoxazolidine ring.[5]

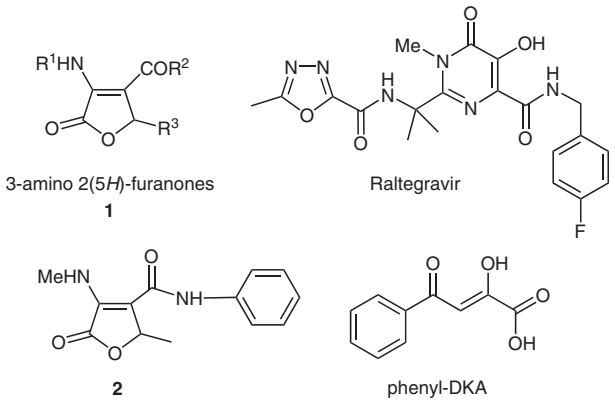
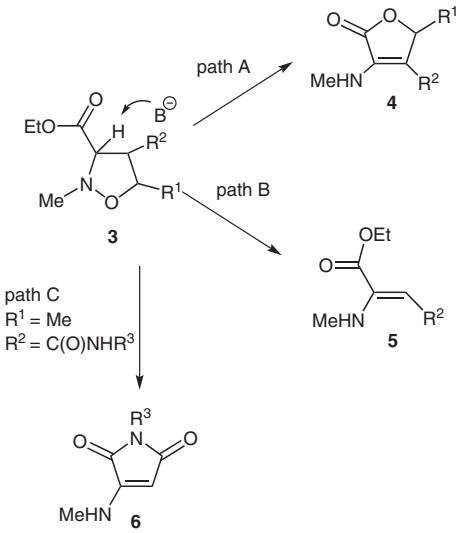


Figure 1 General structure of 3-aminofuran-2(5*H*)-one and some DKA analogues

We report in this paper a novel rearrangement pathway of isoxazolidines which possess an amido group at C_4: treatment of 4-carbamoylisoxazolidines with TBAF leads to the formation of 1*H*-pyrrole-2,5-diones **6** (Scheme 1, path C) as main products, together with lactones **4**.



Scheme 1 Rearrangement pathways of the isoxazolidine nucleus by TBAF treatment

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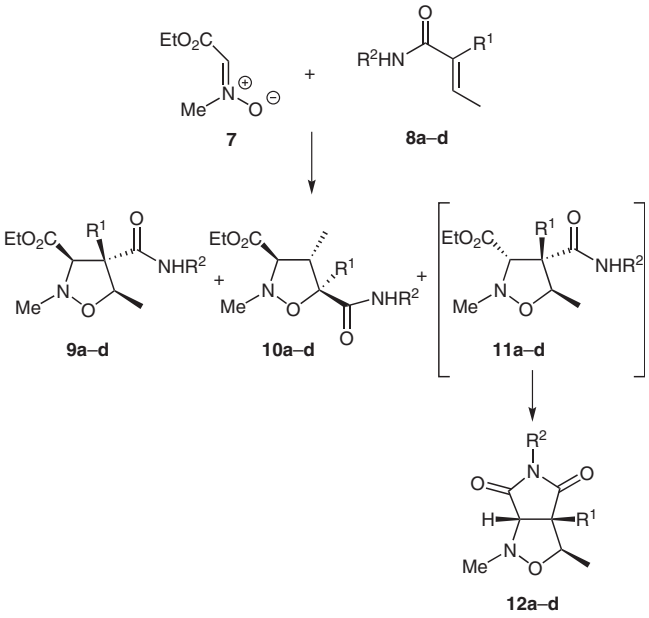
The 1,3-dipolar cycloaddition of *C*-ethoxycarbonyl *N*-methyl nitrone **7** with α,β-unsaturated amides **8a–d**, performed in dry toluene under microwave irradiation (100 W, 120 °C, 30 min), affords a mixture of three cycloadducts **9**, **10**, and **12**, which were separated by MPLC (Scheme 2, Table 1).



Scheme 2 Cycloaddition reaction of nitrone **7** with α,β-unsaturated amides **8a–d**

Table 1 Cycloaddition between Nitrone **7** and α,β-Unsaturated Amides **8a–d**

Alkene	R^1	R^2	Yield (%)[a]	**9/10/12**[b]
8a	H	Ph	70	1.4:1.6:1
8b	H	Bn	72	1.4:1.9:1
8c	H	n-Bu	68	1.5:1.8:1
8d	Me	Bn	55	1:1:4

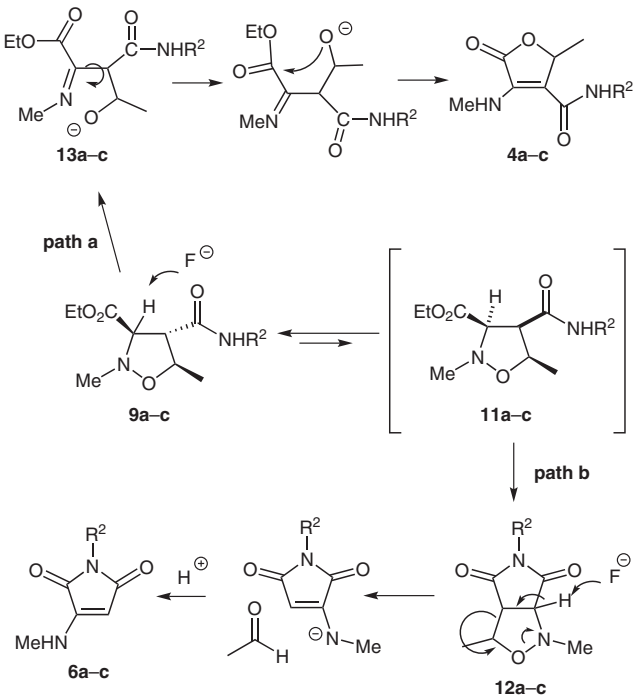
[a] Global yield.
[b] The relative ratio has been determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

The product ratios were determined by ^{1}H NMR spectroscopy of the crude reaction mixture. In all the examined reactions, besides the regioisomers **9** and **10**, a consistent amount of the bicyclic compounds **12** was recovered. Compounds **12** originate from the not isolated cycloadducts **11** which undergo a subsequent transamidification reaction between the two functionalities present at C_3 and C_4, in a *cis* relationship. The regiochemistry of the adducts was readily deduced from ^{1}H NMR data. In agreement with other literature reports for disubstituted electron-poor dipolarophiles,[6] the adducts **9** and **11**, which contain an electron-withdrawing group at C_4 position of the isoxazolidine ring, are predominant (56–67%).

For the trisubstituted dipolarophile **8d** higher regiochemical control was observed with compound **10d** representing only the 16% of the reaction mixture. The observed stereochemical results are in good agreement with the data reported for cycloadditions of nitrones bearing an electron-withdrawing group at the carbon atom.[7]

The adducts **9a–c** and **10a–c** are featured by an *E*-stereochemistry at the C_3–C_4 bond, arising from a transition state where the ethoxycarbonyl group and the amide moiety or the methyl group are *anti* with respect to the rising pentatomic ring, in order to minimize the Van der Waals interactions. In the case of the trisubstituted dipolarophile **8d**, the main cycloadduct **11d**, precursor of bicyclic **12d**, originates from a transition state stabilized by an hydrogen bond between the amido and esteral groups which overcomes the destabilizing effect caused by the proximity of methyl and ester functionalities in a *cis* relationship.

Treatment of isoxazolidines **9a–c** with TBAF, in a 1:1 ratio, led to the formation of a mixture of 3-aminofuran-2(5*H*)-ones **4a–c** (13–15% yield) and 1*H*-pyrrole-2,5-diones **6a–c** (41–44% yield) in a 1:3 ratio, respectively (Scheme 3).



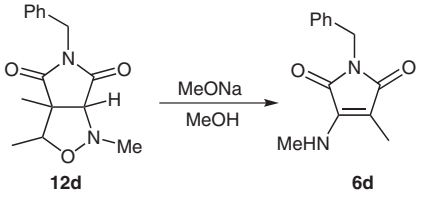
Scheme 3 Rearrangement pathways of **9a–c**

The formation of these compounds can be rationalized according to two different pathways (Scheme 3). In path a, in analogy with previous reports,[5] the fluoride anion removes from isoxazolidines **9a–c** the more acidic proton at C_3. Then, the alkoxy anion intermediate **13**, formed by the ring opening of the isoxazolidine nucleus, evolves towards compounds **4a–c** by intramolecular lactonization. In path b, the base promotes an epimerization reaction at C_3 producing the not-isolated intermediates **11a–c**; the subsequent intramolecular amidation leads to the bicyclic

derivatives **12a–c**.[8] These bicyclic compounds, according to our previous results on furoisoxazolidinones,[4b] undergo the fragmentation of the isoxazolidine nucleus (because of high ring strain), releasing the acetaldehyde and the 1*H*-pyrrole-2,5-diones **6a–c**.

As confirmation, in the reaction of bicyclic compounds **12a–c** with TBAF, 1*H*-pyrrole-2,5-diones **6a–c** were observed and collected as exclusive products.

Treatment of compound **12d**, substituted at C_4 position of the N,O-ring, with TBAF failed and only the unreacted substrate was recovered. The use of the more basic MeONa (in MeOH) proceeds easily leading to the formation, as exclusive product, of 1,3-dimethyl-4-(methylamino)-1*H*-pyrrole-2,5-dione **6d** (Scheme 4).



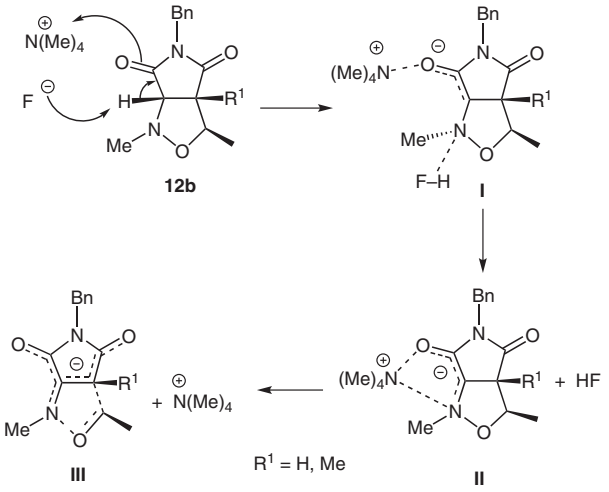
Scheme 4 Reaction of **12d** with MeONa

From a thermodynamic point of view, the conversion of bicyclic compounds **12** to 1*H*-pyrrole-2,5-diones **6** and acetaldehyde is largely exergonic because of the energy released in the fragmentation of the sterically hindered rings and of the large increase of entropy. Nevertheless, retroaldolization does not occur until a suitable base activates the process; hence, the generation of the carbanion represents the reaction driving force.

To understand which factors control the reaction route, we have investigated the active species for **12b** and **12d** employing quantum chemical methods B3PW91/6-31+G**, (see computational detail section). To improve computational performance, $(n\text{-Bu})_4N^+F^-$ was modeled by tetramethylammonium fluoride $Me_4N^+F^-$.

Because of the involvement of neutral and charged species in the reactions, different stabilization effects occur due to the solvent. Therefore, it becomes mandatory to include solvent effects in geometry optimization (B3PW91/6-31+G**/PCM = THF).[9] Schematic elementary reactions involved in the active species generation are reported in Scheme 5.

Hydrogen abstraction from **12b** and **12d** leads to the formation of a first intermediate **I** in which the Me_4N^+ cation coordinates the oxygen atom adjacent to C_3 of the isoxazolidine unit and the formed HF coordinates, through hydrogen bonding, the isoxazolidine nitrogen atom. The HF can be easily released because of the large entropy change and/or hydrogen-bond formation with the solvent, leading to the generation of the contact-ion-pair intermediate **II**. The next step is the heterolytic ion-pair separation of the contact-ion pair **II** caused by the large entropy increase and by the large stabilization of anion **III** and NMe_4^+ cation due to the solvent.



Scheme 5 Active species generated from **12b** and **12d**

Optimized structures of compound **12b** and the plausible intermediates **12b-I**, **12b-II**, and **12b-III** are reported in Figure 2, while Table 2 reports the stability of intermediates **I–III** relative to compounds **12b** and **12d**. All of these structures lie at high energy; therefore, their generation is hardly reached and actually they are the rate-limiting step for retroaldolization. We found that the next step, which involves the aldehyde extrusion, occurs with a negligible energy (<1 kcal/mol) and in fact, during the search for intermediate structures in the geometry optimization, acetaldehyde is often pushed out spontaneously, depending on the starting geometry. Nevertheless, reported structures **I–III** are stable on the Born–Oppenheimer surface and their stability gives a reasonable estimation of the easiness or difficulty of the reaction to occur.

The energies required for the formation of intermediates related to **12d** are about 1 kcal/mol greater than those computed for **12b**. Thus, in agreement with experiments, the reaction of **12d** with TBAF does not occur, while when a stronger base is used (like MeONa) the reaction takes place. The lower stability of **12d** intermediates is due to the electron-release character of the Me substituent group at the C_4 ring position and also to its sterically hindrance that in some degree destabilizes the anionic species. Structural data of intermediate **I** (Figure 2) clearly show the close contact between NMe_4^+ cation and the carbonyl adjacent to the C_3 isoxazolidine ring that largely stabilizes the negative charge of the molecule. The anion is also stabilized by the withdrawing of the electron density and the hydrogen-bond formation with HF. In the intermediate **II** the NMe_4^+ cation moves close to the isoxazolidine nitrogen indicating a larger charge delocalization as reported in Scheme 5. For free anion **III**, the negative charge is largely on the entire bicyclic system.

In conclusion, a novel reaction pathway of 3-alkoxycarbonyl-4-carbamoylisoxazolidines leading to 1*H*-pyrrole-2,5-diones by treatment with TBAF is reported. Due to the presence of an amide group at C_4 position of the isoxazolidine ring, this reaction channel competes with the route

Table 2 Relative Gibbs Free Energy (kcal/mol) for the Intermediates **I**, **II**, and **III** Generated from **12b** and **12d** at the B3PW91/6-31+G**/PCM = THF level[a]

R^1	H	Me
	12b	**12d**
I	20.1	20.7
II	25.1	26.9
III	25.6	26.4

[a] The energy of isolated reagents was taken as reference.

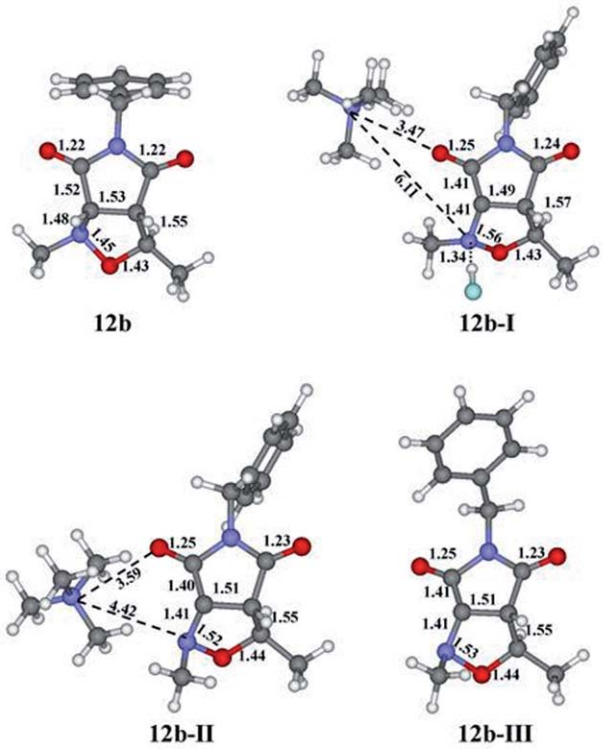


Figure 2 B3PW91/6-31+G**/PCM = THF computed structure of **12b** and intermediates **12b-I**, **12b-II** and **12b-III**

leading to 3-(methylamino)furan-2(5*H*)-ones. 1*H*-Pyrrole-2,5-diones originate from bicyclic compounds which, following the abstraction of the H_3 proton of the isoxazolidine ring by TBAF attack, undergo a rearrangement controlled the by the ring strain. DFT quantum chemical calculations have shown that the early stage of the hydrogen abstraction is modulated by the base strength and, hence, by the stability of the formed various ionic intermediates.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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