New Synthesis of β-Lactams by Ethylene Extrusion from Spirocyclopropane Isoxazolidines

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Recently we have reported a new and general process that provides easy access to the pyrrolo[3,4-*b*]pyridine ring system.[1] The synthetic protocol consists of the preparation of alkylidenecyclopropanes **1** by palladium(0) catalyzed substitution of 1-tosyloxy-1-vinylcyclopropane using α-amino acid derivatives as nucleophiles, followed by simple conversion of the alkoxycarbonyl moiety into a nitrone. Alkylidenecyclopropanes **1** spontaneously undergo intramolecular cycloaddition to spirocyclopropane isoxazolidines **2** that rearrange to octahydropyrrolo[3,4-*b*]pyridin-4-ones **3** upon heating in xylenes at 136−140 °C (Scheme 1).[1]

In this contribution we report a completely different and novel behavior of the same isoxazolidines **2**, which afford valuable β-lactam compounds when treated with strong acids.

To explore the extension of the thermal rearrangement of 5-spirocylopropane isoxazolidines to the synthesis of pyrido[3,4-*b*]pyridones **4** starting from β-amino acid derivatives (Scheme 2), we considered utilizing the readily available and inexpensive anthranilic acid as starting material.

Tosyl (Ts) as well as nosyl (2-nitrobenzenesulfonyl, Ns) groups were used to protect the amino acid nitrogen atom in **7**. The synthetic sequence occurred with total regio- and diastereoselectivity affording the *cis*-fused tetracyclic isoxazolidines **9** in excellent yields (Scheme 3).

The ring-fused structure of cycloadducts **9** could readily be assigned on the basis of ^{1}H and ^{13}C NMR data. Diagnostic resonances of $C_{3a'}$−H (δ_H = 2.54 ppm, δ_C = 43.7 ppm), $C_{9b'}$−H (δ_H = 3.52 ppm, δ_C = 66.5 ppm) and $C_{3'}$ (δ_C = 64.2 ppm) characteristic of 5-spirocyclopropane isoxazolidines[2] have been reported for compound **9a** as an example. Compound **9b** shows analogous values. The value of the vicinal coupling constant between the two bridged hydrogens of 6.5 Hz for **9a** and **9b** suggests a *cis* relationship between the two atoms.

When subjected to the same thermal conditions used to induce the rearrangement of **2**, the adducts **9a**,**b** failed to give pyridones **10a,b** (Scheme 4), but they were stable up to 120 °C and decomposed at higher temperatures. Whether the starting materials **9a,b** or the pyridones **10a,b** decomposed at this temperature was the object of an investigation; however, an unequivocal conclusion could not be reached. We found that a clean reaction occurred when compounds **9a,b** were heated in toluene in the presence of a small excess of trifluoroacetic acid (TFA) (Scheme 4).

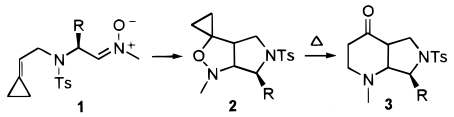
Under these conditions the unexpected β-lactams **11a,b** were obtained in good yield (72%) by ring contraction followed by loss of ethylene (Scheme 4). The structures of **11a** (*Z* = Ts) and **11b** (Z = Ns) were unambiguously established by spectroscopic means. Especially diagnostic were ν_{CO} (1752 and 1750 cm^{-1} for **11a** and for **11b**, respectively), ^{13}C NMR resonances δ_{CO} (166.9 and 166.2 ppm for **11a** and for **11b**, respectively), and ^{1}H NMR resonances of H_{8b} (δ = 4.29 ppm, d, J = 5.1 Hz for **11a** and δ = 4.45 ppm, d, J = 5.1 Hz for **11b**).

The β-lactams **11a,b** could be similarly obtained from **9a,b** in toluene in the presence of *p*-toluenesulfonic acid and in refluxing ethanol with HCl, or directly from the aldehydes **8** with MeNHOH·HCl in refluxing toluene or ethanol in absence of triethylamine. In any case, when the reaction conditions were not completely anhydrous, the ethylketone **12** was also obtained in 1:2 molecular ratio with **11**.

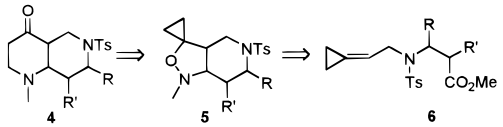
To establish the exact structure of the C_2 fragment eliminated in the acid-induced reorganization of isoxazolidine **9**, a solution of **9a** (Z = Ts) and TFA in CD_3CN was heated in a screw cap NMR tube in an oven at 70 °C. After 1 h the ^{1}H NMR spectrum of the mixture revealed the complete disappearance of **9a** and the formation of **11a** and showed an intense singlet at 5.41 ppm, which indicated the formation of ethylene.

To our knowledge, only a few examples of non-reductive ring-contraction of isoxazolidines to β-lactams have been reported. The examples refer to 5-nitroisoxazolidines,[3] 5-cyanoisoxazolidines,[4] and 5-phenylthioisoxazolidines.[5] In all of these cases,

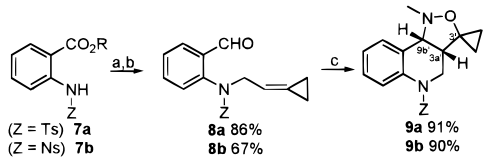
Scheme 1



Scheme 2

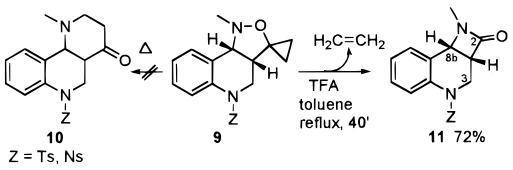


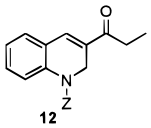
Scheme 3[a]



[a] **a**: *i.* NaH, THF; *ii.* 1-tosyloxy-1-vinylcyclopropane, $Pd(dba)_2$ (6 mol %), dppe (7.2 mol %), THF; **b**: *i.* DIBAL (3 equiv), CH_2Cl_2; *ii.* DMSO, $(COCl)_2$, CH_2Cl_2, TEA; **c**: MeNHOH·HCl, TEA, toluene, reflux temperature, 2 h.

Scheme 4





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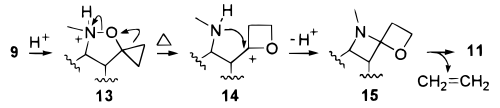
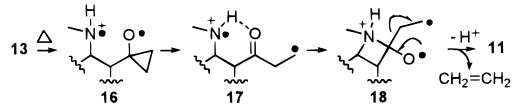
Scheme 5



Scheme 6



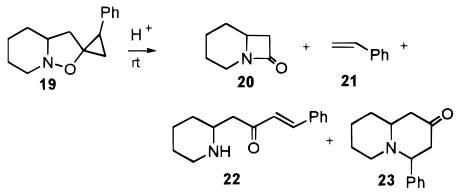
strong basic conditions and an electron-withdrawing group at the five-position of the isoxazolidine ring were required for the rearrangement to occur. The analogy with the present case, therefore, is only minimal.

The double bond fission of the cyclopropane ring in **9** to give ethylene is reminescent of the enzymatic conversion of 1-aminocyclopropane carboxylic acid (ACC) into ethylene during the plant growth regulation and the maturation of fruits.[6] The biosynthesis of the phytohormone ethylene from ACC is believed to occur through a stepwise oxidative process.[7] ACC and other aminocyclopropyl derivatives have been degradated to ethylene also by chemical oxidation under different conditions.[8]

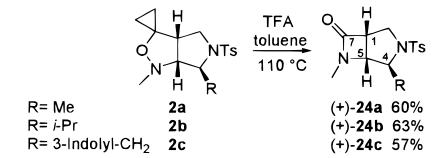
The rationalization of the formation of **11** and ethylene from **9** in the presence of non-oxidative acidic conditions is puzzling. Pyridones **10** as intermediates for the formation of **11** could be excluded, as model compounds tested under the same reaction conditions proved to be stable. The key role of the acid must involve the protonation of the isoxazolidine nitrogen atom, resulting in an easier cleavage of the N−O bond that can occur thermally either in hetero- or homolytic manner. In the first hypothesis, the increasing electron deficiency on the cyclopropyloxy moiety can induce a concomitant rearrangement to **14**, by analogy with the cyclopropylcarbinyl cation[9] behavior (Scheme 5). The transient oxetane cation **14** can be intramolecularly trapped by nitrogen to form the spiro oxetane **15** that can evolve to β-lactam **11** and ethylene by a formal retro-Paterno−Büchi reaction.[10]

In the case that an N−O bond homolysis occurs, by analogy with the Hofmann−Löffler−Freytag reaction[11,12] of the related protonated *N*-haloamines, the diradical cation **16** would be formed (Scheme 6). The oxoethyl diradical cation **17**, originating from **16** in a manner similar to the rearrangement of the parent neutral species, does not undergo the usual intramolecular diradical coupling[13] or 1,5-hydrogen shift[13] because of the presence of a strong intramolecular hydrogen bond. This might stabilize the intermediate conformation with the radical carbon atom far away from the nitrogen atom, settling the carbonyl moiety in the proper position to form a new N−C bond to give the diradical **18**. The product **11** and ethylene derive, then, from **18** through a radical fragmentation and proton loss.

Scheme 7



Scheme 8



A support to the second proposed mechanism might derive from the result of the rearrangement of isoxazolidine **19** obtained from 2,3,4,5-tetrahydropyridine-1-oxide and 1-methylene-2-phenylcyclopropane. In CH_2Cl_2/TsOH isoxazolidine **19** gave a complex mixture of the β-lactam **20**,[14] styrene (**21**), the enone **22**, and the quinolizidinone **23** as the major product already at room temperature (Scheme 7). The newly discovered process, confirmed by the formation of β-lactam **20** and extrusion of styrene, is clearly accelerated by the presence of the phenyl substituent. Formation of the enone **22** (and of quinolizidinone **23** deriving from **22** by conjugated intramolecular addition[15]) derived likely by hydrogen abstraction, occurred in this case in competition with cyclization and fragmentation of the proposed diradical intermediates (Scheme 6). Due to the peculiar nature of the phenyl ring, however, no general conclusion on the mechanism of this new reaction can be drawn at this level of study.

From the synthetic point of view, this new β-lactam synthesis proved to be a general process, as other 5-spirocyclopropane isoxazolidines underwent identical ring contraction when heated under acidic conditions. For example, the enantiomerically pure adducts **2a**−**c**,[1] obtained from L-alanine, L-valine, and L-tryptophan, respectively, gave β-lactams **24a**−**c**[16] in good yields (57−63%) (Scheme 8).

The compounds **24a**−**c** are characterized by β-lactam distinctive spectral data such as ν_{CO} and δ_{CO} (**24a**: ν_{CO} = 1753 cm^{-1}, δ_{CO} 165.9 ppm; **24b**: ν_{CO} = 1756 cm^{-1}, δ_{CO} 165.4 ppm; **24c**: ν_{CO} = 1753 cm^{-1}, δ_{CO} 165.8 ppm). Furthermore, the values of the coupling constants between vicinal C−H are consistent with the depicted stereochemistry (**24a**: H_1-H_5 J = 4.0 Hz and H_4-H_5 J = 0 Hz; **24b**: H_1-H_5 J = 3.7 Hz and H_4-H_5 J = 0 Hz; **24c**: H_1-H_{4a} J = 3.7 Hz and H_4-H_{4a} J = 0 Hz).

In conclusion, a novel chemoselective reaction of 5-spirocyclopropane isoxazolidines has been reported. When heated in neutral conditions these compounds generally undergo ring expansion to tetrahydropyridones, whereas in the presence of protic acids they undergo ring contraction to β-lactam derivatives. This last process, which proceeds with extrusion of ethylene, mimics the biosynthesis of ethylene from ACC. Further studies are in progress to establish the wider scope of this new approach to β-lactams and to verify the mechanistic proposals.

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Supporting Information Available: Experimental procedures and spectral and analytical data for all reaction products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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