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Synthesis and new rearrangements of 4-isoxazolin-4,5-dicarboxylic acid derivatives

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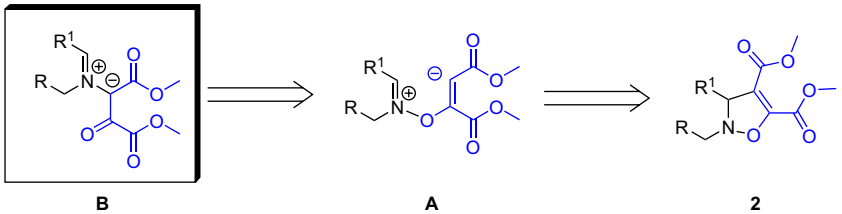
Abstract—Acyclic nitrones react with dimethyl acetylenedicarboxylate (DMAD) to give stable isoxazolines, from which the ones that contain electron-donating aromatic rings at the C3 position (R^1) were shown to undergo unprecedented fragmentation at room temperature, giving the R^1-aldehyde and inseparable product mixtures, probably due to the formation of highly reactive species such as iminocarbenes. Attempts to convert the isoxazolines to the corresponding stable azomethine ylides, by refluxing in toluene, again led to the same product mixtures as above (e.g., the room temperature decomposition). Isoxazolines when reacted with methoxide at room temperature afforded highly functionalised diastereomeric mixtures. Also, isoxazolines, when reacted with propylamine, gave the corresponding amides regioselectively, all of which were more stable than the parent isoxazolines.

1. Introduction

The synthetic utility of the 1,3-dipolar cycloaddition reaction is evident from the number and the scope of targets that can be prepared by this chemistry. In this context, nitrones are the most useful through their ability to generate nitrogen- and oxygen-based functionalities from the cycloaddition reactions.[1] The cycloadducts of di- and triarylimidazoline 3-oxides[2] with a variety of dipolarophiles[3] are bicyclic compounds with potentially interesting biological activities. On the other hand, they are a source of new heterocyclic compounds via interesting ring-opening reactions.[4] Previously we reported the synthesis of stable adducts of 3-imidazolin-3-oxides with dimethyl acetylenedicarboxylate (DMAD)[3d,e] and 3-phenylpropanoic acid alkyl esters.[3f] Thermally and base-induced ring-opening reactions of these adducts were demonstrated.

In a recent report from our laboratory, we described the utility of isoxazolo[3,2-*a*]isoquinolines as stable azomethine ylides.[3h] The substituent effects observed in this rearrangement prompted us to propose a mechanism, which did not involve the largely accepted intermediate, acylaziridine.[5] The way involves scission of the C3–C4 bond to give intermediates **A**, which rearrange to **B** (see Scheme 1). To assess the scope of this reaction for the synthesis of acyclic azomethine ylides **B**, we developed the retrosynthetic analysis described in Scheme 1. This would first require the preparation of *N*-benzyl(methyl)-*C*-aryl nitrones **1**. This would then be subjected to the cycloaddition with DMAD to give isoxazolines **2**. It was envisaged that the rearrangements of isoxazolines **2** would produce azomethine ylides **B**. It is well known that nitrones generally react with alkynes to give unstable adducts. However, those which are stable can be subjected to rearrangements under thermal conditions. The synthesis and rearrangements of the alkyne adducts of some nitrones have been reviewed.[1a,5] 4,5-Dihydroimidazole *N*-oxides undergo 1,3-dipolar cycloaddition with alkyne dipolarophiles and the cycloadducts were shown to convert into the corresponding ene-1,1-diamines.[6] There is still a large interest for



Scheme 1. Retrosynthetic analysis of acyclic azomethine ylides **B**.

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4-isoxazolines due to their biological activities[7a] and as a source of interesting rearrangements.[7b,c]

2. Results and discussion

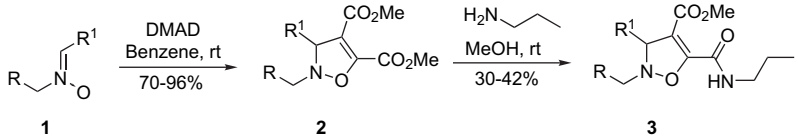
Nitrones **1a–f** were prepared in moderate yields (50–75%) according to the methods reported[8] and their geometry was proved to be (*Z*) by NOESY 1D experiments as the irradiation of benzylic methylene (or the methyl in the case of **1f**) gave enhancements for the imine hydrogens' signals. The reaction of nitrones **1a–e** with DMAD was then investigated in benzene at room temperature. This gave the corresponding isoxazolines **2** in good yields (70–96%) (Scheme 2). Isoxazolines **2** were characterised by spectroscopy as soon as purified by column chromatography.

The IR spectra of isoxazolines **2** have similar C=O and C=C bond profiles as the adducts of imidazolin-3-oxides or 3,4-dihydroisoquinolin-2-oxides with DMAD. The absorption at 1750 cm^{-1} was assigned to the C=O at C5. The characteristic ^{13}C NMR assignments for the C=C bonds of the isoxazolines **2** are ca. 107 and 156 ppm for C4 and C5, respectively. The C3 carbon signal appears about 70 ppm.

Isoxazolines **2** were stable in the condensed phase for prolonged periods of time (remained unchanged for months in a refrigerator). However, when kept in solution at 20 °C for two weeks, some decomposition was observed for **2a** and **2b** (50% and 75%, respectively). On the other hand, **2d** was fully decomposed. Surprisingly, **2c** and **2e** were stable within this period of time. This observation was in good agreement with those of isoxazolo[3,2-*a*]isoquinolines reported.[3h] It seems that the driving force for the rearrangements of simple isoxazolines **2** is the scission of the C3–C4 bond, as in the case of isoxazolo[3,2-*a*]isoquinolines. This gives rise to the formation of zwitterion **B**, as depicted in Scheme 1. However, the differences begin here. In all of the cases studied, one of the decomposition products of isoxazoline **2** was an aldehyde derived from the R^1 at the C3 position of **2**. The probable mechanism for the conversion of isoxazoline **2** into the corresponding R^1-aldehyde is depicted in Scheme 3 and could be rationalised as follows: the initial C3–C4 bond scission gives zwitterions **A**. That electron-donating groups favour the rearrangement supports this assumption. The 1,3-sigmatropic rearrangement of **A** could produce the iminium enolate **B**, the electrocyclization of which gives oxazoline **C**. The retrocyclization of the latter could produce the R^1-aldehyde and an extremely reactive intermediate, like iminocarbene **D** which will serve as a new dipole **E** isomeric with the corresponding azomethine ylide. Although the use of in situ formed oxazolines as precursors of in situ formed azomethine ylides is known,[9] conversion of isoxazoline **2** into the corresponding R^1-aldehyde and probable isoazomethine ylide via oxazoline is reported for the first time.

Since iminocarbene **D** is a very reactive intermediate, intramolecular carbene insertion would occur to generate products, such as **H** (or **I**). This became evident when **2a** was refluxed in dichloroethane. Although a complex mixture was formed, the ^1H NMR analysis indicated two doublets at 4.29 (1H, d, J=16.0) and 4.67 (1H, d, J=16.0) and a singlet at 5.26 ppm. These are characteristic peaks for dimethyl 1,4-dihydroisoquinoline-3,4-dicarboxylate **H**, corresponding to the C-1 and C-4 hydrogens. The attempts to separate the mixture by column chromatography resulted in a much more complex mixture, probably due to the known disproportionations of the dihydroisoquinolines.[10] Further experiments to trap the in situ formed iminocarbene **D** (or isoazomethine ylides) are underway. However, we were lucky to detect the first examples of products pointing to the formation of proposed intermediate **H** (or **I**). Subjecting the isoxazoline **2d** to GC–MS analysis at 200 °C injection temperature clearly revealed that the fragmentation occurs to give the corresponding R^1-aldehyde (isolated in a separate experiment) and a main product **K**, with an *m*/*z* value of 249 amu (100%). This base peak is easily deduced, with the loss of MeO and CO, from the molecular ion of dihydroisoquinoline **H**. Under thermolytic conditions, the formation of **H** (or **F**) is more probable and could readily result from norkaradine **F**, a product of intramolecular carbene insertion **D** and probably is in equilibrium with tropilidene **G** at room temperature. The presence of fragment peaks in the mass spectrum of a minor product implies that the product **J** also formed. These are all summarised in Scheme 3.

The treatment of isoxazolines **2** with methoxide in methanol at room temperature for 28 h gave complex mixtures. However, in the case of **2a**, highly functionalized diastereomeric compounds (**10** and **11**) were successfully isolated as 1:1 mixture upon chromatography (Scheme 4). These compounds are pyrrole derivatives and could be further elaborated to give some biologically active pyrroles. 2-Phenylpyrrolidines are nicotine analogues.[11a] Well-known 1β-methylcarbapenem antibiotics having a (3*S*,5*S*)-*cis*-disubstituted pyrrolidine ring as the C-2 side chain, such as meropenem,[11b] S-4661,[11c] have a broad antibacterial spectrum covering Gram-positive and Gram-negative bacteria including *Pseudomonas aeruginosa*. In contrast, J-114.870, a novel carbapenem, shows ultra-broad antibacterial activity against MRSA as well as *P. aeruginosa*, which contains (3*S*,5*R*)-*trans*-disubstituted pyrrolidine ring C-2 side chain.[11d] (−)-Codonopsinine and (−)-codonopsine (Fig. 1) are two 2-arylpyrrolidine alkaloids isolated from *Codonopsis clematidea*[12] in 1969. They are attractive for both synthetic and medicinal chemists due to the challenging penta-substituted pyrrolidine nucleus and varied biological activities as antibiotics and as antihypertensive agents without any effects



Scheme 2. Synthesis of 4-isoxazolines **2** and amides **3**. Reagents and conditions: (a) R=Ph, R^1=Ph; (b) R=Ph, R^1=2,3-$(MeO)_2$Ph; (c) R=Ph, R^1=2-NO_2Ph; (d) R=2,3-$(MeO)_2$Ph, R^1=2,3-$(MeO)_2$Ph; (e) R=2,3-$(MeO)_2$Ph, R^1= 2-NO_2Ph; (f) R=H, R^1=3,4-$(MeO)_2$Ph; (g) R=2,3-$(MeO)_2$Ph, R^1=Ph.