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

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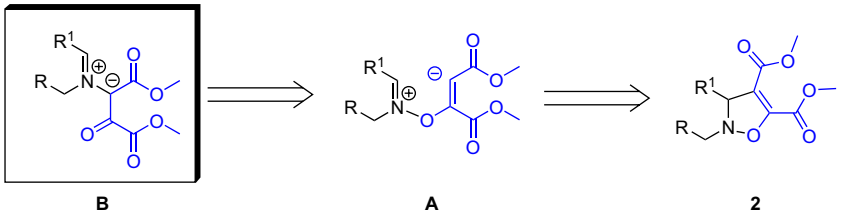
Abstract—Acyclic nitrones react with dimethyl acetylenedicarboxylate (DMAD) to give stable isoxazolines, from which the ones that contain electron-donating aromatic rings at the C3 position (R^1) were shown to undergo unprecedented fragmentation at room temperature, giving the R^1-aldehyde and inseparable 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**.

Keywords: Dipolar cycloaddition; Nitrones; Acyclic azomethine ylides; 4-Isoxazolines; Pyrrole derivative; 1*H*-Pyrrole-3-carboxylic acid methyl ester; Rearrangement.
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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

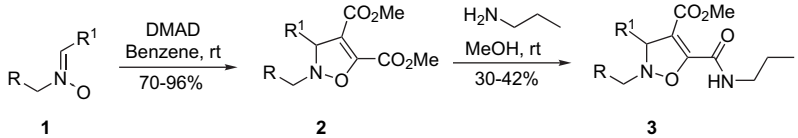
Nitrones **1a–f** were prepared in moderate yields (50–75%) according to the methods reported[8] and their geometry was proved to be (*Z*) by NOESY 1D experiments as the irradiation of benzylic methylene (or the methyl in the case of **1f**) gave enhancements for the imine hydrogens' signals. The reaction 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.

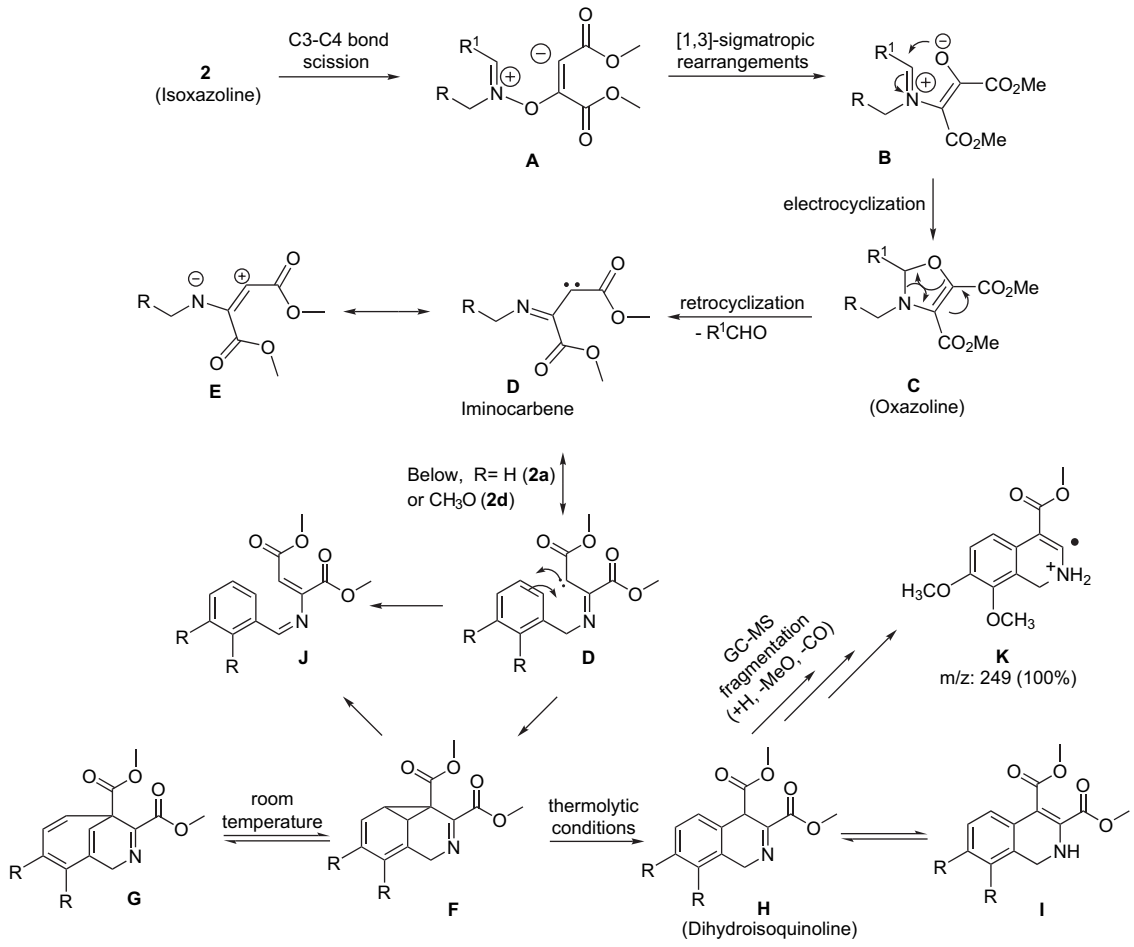
Isoxazolines **2** were stable in the condensed phase for prolonged periods of time (remained unchanged for months in a refrigerator). However, when kept in solution at 20 °C for two weeks, some decomposition was observed for **2a** and **2b** (50% and 75%, respectively). On the other hand, **2d** was 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

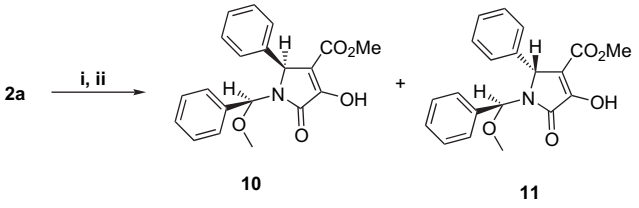


Scheme 2. Synthesis of 4-isoxazolines **2** and amides **3**. Reagents and conditions: (a) R=Ph, R^1=Ph; (b) R=Ph, R^1=2,3-$(MeO)_2$Ph; (c) R=Ph, R^1=2-NO_2Ph; (d) R=2,3-$(MeO)_2$Ph, R^1=2,3-$(MeO)_2$Ph; (e) R=2,3-$(MeO)_2$Ph, R^1= 2-NO_2Ph; (f) R=H, R^1=3,4-$(MeO)_2$Ph; (g) R=2,3-$(MeO)_2$Ph, R^1=Ph.



Scheme 3. Rearrangements of 4-isoxazoline **2** to an R^1-aldehyde and a very reactive iminocarbene **D**, which gives intramolecular cyclisation.

on the central nervous system.[13] The structures of **10** and **11** were elucidated using elemental and detailed NMR analysis (details are given in Section 4).



Scheme 4. Reagents: (i) MeO^-, MeOH, rt, 28 h; (ii) H^+.

The formation of **10** and **11** could be rationalised in the following way and summarised in Scheme 5: a methoxide-induced elimination of **2a** gives resonance stabilised imine enolate **4**. This then, itself or its protonated form **5**, reacts with methoxide to give the diastereoisomers **6** and **7**. The intramolecular cyclisation of **6** and **7** finally gives phenyl-2,5-dihydro-1*H*-pyrrol-3-olates **8** and **9**, the acidification of which affords the diastereoisomers **10** and **11**.

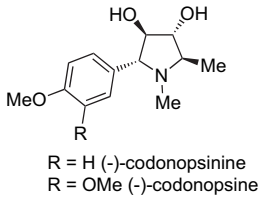
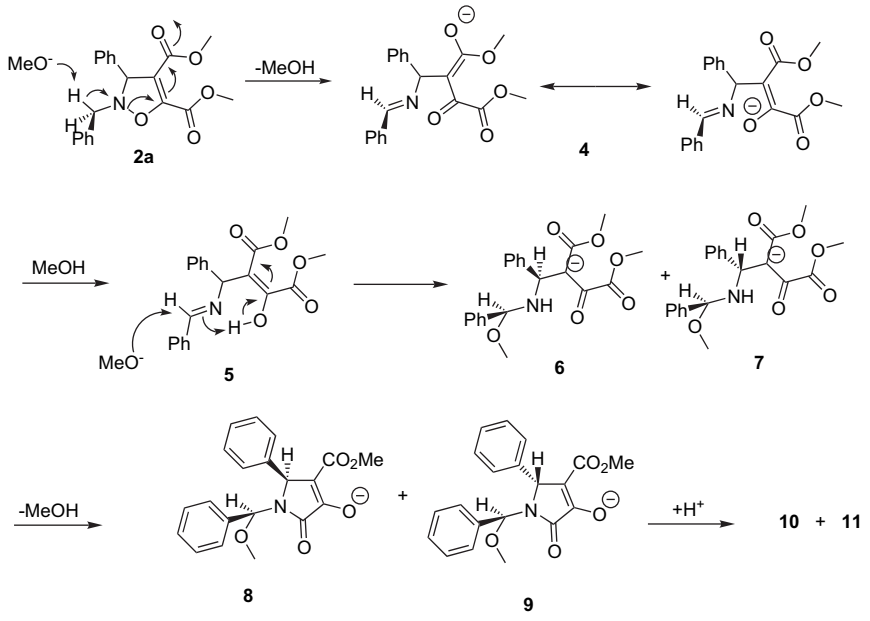


Figure 1. Structures of (−)-codonopsinine and (−)-codonopsine.

The treatment of isoxazolines **2** with propylamine in methanol at room temperature led to selective formation of amides **3** in low yields (30–42%), as depicted in Scheme 2. Selective amide formation was supported by the absence of both the IR absorption peak at 1750 cm^{-1} (corresponds to the ester C═O at the C-5 of **2**) and the ^1H NMR signals at 3.91 ppm (corresponds to the ester CH_3O at the C-5 of **2**). The enhanced reactivity of C-5 carbonyl was similar to those observed in our chemoselective alkyl bromoacetate–Zn mediated transesterification of imidazoisoxazolines[14] and chemoselective alkoxyzinc salts catalysed transesterifications.[15] This preference can be explained in terms of the formation of a hydrogen bonded pre-complex between the amine and the isoxazoline, where the nucleophile ($^nPrNH_2$) and the electrophilic C═O centre are orientated in a geometrically favourable position, as depicted in Figure 2.

Amides **3** were much more stable than their precursors and could be stored at room temperature for months without any significant decomposition. The replacement of the methoxy group by propylamine at the C5 position decreases the electron-withdrawing capacity of the ester carbonyl by resonance effect. This is another important factor determining the formation of zwitterion **B** shown in Scheme 1.



Scheme 5. Mechanism for the rearrangement of isoxazolines **2** into diastereoisomers **10** and **11**.

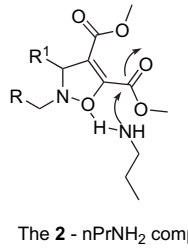
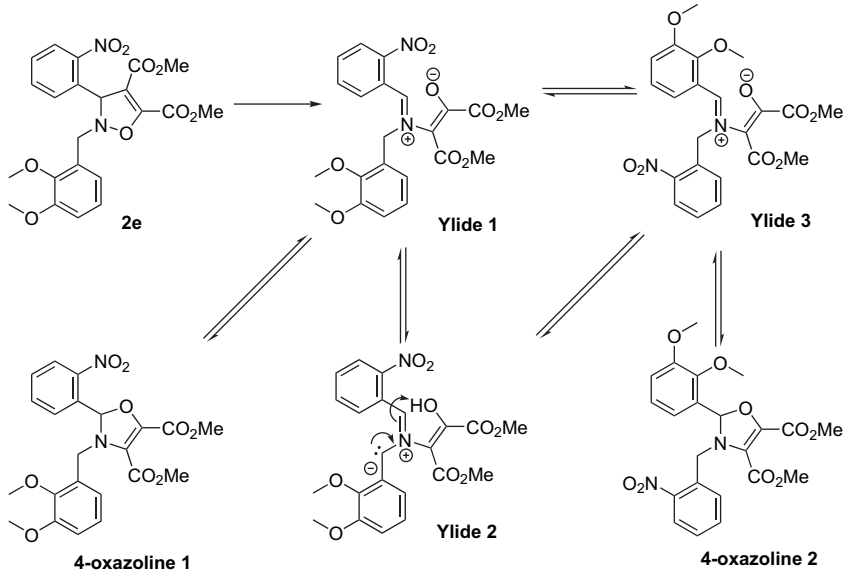


Figure 2. Complex formation between **2** and propylamine, which would lead to selective amide formation **3**.

Although stable at room temperature, amide **3b**, when refluxed in THF, again led to the formation of R^1-aldehyde (2,3-dimethoxybenzaldehyde). Thermal treatment of amide **3d** led to similar results, as above and with those of **2d**, where R^1-aldehyde (2,3-dimethoxybenzaldehyde) and base peak formations with an *m*/*z* value of 249 amu were detected by GC–MS. This time, the loss of $PrNH_2$ and CO (in the case of **3d**), instead of MeO and CO (in the case of **2d**), would account for the formation of base peak (for detailed discussion, refer to Scheme 3).

The thermolysis of asymmetric isoxazoline **2e** in the injection of GC–MS led to the formation of two different aldehydes, the expected R^1-aldehyde (2-nitrobenzaldehyde) and the unexpected R-aldehyde (2,3-dimethoxybenzaldehyde) in the 1:5 ratio, respectively. The other two peaks in the chromatogram corresponded to the products obtained from cyclisations of the minor carbene (*N*-2,3-dimethoxybenzyliminocarbene) and the main carbene (2-nitrobenzyliminocarbene). The rationale for these results is presented in Scheme 6. Isoxazoline **2e** first rearranges to give the **ylide 1**, electrocyclization of which produces **4-oxazoline 1**.



Scheme 6. Probable mechanism for the rearrangement of initially formed azomethine **ylide 1** to the thermodynamically more stable azomethine **ylide 3**.

Due to electron-deficient character of the dipolarophile (2-nitrobenzaldehyde), retrocyclization of the **4-isoxazoline 1** seems to be less favourable than the retrocyclization of **4-oxazoline 2**, where the electron-rich dipolarophile (2,3-dimethoxybenzaldehyde) is present.

How the precursor of the latter **4-oxazoline 2** is formed deserves discussion. Initially formed **ylide 1**, less stable due to the electron-withdrawing nitro group at the phenyl ring, rearranges to give isomeric **ylide 3**. The rearrangement may be assumed as a 1,3-hydride shift to give directly **ylide 3** or as intramolecular proton shift to give **ylide 2**, the concerted rearrangement of which as seen in Scheme 6 would produce the more stable **ylide 3**.

3. Conclusion

Isoxazolines **2**, prepared from the reaction of nitrones **1** with DMAD, underwent a substituent-dependent rearrangement involving consecutive C3–C4 bond scission and 1,3-sigmatropic shift to give the corresponding iminium enolates **B** (azomethine ylides). Isoxazoline amides **3** were obtained selectively and proved to be more stable at room temperature than the corresponding **2**. Electron-donating groups facilitated effectively the rearrangement process of **2**. This was in good agreement with the results we have recently reported for the formation of azomethine ylides from DMAD adducts with 3,4-dihydroisoquinolin-1-oxides.[3h] In situ formed azomethine ylides from the thermolysis of **2** and **3**, for the first time, underwent further transformations, such as electrocyclization to 4-oxazolines **C** and retrocycloaddition to an R^1-aldehyde and a reactive intermediate, iminocarbene **D**. In the case of an asymmetrical ylide, the initially formed **ylide 1** with an electron-deficient aromatic ring at the imine carbon isomerised to thermodynamically more stable one (**ylide 3**), where electron-rich aromatic ring ended up at the imine carbon. Some NMR and mass spectral data for the products of intramolecular cyclisation provided evidences for the structure to be iminocarbene **D**. However, the full elucidation of the structures of more cyclised products is required and investigation to solve this challenging problem is underway. The treatment of isoxazolines **2** with methoxide at room temperature gave a new entry to highly functionalized pyrrolidines, which could serve as precursors for the synthesis of biologically active 2-arylpyrrolidine derivatives.

4. Experimental

4.1. General

Melting points were recorded on an electrothermal digital melting point apparatus. Infrared spectra were recorded on a Mattson 1000 FTIR. 1D and 2D NMR experiments were performed on a Varian Mercury Plus 400 MHz spectrometer. Nitrones **1a–f** were prepared according to the methods we have recently reported.[8] The elemental analyses were performed on a EuroEA 3000 CHNS analyser.

4.1.1. *C*-(2,3-Dimethoxyphenyl)-*N*-2,3-dimethoxybenzylnitrone 1d. Yield 75%; white crystals; mp 122–124 °C; IR (KBr) $\nu_{C=N}$ 1580 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.81 (3H, s), 3.86 (3H, s), 3.80 (3H, s), 3.88 (3H, s) 5.13 (2H, s), 6.93–6.98 (2H, m), 7.05–7.11 (3H, m), 7.91 (1H, s), 8.8 (1H, dd, J=8.0, 1.2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.1; 56.1; 61.2; 61.7; 66.5; 113.7; 114.9; 120.9; 123.2; 124.4; 125.0; 127.5; 129.6; 147.3; 148.0; 152.1; 152.9.

Anal. Calcd for $C_{18}H_{21}NO_5$ (331.36): C, 65.24; H, 6.39; N, 4.23. Found: C, 65.30; H, 6.41; N, 4.22.

4.2. Synthesis of 2-benzyl-3-aryl-2,3-dihydroisoxazole-4,5-dicarboxylic acid dimethyl esters 2. General procedure

DMAD (1 mmol) was added to a solution of nitrone **1** (1 mmol) in benzene (8 mL) and the reaction mixture was stirred for 22 h in the cases of **1a**,**b**,**d**,**f** and 28 h in the cases of **1c**,**e** at room temperature. The solvent was evaporated and the residue was subjected to column chromatography over silica gel eluting with a mixture of ethyl acetate–petroleum ether.

4.2.1. 2-Benzyl-3-phenyl-2,3-dihydroisoxazole-4,5-dicarboxylic acid dimethyl ester 2a. Yield 80%; oil; IR (KBr) $\nu_{C=O}$ 1759, 1713, $\nu_{C=C}$ 1657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.64 (3H, s), 3.91 (3H, s), 4.12 (1H, d, J=13.2), 4.44 (1H, d, J=13.2), 5.23 (1H, s), 7.12–7.35 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.1; 53.6; 63.7; 72.9; 109.5; 127.5; 128.3; 128.4; 128.8; 128.8; 129.7; 134.9; 139.6; 152.1; 159.7; 162.9.

Anal. Calcd for $C_{20}H_{19}NO_5$ (353.37): C, 67.98; H, 5.42; N, 3.96. Found: C, 67.93; H, 5.45; N, 3.93.

4.2.2. 2-Benzyl-3-(2,3-dimethoxyphenyl)-2,3-dihydroisoxazole-4,5-dicarboxylic acid dimethyl ester 2b. Yield 73%; oil; IR (KBr) $\nu_{C=O}$ 1750, 1710, $\nu_{C=C}$ 1654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.62 (3H, s), 3.72 (3H, s), 3.85 (3H, s), 3.92 (3H, s), 4.19 (1H, d, J=13.6), 4.36 (1H, d, J=13.6), 5.75 (1H, s), 6.84–6.88 (2H, m), 7.04 (1H, t, J=7.6), 7.27–7.39 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.1; 53.5; 56.0; 61.0; 63.0; 67.1; 108.9; 112.7; 120.1; 124.6; 128.1; 128.6; 129.8; 132.9; 135.4; 147.2; 152.7; 152.8; 159.8; 162.8.

Anal. Calcd for $C_{22}H_{23}NO_7$ (413.42): C, 63.91; H, 5.61; N, 3.39. Found: C, 63.90; H, 5.60; N, 3.42.

4.2.3. 2-Benzyl-3-(2-nitrophenyl)-2,3-dihydroisoxazole-4,5-dicarboxylic acid dimethyl ester 2c. Yield 85%; oil; IR (KBr) $\nu_{C=O}$ 1753, 1716, $\nu_{C=C}$ 1658 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.62 (3H, s), 3.92 (3H, s), 4.31 (1H, d, J=14.0), 4.41 (1H, d, J=14.0), 6.21 (1H, s), 7.29–7.46 (6H, m), 7.55–7.69 (2H, m), 7.88 (1H, d, J=8.4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.3; 53.7; 64.4; 67.6; 108.9; 124.7; 128.3; 128.7; 129.2; 129.7; 129.8; 133.8; 134.8; 134.9; 148.7; 153.3; 159.2; 162.2.

Anal. Calcd for $C_{20}H_{18}N_2O_7$ (398.37): C, 60.30; H, 4.55; N, 7.03. Found: C, 60.34; H, 4.57; N, 7.00.

4.2.4. 2-(2,3-Dimethoxybenzyl)-3-(2,3-dimethoxyphenyl)-2,3-dihydroisoxazole-4,5-dicarboxylic acid dimethyl ester 2d. Yield 96%; oil; IR (KBr) $\nu_{C=O}$ 1755,

1712, $\nu_{C=C}$ 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.63 (3H, s), 3.76 (3H, s), 3.77 (3H, s), 3.84 (3H, s), 3.85 (3H, s), 3.91 (3H, s), 4.23 (1H, d, J=13.6), 4.45 (1H, d, J=13.6), 5.81 (1H, s), 6.83–6.87 (3H, m), 6.97–7.04 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.0; 53.4; 56.0; 58.3; 61.0; 61.1; 67.5; 109.2; 112.3; 112.6; 120.2; 123.1; 124.1; 124.4; 129.6; 133.1; 147.3; 148.0; 152.6; 152.8; 152.9; 159.9; 162.9.

Anal. Calcd for $C_{24}H_{27}NO_9$ (473.47): C, 60.88; H, 5.75; N, 2.96. Found: C, 60.80; H, 5.79; N, 2.85.

4.2.5. 2-(2,3-Dimethoxybenzyl)-3-(2-nitrophenyl)-2,3-dihydroisoxazole-4,5-dicarboxylic acid dimethyl ester 2e. Yield 70%; oil; IR (KBr) $\nu_{C=O}$ 1753, 1717, $\nu_{C=C}$ 1657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.63 (3H, s), 3.80 (3H, s), 3.85 (3H, s), 3.91 (3H, s) 4.31 (1H, d, J=13.26), 4.53 (1H, d, J=13.26), 6.27 (1H, s), 6.85–6.90 (1H, m), 7.01–7.07 (2H, m), 7.41–7.45 (1H, m), 7.57–7.87 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.3; 53.5; 56.0; 58.6; 61.1; 67.8; 109.3; 112.6; 122.9; 124.1; 124.7; 128.5; 129.0; 129.1; 129.8; 131.2; 133.6; 133.7; 135.0; 148.1; 153.0; 153.0; 159.3; 162.3.

Anal. Calcd for $C_{22}H_{22}N_2O_9$ (458.42): C, 57.64; H, 4.84; N, 6.11. Found: C, 57.61; H, 4.89; N, 6.09.

4.2.6. 3-(3,4-Dimethoxyphenyl)-2-methyl-2,3-dihydroisoxazole-4,5-dicarboxylic acid dimethyl ester 2f. Yield 80%; oil; IR (KBr) $\nu_{C=O}$ 1752, 1714, $\nu_{C=C}$ 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.00 (3H, s), 3.66 (3H, s), 3.86 (3H, s), 3.88 (3H, s), 3.93 (3H, s), 4.77 (1H, s), 4.99 (1H, s), 6.83 (1H, d, J=8.8), 6.90–6.93 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.1; 51.9; 53.3; 55.8; 55.9; 76.0; 109.8; 110.2; 111.1; 119.7; 149.1; 149.2; 150.8; 159.5; 162.7.

Anal. Calcd for $C_{17}H_{21}NO_7$ (351.35): C, 58.11; H, 6.02; N, 3.99. Found: C, 58.13; H, 6.07; N, 3.88.

4.2.7. 2-(2,3-Dimethoxybenzyl)-3-phenyl-2,3-dihydroisoxazole-4,5-dicarboxylic acid dimethyl ester 2g. Yield 85%; oil; IR (KBr) $\nu_{C=O}$ 1750, 1706, $\nu_{C=C}$ 1654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.64 (3H, s), 3.76 (3H, s), 3.86 (3H, s), 3.91 (3H, s), 4.23 (1H, d, J=13.2), 4.35 (1H, d, J=13.2), 5.29 (1H, s), 6.86–6.88 (1H, m), 7.00–7.04 (2H, m), 7.26–7.31 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.1; 53.5; 56.0; 57.9; 61.2; 73.2; 109.7; 112.5; 123.1; 124.2; 127.6; 128.3; 128.6; 128.7; 129.0; 129.8; 140.0; 148.1; 151.97; 153.0; 159.8; 162.9.

Anal. Calcd for $C_{22}H_{23}NO_7$ (413.42): C, 63.91; H, 5.61; N, 3.39. Found: C, 63.94; H, 5.67; N, 3.35.

4.3. Synthesis of 2-benzyl-3-aryl-5-propylcarbamoyl-2,3-dihydroisoxazole-4-carboxylic acid methyl esters 3. General procedure

Propylamine (1.5 mmol) was added to a solution of isoxazoline **2** (0.5 mmol) in methanol and the reaction mixture was stirred at room temperature for 3 h. The solvent was evaporated under vacuum and the product was purified by preparative TLC.

4.3.1. 2-Benzyl-3-phenyl-5-propylcarbamoyl-2,3-dihydroisoxazole-4-carboxylic acid methyl ester 3a. Yield 42%; oil; IR (KBr) $\nu_{C=O}$ 1688, 1669, ν_{NH} 3283 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (3H, t, J=7.6), 1.64 (2H, hex, J=7.6), 3.40 (2H, m), 3.63 (3H, s), 4.12 (1H, d, J=13.26), 4.46 (1H, d, J=13.26), 5.86 (1H, s), 7.13–7.16 (2H, m), 7.24–7.36 (8H, m), 9.61 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8; 22.5; 41.8; 52.5; 63.0; 73.4; 107.1; 127.5; 128.2; 128.3; 128.7; 128.8; 129.9; 134.7; 140.4; 156.2; 156.6; 165.9.

Anal. Calcd for $C_{22}H_{24}N_2O_4$ (380.44): C, 69.46; H, 6.36; N, 7.36. Found: C, 69.50; H, 6.31; N, 7.40.

4.3.2. 2-Benzyl-3-(2,3-dimethoxyphenyl)-5-propylcarbamoyl-2,3-dihydroisoxazole-4-carboxylic acid methyl ester 3b. Yield 37%; oil; IR (KBr) $\nu_{C=O}$ 1688, 1669, ν_{NH} 3283 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (3H, t, J=7.6), 1.60 (2H, hex, J=7.6), 3.34–3.48 (2H, m), 3.56 (3H, s), 3.59 (3H, s), 3.84 (3H, s), 4.16 (1H, d, J=13.2), 4.37 (1H, d, J=13.2), 5.80 (1H, s), 6.75–6.85 (2H, m), 7.00 (1H, t, J=8.0), 7.27–7.40 (5H, m), 9.68 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8; 22.6; 41.8; 52.6; 55.9; 60.8; 63.4; 67.5; 106.6; 112.4; 120.2; 124.4; 128.1; 128.7; 130.2; 133.7; 135.0; 147.0; 152.7; 156.7; 165.9.

Anal. Calcd for $C_{24}H_{28}N_2O_6$ (440.49): C, 65.44; H, 6.41; N, 6.36. Found: C, 65.47; H, 6.43; N, 6.40.

4.3.3. 2-Benzyl-3-(2-nitrophenyl)-5-propylcarbamoyl-2,3-dihydroisoxazole-4-carboxylic acid methyl ester 3c. Yield 33%; oil; IR (KBr) $\nu_{C=O}$ 1694, 1678, ν_{NH} 3282 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.98 (3H, t, J=7.5), 1.63 (2H, hex, J=7.5), 3.40 (2H, m), 3.56 (3H, s), 4.30 (1H, d, J=13.26), 4.42 (1H, d, J=13.26), 6.28 (1H, s), 7.22–7.75 (9H, m), 9.64 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7; 22.5; 41.8; 52.8; 63.8; 67.6; 107.0; 124.1; 128.4; 128.7; 129.1; 130.1; 130.3; 133.7; 134.1; 135.7; 148.5; 156.1; 157.0; 165.0.

Anal. Calcd for $C_{22}H_{23}N_3O_6$ (425.43): C, 62.11; H, 5.45; N, 9.88. Found: C, 62.10; H, 5.48; N, 9.93.

4.3.4. 2-(2,3-Dimethoxybenzyl)-3-(2,3-dimethoxyphenyl)-5-propylcarbamoyl-2,3-dihydroisoxazole-4-carboxylic acid methyl ester 3d. Yield 40%; oil; IR (KBr) $\nu_{C=O}$ 1691, 1673, ν_{NH} 3287 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (3H, t, J=7.2), 1.64 (2H, hex, J=7.2), 3.40 (2H, m), 3.60 (3H, s), 3.66 (3H, s), 3.78 (3H, s), 3.83 (3H, s), 4.22 (1H, d, J=13.3), 4.42 (1H, d, J=13.3), 5.86 (1H, s), 6.75–6.78 (1H, m), 6.82–6.84 (2H, m), 6.96–7.05 (3H, m), 9.61 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7; 22.6; 41.7; 52.5; 55.9; 56.0; 57.5; 60.9; 61.2; 68.0; 106.7; 112.4; 120.3; 123.7; 124.2; 124.4; 129.2; 133.9; 147.1; 148.1; 152.8; 152.9; 156.7; 156.9; 165.9.

Anal. Calcd for $C_{26}H_{32}N_2O_8$ (500.54): C, 62.39; H, 6.44; N, 5.60. Found: C, 62.43; H, 6.45; N, 5.65.

4.3.5. Methyl 2-(2,3-dimethoxybenzyl)-3-(2-nitrophenyl)-5-(propylcarbamoyl)-2,3-dihydroisoxazole-4-carboxylate 3e. Yield 30%; oil; IR (KBr) $\nu_{C=O}$ 1694, 1678, ν_{NH} 3280 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.96 (3H, t,

J=7.41), 1.61 (2H, hex, J=7.41), 3.34 (2H, m), 3.63 (3H, s), 3.81 (3H, s), 3.83 (3H, s), 4.25 (1H, d, J=13.3), 4.52 (1H, d, J=13.3), 6.31 (1H, s), 6.85 (1H, m), 6.86–7.02 (2H, m), 7.37–7.77 (4H, m), 9.40 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7; 22.5; 41.8; 53.1; 56.0; 57.8; 61.2; 68.1; 107.0; 112.7; 123.5; 124.2; 124.3; 128.5; 129.0; 130.1; 133.6; 135.6; 148.1; 148.6; 152.9; 156.4; 157.1; 164.9.

Anal. Calcd for $C_{24}H_{27}N_3O_8$ (485.49): C, 59.37; H, 5.61; N, 8.66. Found: C, 59.39; H, 5.63; N, 8.73.

4.3.6. 2-(2,3-Dimethoxybenzyl)-3-phenyl-5-propylcarbamoyl-2,3-dihydroisoxazole-4-carboxylic acid methyl ester 3g. Yield 42%; oil; IR (KBr) $\nu_{C=O}$ 1691, 1672, ν_{NH} 3280 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (3H, t, J=7.5), 1.63 (2H, hex, J=7.5), 3.40 (2H, m), 3.63 (3H, s), 3.76 (3H, s), 3.85 (3H, s), 4.24 (1H, d, J=12.9), 4.43 (1H, d, J=12.9), 5.35 (1H, s), 6.86 (1H, m), 7.00 (2H, m), 7.19–7.25 (5H, m), 9.69 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.8; 22.5; 41.8; 52.5; 56.0; 57.0; 61.3; 73.7; 107.3; 112.4; 123.5; 124.3; 127.6; 128.2; 128.6; 128.8; 140.8; 148.1; 152.9; 156.1; 156.8; 166.0.

Anal. Calcd for $C_{24}H_{28}N_2O_6$ (440.49): C, 65.44; H, 6.41; N, 6.36. Found: C, 65.45; H, 6.48; N, 6.31.

4.3.7. 4-Hydroxy-1-(methoxyphenylmethyl)-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylic acid methyl esters 10 and 11. Yield 55%; mp 132 °C; IR (KBr) $\nu_{C=O}$ 1694; 1678, ν_{OH} 3282 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.13 (3H, s, CHOMe), 3.45 (3H, s, CHOMe), 3.56 (3H, s, CO_2Me), 3.62 (3H, s, CO_2Me), 4.71 (1H, s, C-3H), 5.27 (1H, s, C-3H), 6.40 (2H, s, MeOC*H*N), 6.76–6.78 (2H, m), 6.87–6.94 (6H, m), 7.00–7.03 (3H, m), 7.22–7.29 (6H, m), 7.36–7.38 (3H, m), 9.0 (2H, br s, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.2, MeO, ether; 52.2, MeO, ester; 56.1, MeO, ester; 57.0, MeO, ester; 57.8, C-3; 58.4, C-3, 84.28, NCO; 84.33, N*C*O; 114.1, C-4; 114.6, C-4; 126.2; 126.5; 127.7; 127.8; 127.9; 128.0; 128.4; 128.6; 128.7; 128.8; 134.9; 135.8; 136.3; 137.7; 156.5, C-5; 156.6, C-5; 165.6, C=O, 165.7, C=O; 165.8, C=O; 165.9, C=O.

Anal. Calcd for $C_{20}H_{19}NO_5$ (353.37): C, 67.98; H, 5.42; N, 3.96. Found: C, 67.95; H, 5.40; N, 3.93.

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