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4-Isoxazolines and pyrroles from allenoates

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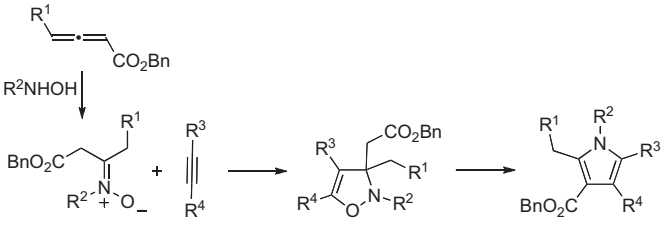
ABSTRACT

The synthesis of 4-isoxazolines via 1,3-dipolar cycloaddition of nitrones generated from allenoates and the subsequent thermal rearrangement to pyrroles is reported. The selection of the reaction conditions allowed the isolation of the initial 1,3-dipolar cycloadducts, the 4-isoxazolines, or the pyrrole derivatives. The isomerization of the parent system (4-isoxazoline) was examined by carrying out quantum chemical calculations and corroborated the favourability of the 4-isoxazoline rearrangement to five-membered heterocycles via 2-acylaziridine intermediates.

1. Introduction

Allenes are particularly interesting molecules due to the inherent instability associated to the cumulated double bonds, which has been explored for various synthetic purposes.[1–5] Despite various known contributions to the chemistry of these building blocks, their use in 1,3-dipolar cycloadditions either as dipolarophiles or 1,3-dipole precursors is a less explored research area.[5] Nevertheless, allenes have been used to generate cyclic and acyclic nitrones through the reaction with hydroxylamines.[6] On the other hand, the main strategy to obtain 4-isoxazolines (2,3-dihydroisoxazoles) has been the 1,3-dipolar cycloaddition between nitrones and alkynes or allenes.[7–9] These heterocycles are also particularly interesting synthons for cyclic and acyclic compounds due to their readiness to undergo rearrangement reactions; the driving force being the relatively low thermochemical stability of the N–O bond. The most general reactivity pattern of 4-isoxazolines is the thermal isomerization to 2-acylaziridines. The azomethine ylides generated via conrotatory aziridine ring opening can undergo a proton shift followed by cyclization leading to pyrroles.[7,8,10] The development of synthetic routes to pyrroles is also a relevant research goal since these compounds represent an important class of heterocycles due to their broad distribution in nature as constituents of the framework of a range of natural products and also of synthetic bioactive molecules.[11]

We have been interested in the use of allenes as starting materials for the preparation of acyclic and cyclic derivatives.[12] In this context, we decided to further explore the synthesis of 4-isoxazolines via 1,3-dipolar cycloaddition of nitrones generated from allenoates and the subsequent thermal rearrangement to pyrrole derivatives (Scheme 1).



Scheme 1.

2. Results and discussion

Buta-2,3-dienoates **1**[13] were efficiently converted into the corresponding nitrones **2** upon reaction with *N*-methylhydroxylamine hydrochloride at room temperature in the presence of triethylamine (Scheme 2). The isolation of the nitrones did not required further purification other than washing the organic phase with water followed by evaporation of the dichloromethane. Triethylamine can be replaced by sodium hidrogenocarbonate making the isolation of the nitrones even easier, only filtration of the reaction mixture followed by evaporation of the organic solvent is required.

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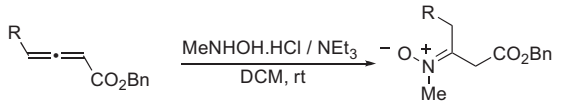
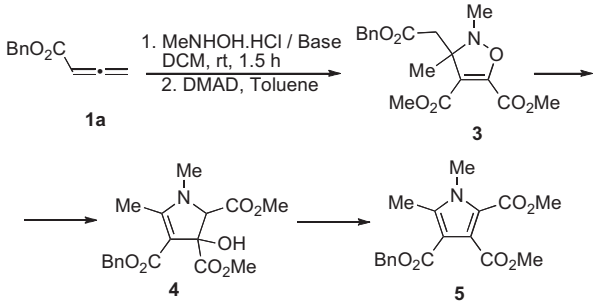


1a R = H
1b R = Me
1c R = Ph

2a R = H 86%
2b R = Me 88%
2c R = Ph 89%

Scheme 2.

The reactivity of nitrone **2a**, generated from allene **1a**, towards dimethyl acetylenedicarboxylate (DMAD) was explored (Table 1). Carrying out the reaction at room temperature for 15 min the corresponding 1,3-dipolar cycloadduct **3** was isolated as single product in 66% overall yield (entry 1). The same 4-isoxazoline was obtained in slightly lower yield performing the reaction at 50 °C for 1 h (entry 2). Interestingly, the condensation of nitrone **2a** with DMAD at 120 °C afforded 3-hydroxy-2,3-dihydro-1*H*-pyrrole **4** as the only product (entry 3).



1a **3** **4** **5**

Table 1
Reaction of nitrone **2a** with DMAD

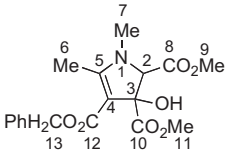
Entry	Reaction conditions (Second step)	Products (overall yield %)
1	Rt, 15 min	**3** (66%)
2	50 °C, 1 h	**3** (59%)
3	120 °C, 3 h	**4** (45%)
4	MW, 40 °C, 1 min	**3** (57%)
5	MW, 50 °C, 1 min	**3** (60%)
6	MW, 60 °C, 1 min	**3** (78%)+**4** (3%)
7	MW, 150 °C, 1 h	**4** (25%)+**5** (32%)
8	MW, 200 °C, 15 min[a]	**5** (46%)
9	MW, 250 °C, 5 min[a]	**5** (43%)

[a] Carried out in trichlorobenzene.

^{1}H NMR and ^{13}C NMR data of compound **4**, are collected in Table 2. The assignment was supported by a two-dimensional HMQC spectrum (400 MHz). The assignment of the hydroxylic proton of alcohol **4** in the ^{1}H NMR spectrum was confirmed by a D_2O exchange experiment.

The reaction of nitrone **2a** with DMAD under microwave irradiation was also explored (Table 1). Carrying out the microwave-assisted reaction at 40 °C for just 1 min afforded 4-isoxazoline **3** in 57% yield, whereas, at 50 °C the same heterocycle was obtained in 60% yield (Entries 4 and 5). The irradiation at 60 °C for 1 min led to 4-isoxazoline **3** as the major product (78%) together with the formation of 2,3-dihydro-1*H*-pyrrole **4** in 3% yield (entry 6). At higher temperature and longer reaction time (150 °C, 1 h) the products were 2,3-dihydro-1*H*-pyrrole **4** (25%) and 1*H*-pyrrole **5** (32%) (entry 7). The irradiation at higher temperature (200–250 °C, 5–15 min) using trichlorobenzene as solvent allowed the synthesis of 1*H*-pyrrole **5** as the only product (Entries 8 and 9).

Table 2
^{1}H and ^{13}C NMR data for 2,3-dihydro-1*H*-pyrrole **4**[a]



4

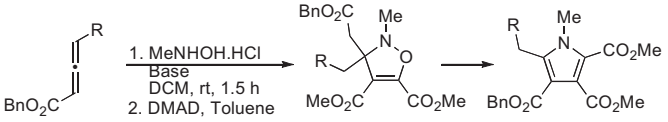
C	^{1}H (ppm)	^{13}C (ppm)
C-6	2.36 (s, 3H)	12.6
C-7	2.93 (s, 3H)	32.5
C-9	3.65 (s, 3H)	52.4
C-11	3.78 (s, 3H)	53.4
C-2	4.43 (s, 1H)	74.3
C-13	5.00 (d, 1H, *J*=12.4 Hz)	64.8
	5.21 (d, 1H, *J*=12.4 Hz)	
C-3	—	81.1
C-4	—	100.5
C-5	—	164.4

[a] Chemical shifts of the phenyl group and the carbonyl carbons are not included.

2,3-Dihydro-1*H*-pyrrole **4** could also be prepared in 56% yield by heating at 120 °C a solution of 4-isoxazoline **3** in toluene for 8 h. On the other hand, compound **4** undergoes dehydration in refluxing toluene to give pyrrole **5** in 69% yield. These results allowed to conclude that 2,3-dihydro-1*H*-pyrrole **4** results from the thermal rearrangement of 4-isoxazoline **3** and is an intermediate of the 4-isoxazoline-pyrrole rearrangement.

The work was extended to the reaction of allenes **1b** and **1c** with *N*-methylhydroxylamine to generate the corresponding nitrones followed by cycloaddition with DMAD (Table 3). Carrying out the cycloaddition of nitrone **2b** at room temperature for 30 min 4-isoxazoline **6a** was isolated in 42% overall yield (entry 1). A slight decrease in yield was observed when the reaction was performed at room temperature with a longer reaction time (entry 2). The reaction of nitrone **2b** with DMAD at 120 °C for 20 h gave pyrrole **7a** in modest yield (entry 3). More efficient process was achieved under microwave irradiation. Isoxazoline **6a** could be obtained in 56% overall yield via microwave-induced cycloaddition at 60 °C for just 1 min (entry 4). On the other hand, pyrrole **7a** was isolated as single product in 35% yield carrying out the microwave irradiation at 200 °C for 15 min (entry 5). In this case, no evidence of the formation of the 3-hydroxy-2,3-dihydro-1*H*-pyrrole that would result from the thermal rearrangement of 4-isoxazoline **6a** was observed.

Table 3
Reaction of nitrones **2b** and **2c** with DMAD



1b R = Me
1c R = Ph

6a R = Me
6b R = Ph

7a R = Me
7b R = Ph

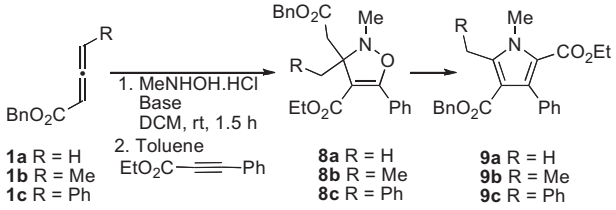
Entry	Allene	Reaction conditions (Second step)	Product (overall yield %)
1	**1b**	rt, 30 min	**6a** (42%)
2	**1b**	rt, 2 h	**6a** (38%)
3	**1b**	120 °C, 20 h	**7a** (18%)
4	**1b**	MW, 60 °C, 1 min	**6a** (56%)
5	**1b**	MW, 200 °C, 15 min[a]	**7a** (35%)
6	**1c**	rt, 1 h	**6b** (55%)
7	**1c**	rt, 4 h	**6b** (28%)
8	**1c**	120 °C, 24 h	**7b** (37%)
9	**1c**	MW, 60 °C, 1 min	**6b** (52%)
10	**1c**	MW, 200 °C, 15 min[a]	**7b** (39%)

[a] Carried out in trichlorobenzene.

The reaction of nitrone **2c** with DMAD carried out at room temperature for 1 h afforded 4-isoxazoline **6b** in 55% overall yield (entry 6), whereas, with a longer reaction time the same product was obtained in lower yield (entry 7). Under conventional thermolysis the cycloaddition led to pyrrole **7b** in 37% yield (entry 8). The microwave-induced reaction allowed the selective synthesis of 4-isoxazoline **6b** or pyrrole **7b** depending on the reaction conditions (Entries 9 and 10).

The behaviour of nitrones **2** towards ethyl phenylpropiolate was then studied (Table 4). The room temperature cycloaddition of nitrone **2a** led to 4-isoxazoline **8a** in a regioselective fashion (Entries 1 and 2). Carrying the reaction at 50 °C for 17 h, the same product was obtained in 54% yield (entry 3). However, at higher temperature (120 °C) pyrrole **9a** was obtained as single product in good overall yield (Entries 4 and 5). Microwave-assisted cycloaddition for a period of 10 min at 60 °C, followed by irradiation at 120 °C for 3 min allowed the synthesis of 4-isoxazoline **8a** in 79% yield (entry 7). Under microwave irradiation at 120 °C for 4 min the reaction of nitrone **2a** with ethyl phenylpropiolate gave 4-isoxazoline **8a** in lower yield (entry 8). Pyrrole **9a** could be obtained selectively in 62% overall yield carrying out the microwave-induced reaction at 200 °C for 15 min (entry 9). The structural assignment of pyrrole **9a** was confirmed by a NOESY experiment. In fact, in the NOESY spectrum no connectivity was observed between the methyl protons at N-1 and the phenyl protons at C-3.

Table 4
Reaction of nitrones **2a**, **2b** and **2c** with ethyl phenylpropiolate



1a R = H
1b R = Me
1c R = Ph

8a R = H
8b R = Me
8c R = Ph

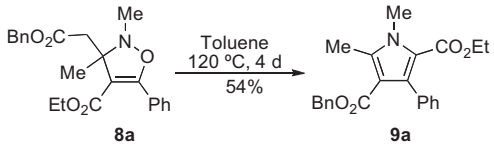
9a R = H
9b R = Me
9c R = Ph

Entry	Allene	Reaction conditions (Second step)	Product (overall yield %)
1	**1a**	rt, 48 h[a]	**8a** (59%)
2	**1a**	rt, 6 d[b]	**8a** (35%)
3	**1a**	50 °C, 17 h[b]	**8a** (54%)
4	**1a**	120 °C, 48 h[a]	**9a** (57%)
5	**1a**	60 h, 120 °C [b]	**9a** (38%)
7	**1a**	MW, 60 °C, 10 min+120 °C, 3 min[a]	**8a** (79%)
8	**1a**	MW, 120 °C, 4 min[a]	**8a** (44%)
9	**1a**	MW, 200 °C, 15 min[a,c]	**9a** (62%)
10	**1b**	120 °C, 48 h[a]	**8b** (25%)
11	**1b**	120 °C, 5 d[a]	**8b** (25%)+**9b** (13%)
12	**1b**	MW, 60 °C, 10 min+120 °C, 3 min[a]	**8b** (24%)
13	**1b**	MW, 120 °C, 10 min	**8b** (28%)
14	**1b**	MW, 200 °C, 15 min[a,c]	**9b** (36%)
15	**1c**	120 °C, 3.5 h[a]	**8c** (36%)
16	**1c**	MW, 120 °C, 5 min	**8c** (37%)
17	**1c**	MW, 200 °C, 15 min[a,c]	**9c** (26%)

[a] 1.5 equiv of ethyl phenylpropiolate.
[b] 1 equiv of ethyl phenylpropiolate.
[c] Carried out in trichlorobenzene.

Pyrrole **9a** was also obtained by thermolysis of 4-isoxazoline **8a**. In fact, heating at reflux a solution of compound **8a** in toluene afforded pyrrole **9a** in 54% yield via the 4-isoxazoline-pyrrole rearrangement (Scheme 3).

Nitrone **2b** also reacted with ethyl phenylpropiolate in a regioselective fashion (Table 4). In this case, the reaction carried out at room temperature did not lead to the expected 1,3-dipolar cycloadduct. However, 4-isoxazoline **8b** could be isolated in 25% overall yield when the reaction was performed at 120 °C for 48 h (entry



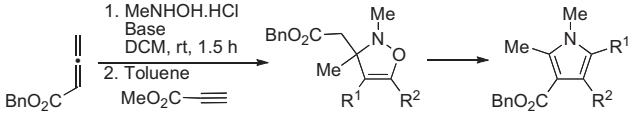
8a **9a**

Scheme 3.

10). The thermolysis at 120 °C for 5 d afforded 4-isoxazoline **8b** and pyrrole **9b** in 25% and 13% yield, respectively (entry 11). Selecting the appropriated reaction conditions the microwave-induced cycloaddition of **2b** with ethyl phenylpropiolate allowed the selective synthesis of either 4-isoxazoline **8b** or pyrrole **9b** (Entries 12–14). The reactivity of nitrone **2c** in the presence of ethyl phenylpropiolate was also studied. 4-Isoxazoline **8c** could be obtained in moderate yield carrying out the reaction under conventional heating or under microwave irradiation (Entries 15 and 16). The microwave-assisted reaction of nitrone **2c** performed at 200 °C for 15 min afforded to pyrrole **9c** in 26% yield (entry 17).

The reaction of nitrone **2a**, generated from allenoate **1a**, with methyl propiolate was explored (Table 5). Interestingly, the room temperature cycloaddition led to pyrrole **11b** as single regioisomer (Entries 1 and 2), whereas, at 120 °C pyrrole **11a** was the major product or even the only product. In fact, with a reaction time of 2.5 h **11a** was isolated in 58% yield together with the pyrrole **11b** in 9% yield (entry 4) and with a longer reaction time only pyrrole **11a** was formed in 58% yield (entry 5). Carrying out the cycloaddition at 50 °C for 2 h a mixture of isoxazolines **10** was obtained (entry 3). These isoxazolines showed low stability on standing at room temperature. These results indicate that the 1,3-dipolar cycloaddition of nitrone **2a** with methyl propiolate leads to a mixture of regioisomeric 4-isoxazolines. However, due to the lack of stability of the cycloadducts and with the appropriate reaction conditions pyrrole **11a** or **11b** can be isolated as single products. Another conclusion can be drawn, 4-isoxazoline **10b** is less stable than **10a**, since higher temperature favours the synthesis of pyrrole **11a** (Entries 4 and 5). In line with this observation, from the microwave-assisted cycloaddition only pyrrole **11a** could be isolated. In fact, although microwave irradiation at 50 °C for 2 min gave isoxazolines **10** (entry 6) at 60 °C with 1 min irradiation time, isoxazolines were formed together with pyrrole **11a** (entry 7) and at higher temperature only pyrrole **11a** was isolated (entry 8 and 9).

Table 5
Reaction of nitrone **2a** with methyl propiolate



1a

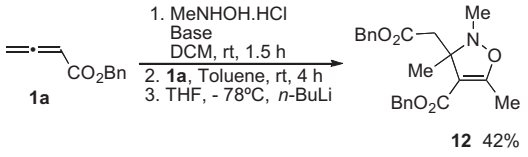
10a R^1 = CO_2Me; R^2 = H **11a** R^1 = CO_2Me; R^2 = H
10b R^1 = H; R^2 = CO_2Me **11b** R^1 = H; R^2 = CO_2Me

Entry	Reaction conditions (Second step)	Products (overall yield %)
1	6.5 h, rt	**11b** (43%)
2	6 d, rt	**11b** (31%)
3	2 h, 50 °C	**10a**/**10b** (40%)
4	2.5 h, 120 °C	**11a** (58%)+**11b** (9%)
5	20 h, 120 °C	**11a** (58%)
6	MW, 50 °C, 2 min	**10a**/**10b** (47%)
7	MW, 60 °C, 1 min	**10a**/**10b** (32%)+**11a** (14%)
8	MW, 150 °C, 15 min	**11a** (23%)
9	MW, 200 °C, 15 min[a]	**11a** (35%)

[a] Carried out in trichlorobenzene.

In the NOESY spectrum of pyrrole **11b** connectivity was observed between the methyl protons at N-1 and the proton at C-5 confirming the structural assignment.

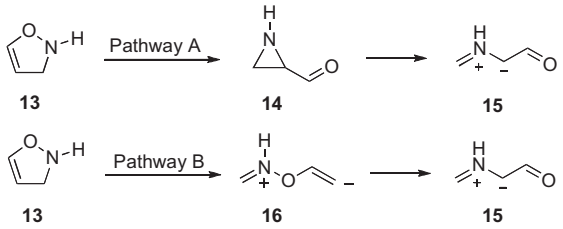
The 1,3-dipolar cycloaddition of nitrone **2a** with butadienoate **1a** was also examined (Scheme 4). Carrying out the reaction in refluxing toluene led to a complex mixture. Padwa et al. have described the reaction of *N*-methyl-*C*-phenylnitrone with allenes and observed the formation of estereoisomeric mixtures of methyleneisoxazolidine derivatives, which undergo rearrangement to corresponding 4-isoxazoles on treatment with *n*-butyllithium.[14] Accordingly, the reaction of nitrone **2a** with butadienoate **1a** was performed at room temperature for 4 h, followed by treatment with a solution of *n*-butyllithium in hexane, which gave the corresponding 4-isoxazoline **12** in a regioselective fashion in 42% overall yield.



Scheme 4.

The formation of 4-isoxazolines and pyrroles from allenoates can be explained as outlined in Scheme 5. The initial 1,3-dipolar cycloaddition of the nitrones generated from allenoates affords the target 4-isoxazolines. These heterocycles undergo thermal rearrangement isomerization to 2-acylaziridines via N–O bond cleavage. The corresponding azomethine ylides, generated via conrotatory aziridine ring opening undergo a proton shift followed by 5-*exo*-*trig* cyclization leading to 2,3-dihydro-1*H*-pyrroles, which are converted into 1*H*-pyrroles via dehydration.

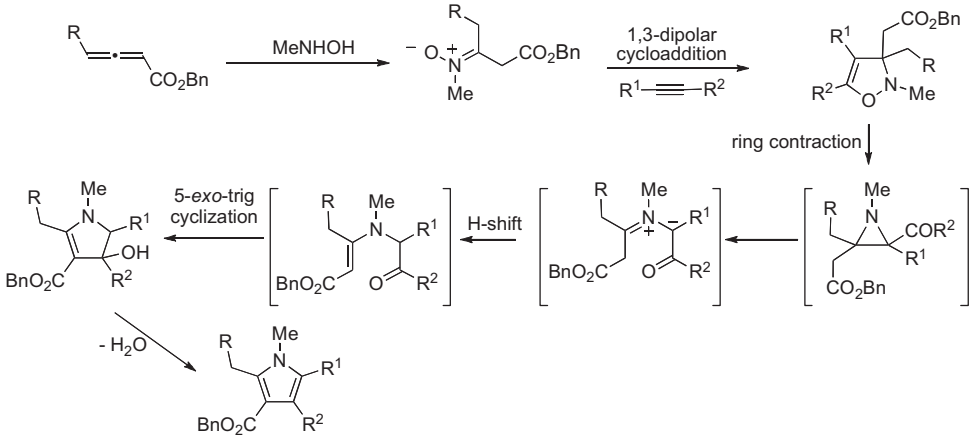
The two possible pathways depicted in Scheme 6. However, transition states could only be found for the pathway involving the generation of 2-acylaziridine **14** (pathway A).



Scheme 6.

The quantum chemical calculations were performed with Gaussian 03[16] at the DFT level of theory, using the standard 6-31G* basis set[17] and the three-parameter density functional B3LYP, which includes Becke's gradient exchange correction[18] and the Lee, Yang and Parr correlation functional.[19] Full geometry optimizations were performed for molecules **13**–**15** and true minima were confirmed through vibrational analysis. Four different conformers were found for structures **14** and **15** by performing relaxed scans on the potential energy surface along the relevant coordinates. An exhaustive transition state search was carried out, with the eigenvector following (EF) option, between all minima found in the potential energy surface. All transition states found were characterized by having only one imaginary frequency (see Supplementary data). The calculations of the intrinsic reaction coordinate (IRC) were performed to check whether the transition states under consideration connect the expected reactants and products.

The potential energy profile for thermal isomerization of 4-isoxazoline (**13**) to azomethine ylide **15** is shown in Figure 1.



Scheme 5.

This is the most general reactivity pattern of 4-isoxazolines bearing a methyl or methylene group at C-3. However, thermally induced conversion of 4-isoxazolines into azomethine ylides via an alternative mechanism has been proposed. In fact, the formation of stable azomethine ylides from isoxazolo[3,2-*a*]isoquinolines has been rationalized considering a mechanism involving consecutive C3–C4 bond heterolysis and 1,3-sigmatropic shift rather than the accepted mechanism pathway involving acylaziridines as intermediates.[15]

Therefore, we decided to study the isomerization of the parent system **13** carrying out quantum chemical calculations, conducting a very thorough search for the transition states corresponding to

As it can be seen, the ring contraction of 4-isoxazoline to 2-acylaziridine is a very favourable process. On the other hand, the aziridine and the 1,3-dipole resulting from the aziridine ring opening have similar potential energy. The generation of the azomethine ylide is always followed by a stabilizing process either a ring closure to oxazoline or a proton shift followed by cyclization leading to pyrroles (for derivatives having a methyl or methylene group at C-4).[7] Thus, the quantum chemical calculations corroborate the favourability of the 4-isoxazoline rearrangement to five-membered heterocycles via 2-acylaziridine intermediates.

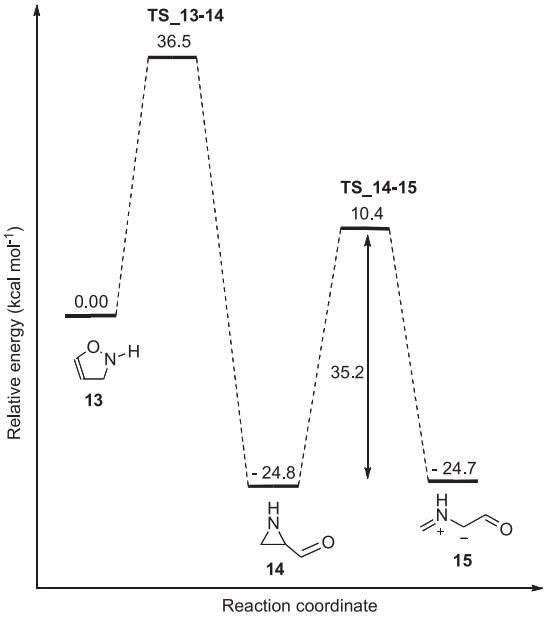


Figure 1. Potential energy profile for thermal isomerization of 4-isoxazoline **13** to azomethine ylide **15** calculated at B3LYP/6-31G* level of theory.

3. Conclusion

A deeper insight into the synthesis of 4-isoxazolines via 1,3-dipolar cycloaddition of nitrones generated from allenoates and the subsequent thermal rearrangement to pyrroles is reported. The cycloaddition of nitrones and alkynes carried out under mild conditions led to 4-isoxazolines, whereas, forcing the reaction conditions the corresponding pyrroles are obtained. The synthetic methodology was successful using conventional reaction conditions or under microwave irradiation.

Quantum chemical calculations indicate the favourability of the parent system (4-isoxazoline) rearrangement to five-membered heterocycles via 2-acylaziridine intermediates.

4. Experimental section

4.1. General

^{1}H NMR spectra were recorded on a Bruker Avance III instrument operating at 400 MHz. ^{13}C NMR spectra were recorded on a Bruker Avance III instrument operating at 100 MHz. The solvent is deuteriochloroform. IR spectra were recorded on a Perkin Elmer 1720X FTIR spectrometer. Mass spectra were recorded under electron impact (EI) or electrospray ionization (ESI). HRMS spectra were recorded on a Finnigan MAT95 S instrument. Mp were recorded on a Reichert hot stage and are uncorrected. Flash column chromatography was performed with Merck 9385 silica as the stationary phase.

4.2. General procedure for the synthesis of nitrones 2

To a stirred solution of allene (1.15 mmol) and *N*-methylhydroxylamine hydrochloride (1.26 mmol) in CH_2Cl_2 (40 mL) triethylamine (2.87 mmol) or $NaHCO_3$ (11.5 mmol) was added at room temperature. The reaction mixture was stirred for 90 min (synthesis of nitrones **2a** and **2b**) or stirred overnight (synthesis of nitrone **2c**). The organic layer was washed with water, dried over anhydrous Na_2SO_4 and the solvent evaporated off to give nitrones **2**, which were used without purification.

*4.2.1. Nitrone **2a**.* Nitrone **2a** was obtained as a colourless oil (86%); ^{1}H NMR 2.16 (3H, s), 3.62 (2H, s), 3.73 (3H, s), 5.16 (2H, s), 7.27–7.37 (5H, m, Ar*H*); ^{13}C NMR 19.7, 38.4, 47.7, 66.9, 128.3, 128.4, 128.6, 128.8, 135.6, 168.3.

*4.2.2. Nitrone **2b**.* Nitrone **2b** was obtained as a colourless oil (88%); ^{1}H NMR 1.14 (3H, t, *J*=7.6 Hz), 2.41 (1H, q, *J*=7.6 Hz), 2.61–2.91 (1H, m), 2.27 (1H, br d), 3.55 (1H, br s), 3.72 (3H, s), 5.16 (2H, s), 7.27–7.36 (5H, m, Ar*H*).

*4.2.3. Nitrone **2c**.* Nitrone **2c** was obtained as a colourless oil (89%); ^{1}H NMR 3.51 (2H, br s), 3.82 (3H, s), 3.86 (2H, s), 5.12 (2H, s), 7.12–7.43 (10H, m, Ar*H*).

4.3. General procedure for the synthesis of 4-isoxazoles and pyrroles from allenoates

Method A. Nitrone **2** (1 mmol) was dissolved in toluene (5 mL) and the appropriate dipolarophile (1.73 mmol) was added. The mixture was then stirred at room temperature or at reflux and the reaction monitored by TLC. After the reaction was completed, the solvent was evaporated off and the product purified by flash chromatography [ethyl acetate/hexane].

Method B. A solution of nitrone **2** (1 mmol) in toluene or 1,2,4-TCB (2 mL) and the appropriate dipolarophile (1.73 mmol) was irradiated in a microwave reactor (CEM Focused Synthesis System, Discover S-Class) for 1 min with the temperature set to 60 °C for the synthesis of 4-isoxazolines **3** and **6**, 4–10 min at 120 °C for compounds **8**, 2 min at 50 °C for compounds **10** and 15 min at 200 °C for pyrroles **5**, **7**, **9** and **11a**. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography [ethyl acetate/hexane].

*4.3.1. Dimethyl 3-(2-(benzyloxy)-2-oxoethyl)-2,3-dimethyl-2,3-dihydroisoxazole-4,5-dicarboxylate (**3**).* Compound **3** was purified by flash chromatography [ethyl acetate/hexane (1:2)] and obtained as an oil. Yield: *Method A* 66% and *Method B* 78%. IR (film) 1117, 1209, 1318, 1437, 1648, 1713, 1739, 2954 cm^{-1}; ^{1}H NMR 1.52 (3H, s), 2.71 (1H, d, *J*=14.4 Hz), 2.82 (3H, s), 2.98 (1H, d, *J*=14.4 Hz), 3.68 (3H, s), 3.86 (3H, s), 5.11 (2H, s), 7.26–7.37 (5H, m, Ar*H*); ^{13}C NMR 19.1, 39.0, 42.8, 51.7, 53.1, 65.4, 66.5, 71.5, 112.6, 126.9, 128.1, 128.3, 128.5, 128.6, 135.8, 151.7, 159.6, 162.9, 169.6; MS (ESI) *m*/*z* 364 (MH^+, 34%), 315 (2) and 229 (2). HRMS (ESI) *m*/*z* 364.13759 ($C_{18}H_{22}NO_7$ [MH^+], 364.13908).

*4.3.2. 4-Benzyl 2,3-dimethyl 3-hydroxy-1,5-dimethyl-2,3-dihydro-1H-pyrrole-2,3,4-tricarboxylate (**4**).* Compound **4** was purified by flash chromatography [ethyl acetate/hexane (1:1)] and obtained as a white solid. Yield: *Method A* 56%. Mp 141.8–143.0 °C (from ethyl acetate/hexane). IR (KBr) 1169, 1216, 1594, 1680, 1745, 3485 cm^{-1}; ^{1}H NMR 2.36 (3H, s), 2.93 (3H, s), 3.65 (3H, s), 3.78 (3H, s), 3.96 (1H, s, O*H*), 4.44 (1H, s), 5.00 (1H, d, *J*=12.4 Hz), 5.21 (1H, d, *J*=12.4 Hz), 7.26–7.35 (5H, m, Ar*H*); ^{13}C NMR 12.6, 32.5, 52.4, 53.4, 60.4, 64.8, 74.3, 81.1, 100.5, 127.8, 128.1, 128.4, 136.9, 164.5, 165.0, 166.9, 173.8; MS (ESI) *m*/*z* 364 (MH^+, 30%), 346 (14) and 315 (6). HRMS (ESI) *m*/*z* 364.13989 ($C_{18}H_{22}NO_7$ [MH^+], 364.13908).

*4.3.3. 4-Benzyl 2,3-dimethyl 1,5-dimethyl-1H-pyrrole-2,3,4-tricarboxylate (**5**).* Compound **5** was purified by flash chromatography [ethyl acetate/hexane (1:1)] and obtained as a white solid. Yield: *Method B* 46%. Mp 103.8–104.9 °C (from ethyl acetate/hexane). IR (KBr) 1113, 1157, 1259, 1553, 1701, 1743 cm^{-1}; ^{1}H NMR 2.56 (3H, s), 3.57 (3H, s), 3.79 (3H, s), 3.84 (3H, s), 5.23 (2H, s), 7.32–7.38 (5H, m, Ar*H*); ^{13}C NMR 11.4, 32.7, 51.8, 52.3, 66.3, 110.3, 119.1, 125.8, 128.2, 128.4, 128.5, 135.8, 141.7, 160.3, 163.1, 166.8; MS (EI) *m*/*z* 345 (M^+,

11%), 238 (100), 222 (67), 211 (20), 180 (27), 149 (21) and 91 (85). HRMS (EI) *m/z* 345.1205 ($C_{18}H_{19}NO_6$ [M^+], 345.3466).

*4.3.4. Dimethyl 3-(2-benzyloxy-2-oxoethyl)-3-ethyl-2-methyl-2,3-dihydroisoxazole-4,5-dicarboxylate (**6a**).* Compound **6a** was purified by flash chromatography [ethyl acetate/hexane (1:2)] and obtained as an oil. Yield: *Method A* 42% and *Method B* 56%. IR (film) 699, 1112, 1170, 1317, 1437, 1646, 1712, 1751, 3447 cm^{-1}; ^1H NMR 0.97 (3H, t, *J*=7.6 Hz), 1.73–1.82 (1H, m), 1.92–2.01 (1H, m), 2.74 (1H, d, *J*=14.8 Hz), 2.91 (3H, s), 2.97 (1H, d, *J*=14.8 Hz), 3.65 (3H, s), 3.86 (3H, s), 5.09 (2H, s), 7.29–7.37 (5H, m, Ar*H*); ^{13}C NMR 8.9, 28.5, 38.3, 39.6, 51.7, 53.1, 53.5, 66.6, 74.7, 110.6, 128.2, 128.3, 128.5, 135.7, 152.0, 159.5, 163.1, 169.9; MS (ESI) *m/z* 378 (MH^+, 100%), 306 (12), 288 (8) and 233 (6). HRMS (ESI) *m/z* 378.15549 ($C_{19}H_{24}NO_7$ [MH^+], 378.15473).

*4.3.5. Dimethyl 3-benzyl-3-(2-benzyloxy-2-oxoethyl)-2-methyl-2,3-dihydroisoxazole-4,5-dicarboxylate (**6b**).* Compound **6b** was purified by flash chromatography [ethyl acetate/hexane (1:2)] and obtained as oil. Yield: *Method A* 55% and *Method B* 52%. IR (film) 700, 1101, 1167, 1313, 1437, 1717, 1734, 1752, 2953 cm^{-1}; ^1H NMR 2.77 (3H, s), 2.81 (1H, d, *J*=15.6 Hz), 3.07 (1H, d, *J*=15.6 Hz), 3.17 (2H, s), 3.58 (3H, s), 3.84 (3H, s), 5.10 (2H, s), 7.23–7.37 (10H, m, Ar*H*); ^{13}C NMR 37.4, 39.4, 43.4, 51.6, 53.1, 66.8, 74.3, 111.1, 126.8, 128.0, 128.3, 128.4, 128.5, 131.0, 135.5, 135.6, 152.1, 159.5, 163.1, 170.0. MS (ESI) *m/z* 440 (MH^+, 39%) and 201 (4). HRMS (ESI) *m/z* 440.17033 ($C_{24}H_{26}NO_7$ [MH^+], 440.17038).

*4.3.6. 4-Benzyl 2,3-dimethyl 5-ethyl-1-methyl-1H-pyrrole-2,3,4-tricarboxylate (**7a**).* Compound **7a** was purified by flash chromatography [ethyl acetate/hexane (1:2)] and obtained as a white solid. Yield: *Method A* 18% and *Method B* 35%. Mp 60.1–61.3 °C (from ethyl acetate/hexane). IR (KBr) 759, 1154, 1219, 1259, 1476, 1706, 1733 cm^{-1}; ^1H NMR 1.16 (3H, t, *J*=7.2 Hz), 3.03 (2H, q, *J*=7.2 Hz), 3.57 (3H, s), 3.78 (3H, s), 3.85 (3H, s), 5.22 (2H, s), 7.27–7.38 (5H, m, Ar*H*); ^{13}C NMR. 13.0, 18.4, 32.5, 51.8, 52.3, 66.3, 109.6, 119.2, 125.9, 128.2, 128.4, 128.5, 135.8, 147.0, 160.3, 162.8, 166.8; MS (ESI) *m/z* 359 (M^+, 8%), 252 (88), 236 (100), 204 (17), 194 (17), 135 (20) and 91 (100). HRMS (ESI) *m/z* 359.1370 ($C_{19}H_{21}NO_6$ [M^+], 359.1369).

*4.3.7. 4-Benzyl 2,3-dimethyl 5-benzyl-1-methyl-1H-pyrrole-2,3,4-tricarboxylate (**7b**).* Compound **7b** was purified by flash chromatography [ethyl acetate/hexane (1:2)] and obtained as a white solid. Yield: *Method A* 37% and *Method B* 39%. Mp 127.4–128.6 °C (from ethyl acetate/hexane). IR (KBr) 746, 1109, 1143, 1240, 1509, 1701, 1717, 1729, 3031 cm^{-1}; ^1H NMR 3.59 (3H, s), 3.74 (3H, s), 3.79 (3H, s), 4.48 (2H, s), 5.22 (2H, s), 7.05–7.07 (2H, m, Ar*H*), 7.18–7.33 (8H, m, Ar*H*); ^{13}C NMR 30.7, 33.1, 51.9, 52.3, 66.5, 111.2, 119.9, 126.7, 128.0, 128.5, 128.5, 128.8, 135.6, 136.6, 142.8, 160.2, 163.0, 166.7. MS (ESI) *m/z* 422 (MH^+, 25%), 259 (4), 247 (3) and 201 (5). HRMS (ESI) *m/z* 422.15948 ($C_{24}H_{24}NO_6$ [MH^+], 422.15981).

*4.3.8. Ethyl 3-(2-benzyloxy-2-oxoethyl)-2,3-dimethyl-5-phenyl-2,3-dihydroisoxazole-4-carboxylate (**8a**).* Compound **8a** was purified by flash chromatography [ethyl acetate/hexane (1:3)] and obtained as a white solid. Yield: *Method A* 59% and *Method B* 44%. Mp 67.7–68.3 °C (from ethyl acetate/hexane). IR (KBr) 761, 1118, 1290, 1342, 1639, 1685, 1727 cm^{-1}; ^1H NMR 1.09 (3H, t, *J*=7.2 Hz), 1.58 (3H, s), 2.79 (1H, d, *J*=14 Hz), 2.84 (3H, s), 3.01 (1H, d, *J*=14 Hz), 4.07 (2H, q, *J*=7.2 Hz), 5.11 (2H, s), 7.27–7.44 (8H, m, Ar*H*), 7.54–7.56 (2H, m, Ar*H*); ^{13}C NMR 13.8, 19.5, 38.8, 43.4, 59.8, 66.3, 71.8, 106.6, 127.7, 128.0, 128.1, 128.2, 128.4, 129.5, 130.6, 136.0, 162.7, 164.1, 170.3; MS (ESI) *m/z* 396 (MH^+, 100%), 359 (3), 306 (7) and 246 (4). HRMS (ESI) *m/z* 396.18156 ($C_{23}H_{26}NO_5$ [MH^+], 396.18055).

*4.3.9. Ethyl 3-(2-benzyloxy-2-oxoethyl)-3-ethyl-2-methyl-5-phenyl-2,3-dihydroisoxazole-4-carboxylate (**8b**).* Compound **8b** was purified by flash chromatography [ethyl acetate/hexane (1:5)] and obtained as oil. Yield: *Method A* 25% and *Method B* 28%. IR (film) 696, 1107, 1302, 1375, 1447, 1598, 1635, 1691, 1736, 2978 cm^1; ^1H NMR 1.01 (3H, t, *J*=7.2 Hz), 1.06 (3H, t, *J*=7.2 Hz), 1.76–1.85 (1H, m), 2.04–2.14 (1H, m), 2.80 (1H, d, *J*=14 Hz), 2.93 (3H, s), 3.02 (1H, d, *J*=14 Hz), 4.04 (2H, q, *J*=7.2 Hz), 5.08 (2H, s), 7.31–7.43 (8H, m, Ar*H*) 7.52–7.54 (2H, m, Ar*H*); ^{13}C NMR 9.2, 13.8, 28.5, 37.8, 40.0, 59.7, 66.4, 75.0, 104.8, 127.7, 128.1, 128.2, 128.4, 129.5, 130.5, 135.9, 163.0, 164.3, 170.6. MS (ESI) *m/z* 410 (MH^+, 100%), 262 (3) and 201 (3). HRMS (ESI) *m/z* 410.19623 ($C_{24}H_{28}NO_5$ [MH^+], 410.19620).

*4.3.10. Ethyl 3-benzyl-3-(2-benzyloxy-2-oxoethyl)-2-methyl-5-phenyl-2,3-dihydroisoxazole-4-carboxylate (**8c**).* Compound **8c** was purified by flash chromatography [ethyl acetate/hexane (1:4)] and obtained as oil. Yield: *Method A* 36% and *Method B* 37%. IR (film) 697, 1110, 1153, 1375, 1689, 1735, 3031 cm^{-1}; ^1H NMR 1.01 (3H, t, *J*=7.2 Hz), 2.83 (3H, s), 2.94 (1H, d, *J*=15.6 Hz), 3.19 (1H, d, *J*=15.6 Hz), 3.21 (1H, d, *J*=14 Hz), 3.26 (1H, d, *J*=14 Hz), 3.88–3.96 (1H, m), 3.98–4.06 (1H, m), 5.10 (s, 2H), 7.16–7.37 (15H, m, Ar*H*); ^{13}C NMR 13.8, 38.2, 39.2, 43.7, 59.7, 66.6, 74.9, 105.2, 126.5, 127.6, 128.2, 128.4, 128.5, 129.4, 130.4, 131.4, 135.6, 135.8, 163.1, 164.2, 170.5. MS (ESI) *m/z* 472 (MH^+, 100%), 291 (5) and 201 (7). HRMS (ESI) *m/z* 472.21128 ($C_{29}H_{30}NO_5$ [MH^+], 472.21185).

*4.3.11. 4-Benzyl 2-ethyl 1,5-dimethyl-3-phenyl-1H-pyrrole-2,4-dicarboxylate (**9a**).* Compound **9a** was purified by flash chromatography [ethyl acetate/hexane (1:5)] and obtained as a white solid. Yield: *Method A* 57% and *Method B* 62% mp 81.9–83.0 °C (from ethyl acetate/hexane). IR (KBr) 715, 1107, 1159, 1243, 1284, 1683, 1704 cm^{-1}; ^1H NMR 0.79 (3H, t, *J*=7.2 Hz), 2.59 (3H, s), 3.86 (3H, s), 3.92 (2H, q, *J*=7.2 Hz), 5.00 (2H, s), 6.86–6.88 (2H, m, Ar*H*), 7.16–7.25 (8H, m, Ar*H*); ^{13}C NMR 11.7, 13.3, 32.8, 59.8, 65.4, 112.4, 120.7, 126.4, 127.0, 127.5, 127.7, 128.1, 129.7, 133.8, 136.0, 136.7, 141.0, 161.7, 164.9; MS (EI) *m/z* 377 (M^+, 27%), 286 (100), 240 (79), 198 (10), 127 (11) and 91 (31). HRMS (EI) *m/z* 377.1626 ($C_{23}H_{23}NO_4$ [M^+], 377.1627).

*4.3.12. 4-Benzyl 2-ethyl 5-ethyl-1-methyl-3-phenyl-1H-pyrrole-2,4-dicarboxylate (**9b**).* Compound **9b** was purified by flash chromatography [ethyl acetate/hexane (1:5)] and obtained as a white solid. Yield: *Method A* 13% and *Method B* 36%. Mp 61.7–63.6 °C (from ethyl acetate/hexane). IR (KBr) 735, 1105, 1157, 1243, 1513, 1683, 1704, 2980 cm^{-1}; ^1H NMR 0.79 (3H, t, *J*=7.2 Hz), 1.22 (3H, t, *J*=7.6 Hz), 3.05 (2H, q, *J*=7.6 Hz), 3.88 (3H, s), 3.92 (2H, q, *J*=7.2 Hz), 5.01 (2H, s), 6.87 (2H, d, *J*=7.2 Hz, Ar*H*), 7.16–7.45 (8H, m, Ar*H*); ^{13}C NMR 13.4, 18.8, 32.6, 59.8, 65.4, 111.7, 120.8, 126.4, 127.0, 127.5, 127.7, 128.1, 129.7, 133.8, 136.0, 136.7, 146.4, 161.8, 164.6. MS (ESI) *m/z* 392 (MH^+, 57%), 378 (13) and 201 (3). HRMS (ESI) *m/z* 392.18582 ($C_{24}H_{26}NO_4$ [MH^+], 392.18563).

*4.3.13. 4-Benzyl 2-ethyl 5-benzyl-1-methyl-3-phenyl-1H-pyrrole-2,4-dicarboxylate (**9c**).* Compound **9c** was purified by flash chromatography [ethyl acetate/hexane (1:4)] and obtained as a white solid. Yield: *Method B* 26%. Mp 117.8–120.2 °C (from ethyl acetate/hexane). IR (KBr) 705, 1105, 1241, 1500, 1686, 1706 cm^{-1}; ^1H NMR 0.79 (3H, t, *J*=7.2 Hz), 3.75 (3H, s), 3.93 (2H, q, *J*=7.2 Hz), 4.50 (2H, s), 5.00 (2H, s), 6.81 (2H, d, *J*=6.8 Hz, Ar*H*), 7.11–7.45 (13H, m, Ar*H*); ^{13}C NMR 13.3, 31.1, 33.2, 59.9, 65.6, 113.4, 121.4, 126.4, 126.5, 127.1, 127.5, 127.7, 128.1, 128.1, 128.7, 129.8, 133.7, 135.8, 136.6, 137.5, 142.1, 161.7, 164.7. MS (ESI) *m/z* 454 (MH^+, 34%), 259 (8) and 201 (7). HRMS (ESI) *m/z* 454.20100 ($C_{29}H_{28}NO_4$ [MH^+], 454.20128).

*4.3.14. Methyl 3-(2-benzyloxy-2-oxoethyl)-2,3-dimethyl-2,3-dihydroisoxazole-4-carboxylate (**10a**) and methyl 3-(2-benzyloxy-2-oxoethyl)-2,3-dimethyl-2,3-dihydroisoxazole-5-carboxylate*

(***10b***). Compounds **10a** and **10b** were obtained as a mixture after purification by flash chromatography [ethyl acetate/hexane (1:2)]. Yield: *Method A* 40% and *Method B* 47%. IR (film) 1089, 1151, 1237, 1652, 1704, 1738 cm^{-1}. *Major component*: ^1H NMR 1.51 (3H, s), 2.75 (1H, d, J=14.4 Hz), 2.80 (3H, s), 2.93 (1H, d, J=14.4 Hz), 3.67 (3H, s), 5.06–5.14 (2H, m), 7.24 (1H, s), 7.33–7.36 (5H, m, Ar*H*); ^{13}C NMR 19.3, 39.4, 51.1, 66.3, 69.0, 100.7, 112.4, 128.1, 128.2, 128.3, 128.5, 128.6, 135.9, 153.2, 164.0, 170.0; MS (ESI) m/z 306 (MH^+, 100%). HRMS (ESI) m/z 306.13333 ($C_{16}H_{20}NO_5$ [MH^+], 306.13360).

4.3.15. 4-Benzyl 2-methyl 1,5-dimethyl-1H-pyrrole-2,4-dicarboxylate (***11a***). Compound **11a** was purified by flash chromatography [ethyl acetate/hexane (1:3)] and obtained as a white solid. Yield: *Method A* 58% and *Method B* 35%. Mp 73.0–74.4 °C (from ethyl acetate/hexane). IR (KBr) 1055, 1230, 1259, 1694, 1730 cm^{-1}; ^1H NMR 2.56 (3H, s), 3.80 (3H, s), 3.85 (3H, s), 5.26 (2H, s), 7.30–7.42 (6H, m, Ar*H* and C*H*); ^{13}C NMR 11.4, 32.5, 51.2, 65.5, 112.0, 119.3, 121.5, 127.9, 128.2, 128.5, 136.6, 142.3, 161.5, 164.4; MS (EI) m/z 287 (M^+, 10%), 196 (100), 180 (71) and 91 (26). HRMS (EI) m/z 287.1161 ($C_{16}H_{17}NO_4$ [M^+], 287.1158).

4.3.16. 3-Benzyl 4-methyl 1,2-dimethyl-1H-pyrrole-3,4-dicarboxylate (***11b***). Compound **11b** was purified by flash chromatography [ethyl acetate/hexane (1:2)] and obtained as a white solid. Yield: *Method A* 43%. Mp 56.5–57.9 °C (from ethyl acetate/hexane). IR (KBr) 1072, 1170, 1285, 1696, 1718 cm^{-1}; ^1H NMR 2.37 (3H, s), 3.51 (3H, s), 3.17 (3H, s), 5.29 (2H, s), 7.06 (1H, s), 7.28–7.37 (3H, m, Ar*H*), 7.42–7.44 (2H, m, Ar*H*); ^{13}C NMR 10.9, 34.1, 51.3, 66.2, 112.6, 114.8, 126.9, 127.9, 128.3, 128.4, 135.9, 136.4, 164.6, 164.9; MS (EI) m/z 287 (M^+, 8%), 180 (100), 166 (17), 164 (68), 150 (40), 121 (29) and 91 (74). HRMS (EI) m/z 287.1168 ($C_{16}H_{17}NO_4$ [M^+], 287.1158).

4.3.17. Benzyl 3-(2-benzyloxy-2-oxoethyl)-2,3,5-trimethyl-2,3-dihydroisoxazole-4-carboxylate (***12***). The nitrone **2a** (0.22 g, 1 mmol) was dissolved in toluene (5 mL) and benzyl buta-2,3-dienoates **1a** (0.3 g, 1.73 mmol) was added. The mixture was then stirred at room temperature for 4 h and the solvent was evaporated off. To a solution of the crude product in anhydrous tetrahydrofuran at −78 °C was slowly added 0.7 mL of a 2.5 M solution of *n*-butyllithium in hexane. The resulting solution was warmed to 0 °C, quenched by the addition of a saturated aqueous ammonium chloride solution and extracted with ether. The organic phase was washed with water, dried over sodium sulfate and concentrated under reduced pressure to give the compound **12**, which was purified by flash chromatography [ethyl acetate/hexane (1:5)] and obtained as an oil in 42% yield. IR (film) 697, 1094, 1384, 1636, 1696, 1734, 3447 cm^{-1}; ^1H NMR 1.47 (3H,s), 2.11 (3H, s), 2.68 (1H, d, J=14.4 Hz), 2.74 (3H, s), 2.91 (1H, d, J=14.4 Hz), 5.04 (1H, d, J=12.4 Hz), 5.09 (1H, d, J=12.4 Hz), 5.14 (2H, s), 7.25–7.36 (10H, m, Ar*H*); ^{13}C NMR 13.1, 19.7, 39.1, 43.6, 65.6, 66.2, 70.4, 106.4, 128.1, 128.2, 128.5, 128.6, 136.0, 136.2, 164.4, 165.4, 170.3; MS (ESI) m/z 396 (M^+, 100%), 376 (6), 246 (15) and 215 (24). HRMS (ESI) m/z 396.18215 ($C_{23}H_{26}NO_5$ [M^+], 396.18055).

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Supplementary data

Computational data are available. Supplementary data for this article can be found in the online version, at doi:10.1016/j.tet.2010.06.010.

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