N-heteroatom substitution effect in 3-aza-cope rearrangements

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Abstract

Background: The nature of the heteroatom substitution in the nitrogen of a 3-aza-Cope system is explored.

Results: While N-propargyl isoxazolin-5-ones suffer 3-aza-Cope rearrangements at 60°C, the corresponding N-propargyl pyrazol-5-ones need a higher temperature of 180°C for the equivalent reaction. When the propargyl group is substituted by an allyl group, the temperature of the rearrangement for both type of compounds is less affected by the nature of the heteroatom present. Treatment with a base, such as ethoxide, facilitates the rearrangement, and in the case of isoxazol-5-ones other ring opening reactions take precedence, involving N–O ring cleavage of the 5-membered ring. However when base-catalysed decomposition is prevented by substituents, products arising from a room temperature aza-Cope rearrangement are isolated. A possible mechanistic pathway based on free energies derived from density functional calculations involving cyclic intermediates is proposed.

Conclusions: The nature of the heteroatom substitution in the nitrogen of a 3-aza-Cope system leads to a remarkable difference in the energy of activation of the reaction.

Background

Cope-type rearrangements constitute a highly efficient means for carbon–carbon bond formation, offering high regio- and stereocontrol which renders them especially useful in synthesis [1]. The Aza-Cope rearrangement in particular has some advantages over its oxo-counterpart, namely the fine tuning of the reaction temperature which can be achieved by attaching different substituents to the nitrogen of the rearranging system [2–5], by adding charges or by encapsulating it [6]. As previously reported by us appropriately substituted N-alkyl(silyl) oxy-N-allyl enamines undergo smooth 3,3-sigmatropic rearrangements to the corresponding N-alkyl(silyl)oxy imino ethers in good to excellent yields [7]. Theoretical studies also indicate that an oxyanionic substituent on the nitrogen atom reduces substantially the activation energies for these rearrangements [8]. We report in this manuscript the results obtained with the N-propargyl and N-allyl 5-membered heterocycles, pyrazolin-5-ones and isoxazolin-5-ones, either under thermolysis or in the presence of a base.

Results and discussion

The required compounds 1 for the rearrangement studies were obtained by alkylation of 3 using a Mitsunobu reaction [9] as in Scheme 1. The isolated compounds 1 and 2 were easily separated by chromatography (cf. Experimental). Heating either 1 or 2 gave rise to a 3,3-sigmatropic rearrangement [5,10] and the same final compound 4 as in Scheme 1 (Table 1, entries 1–4).

In the presence of EtOK and 18-crown-6 ether at r.t., it was found that the propargyl group of 1a isomerized to the corresponding allene 5a as in Scheme 2, which could in turn suffer upon heating a 3,3-sigmatropic rearrangement leading to 6a. This last compound could also be reached from 2a by treatment with base to give 7a, followed by thermolysis. Thus coupling of these two reactions opened the way to 3 isomeric compounds of 1a. It is worth noticing that, while the N-allenyl 5a (Table 1, entry 5) reacts in a similar way to the N-propargyl 1a (entry 1) in the 3-aza-Cope rearrangement, the corresponding O-allenyl 7a (entry 6) and the O-propargyl 2a (entry 3) rearrange faster and give better yields. Similar results are found for the pair 1a/2a and
The reason is probably related to the more facile nature of the 3-oxa-Cope (Claisen) versus the 3-aza-Cope rearrangements [3].

Next, the N-propargyl isoxazolinones 8a,b and the N-allyl 8c,d [11] were synthesised (cf. Experimental) and heated to give the corresponding rearranged compounds, the allenes 9a,b (Scheme 3, Table 2, entries 1,2) and the allyl 9c,d (Scheme 4, Table 2, entries 3,4). It was found that the first ones required a much lower temperature for the rearrangement.

The synthesis of 8e is depicted in Scheme 5 as well as its product after heating (Table 2, entry 5). Desilylation [12] of compound 10 yielded the corresponding ene-hydroxylamine 11, which was found to be unstable and to lactonise spontaneously to the 2-allyl-isoxazolone 8e (Scheme 5). The latter on thermolysis (180°C) furnished 2-cyano-pent-4-enoic acid ethyl ester 12, as shown. In this case the thermodynamic gain resulting from the loss of carbon dioxide from the rearranged product 9e is also accompanied by the formation of the cyano derivative 12 [13]. When treated with potassium ethoxide, 8e led to the formation of N-allyl-malonamic acid ethyl ester 13 instead of the rearranged product (Scheme 6).

Table 1 Rearrangements of pyrazolin-5-ones 1 and their isomers 2

| # | Pyrazolinones 1 & isomers 2 | Conditions temp./time | Products yielda (%) |
|---|-----------------------------|-----------------------|---------------------|
| 1 | 1a: R = Me                  | 180°C / 60 m          | 4a: R = Me (35)     |
| 2 | 1b: R = Ph                  | 180°C / 10 m          | 4b: R = Ph (72)     |
| 3 | 2a: R = Me                  | 180°C / 10 m          | 4a: R = Me (90)     |
| 4 | 2b: R = Ph                  | 180°C / 10 m          | 4b: R = Ph (99)     |
| 5 | 5a: R = Me                  | 180°C / 30 m          | 6a: R = Me (30)     |
| 6 | 7a: R = Me                  | 180°C / 10 m          | 6a: R = Me (80)     |

*a Isolated yields after flash-chromatography.

Again loss of carbon dioxide, as found earlier by Woodman [14], occurred with a rearrangement possibly involving cyclic intermediates to provide the amide group of 13 [15]. The energetics of possible mechanistic pathways for this process were explored using a density functional approach ($\omega$B97XD functional, 6-311G(d,p) basis set and SCRF(CPCM) continuum solvation method for ethanol as a model polar solvent). The reaction is sufficiently complex that a significant number of possible mechanistic pathways can be envisaged using the classical “arrow pushing” approach. Here we adopt the approach of incrementally locating pathways to the product and optimizing them for the lowest overall activation free energy. Such an approach of course does not guarantee finding the global energetic minimum in mechanistic pathways. Instead the objective is to find a thermally reasonable pathway that might approximately correspond to the observed rate of the reaction, and along the way eliminating pathways that have unreasonably high activation free energies.

The mechanistic exploration is set out in Scheme 6. The first route explored involved 8e and ethoxide anion acting as a nucleophile. Addition of the ethoxide gives 8e-1 as the first intermediate, followed by ring closure to 8e-2 [16]. The most direct route (Occam’s razor) to 13 is by a dyotropic rearrangement of 8e-2 to 8e-3, followed by protonation and decarboxylation. The energetic high point of this pathway is the transition state for the dyotropic rearrangement of the intermediate oxaziridine (8e-TS1) which manifests as unreasonably high (Additional file 1: Table S1, entry 4).

The next route explored was with ethoxide acting as a base, abstracting the allylic proton to give the intermediate 8e-4. A ring closure to 8e-5, followed by 1,3 intramolecular proton transfer to give 8e-6, a second proton transfer to reform alkoxide anion and final ring opening to 8e-7 gives 8e-8, which is merely a tautomer of 8e-3 and can decarboxylate as before to give 13. The
high point of this pathway is 8e-TS2, which shows as an entirely reasonable barrier for the reaction (Additional file 1: Table S1, entry 5). Whilst this does not constitute a formal mechanistic proof of the reaction, it does imply a reasonable one, and further that any alternative mechanism must have an overall lower energy barrier than this one.

Whereas it is traditional, indeed conventional, for the mechanism of a synthetic pathway to be speculated upon using mechanistic reaction arrows, we suggest here that increasingly such speculations must be supported by a computational exploration of the potential free energy surface. In this case, this has been done with a procedure which, including as it does dispersion corrections for all species, a triple-zeta quality basis with polarization functions, and a correction for continuum solvation, is suggested to be the minimum in quality appropriate for such exploration.

Exposure of 2-allyl-3,4-diphenyl-isoxazolin-5-one (8d) to similar conditions gave rise after 10 minutes to 14 in 25% yield (along with desoxybenzoin in 45%, Scheme 7) with no 3-aza-Cope rearrangement being observed. Compound 14 was found to generate desoxybenzoin (15 R = H) by quenching under aqueous acidic conditions. Quenching the reaction with deuterated acetic acid (CH₃COOD) resulted in the isolation of monodeuterated benzoin (15 R = D). A possible mechanism is shown and follows along equivalent intermediates. 8d-3 or the oxaziridine derived 8d-4 [17], until reaching 8d-5. A phenyl substituent on carbon 3 in the β-lactone ring of 8d-5 now leads instead to 14.

Substrate 8b, where formation of the carbanion adjacent to the ring nitrogen of the oxazolidinone is blocked by substitution, was next treated with potassium ethoxide (0.1 eq), in the presence of 18-crown-6 ether, at room temperature (5 days), and gave rise to 9b in 55% yield (cf. Scheme 8). Here the opening of the five-membered ring leading to 8b-1 might lower the energy of the reaction either by allowing an easier access to the conformation leading to the transition state or by anionic charge acceleration of the rearrangement. The importance of EtOK was noticed further when, after 5 days at r. t., in its absence, the rearrangement of 8b was observed to occur, but in a much lower yield (<10%). The same compound treated with LDA or tert-BuLi, in the

Table 2 Thermolysis of isoxazolin-5-ones 8 in the presence and absence of potassium ethoxide

| # | Compounds 8 | Conditions | Products | Yield (%) |
|---|---|---|---|---|
| 1 | 8a: R = H | 60°C / 30 m | 9a | 75 |
| 2 | 8b: R = Me | 60°C / 10 m | 9b | 85 |
| 3 | 8c: R' = Me | 180°C / 7 h | 9c | 95 |
| 4 | 8d: R' = Ph | 180°C / 5 h | 9d | 97 |
| 5 | 8e | 180°C / 5 h | 12 | 80 |
| 6 | 8e | EtOKC₆H₅ / RT / 5 h | 13 | 80 |
| 7 | 8d: R' = Ph | EtOKC₆H₅ / RT / 10 m | 14 | 25 |
| 8 | 8b: R = Me | EtOKC₆H₅ / RT / 5 d | 9b | 55 |
| | | EtOKC₆H₅ / RT / 10 m | 9b | 30 |

*Isolated yields after flash-chromatography. *See ref. 11. *In the presence of 18-crown-6 ether. *In the presence of EIOK (1.5 eq). *In the presence of EIOK (0.1 eq)
presence of 12-crown-6 ether and in the same conditions of concentration and temperature, showed no reaction. Thus the anion derived from the possible base removal of the terminal triple bond proton does not appear to accelerate the rearrangement, but the oxyanion formed upon the isoxazolidinone ring opening did have a moderately positive effect enabling the rearrangement to occur at room temperature.

Conclusions
In conclusion: 1) substitution of the nitrogen-1 of pyrazolin-5-ones by oxygen lowers the temperature of the 3-aza-Cope rearrangement of isoxazolin-5-ones vis-à-vis the corresponding pyrazolin-5-ones when the rearranging element includes a propargyl group attached to the heterocyclic nitrogen-2; 2) when the propargyl group is replaced by an allyl group the rearranging temperature is higher and similar in both compounds; 3) treatment with potassium ethoxide as base in the presence of 12-crown-6 ether at room temperature, while leaving the pyrazolin-5-one heterocycle untouched, leads to ring opening of isoxazolin-5-ones, followed by further reactions. The putative oxaziridine or other cyclic intermediate then suffer base catalysed ring opening reaction whenever there are protons available in the carbon α to the ring nitrogen, leading to a 6-membered aza,oxa-ring system. When such position is blocked by substituents the 3-aza-Cope rearrangement occurs at room temperature.

Experimental

General
Melting points were determined on a Reichert Thermovar apparatus and are uncorrected. Ordinary mass spectra were recorded on a Fisons TRIO 2000 or AEI MS-9 spectrometer. High-resolution MS spectra (HRMS) were obtained on a FT-ICR/ MS Finnigan FT/MS 2001-DT spectrometer at 70 eV by electron impact or on a Finnigan MAT 900 ST spectrometer by ESI. Infrared (IR) spectra were recorded on a Perkin–Elmer 1000X FT-IR spectrometer. Proton and $^{13}$C NMR spectra were recorded in CDCl$_3$ on a Bruker ARX 400 spectrometer (400 MHz for $^1$H, 100.63 MHz for $^{13}$C). Chemical shifts are reported relative to tetramethylsilane as the internal reference ($\delta_H$ 0.00) for $^1$H NMR spectra and to CDCl$_3$ ($\delta_C$ 77.00) for $^{13}$C NMR spectra. IR spectra were run on an FT Perkin–Elmer 1000 instrument, with absorption frequencies expressed in reciprocal centimeters. Thin-layer chromatography was performed on Merck silica gel 60 F$_{254}$ 0.2 mm thick plates, visualized under UV light or by exposing to iodine vapour. For preparative separations the plates were 0.5–1 mm thick. For flash chromatography silica Merck Kieselgel 60, 70–230 mesh was used. Usual work-up implies drying the water- or brine-washed organic extracts over anhydrous sodium sulfate or magnesium sulfate, followed by filtration and solvent removal under reduced pressure. Anhydrous solvents were dried and freshly distilled by standard methods [18].

Synthesis of starting materials

**Ethyl 3-oxo-2-phenyl-butanoate**

To a solution of ethyl acetoacetate (1.5 g, 11.5 mmol) in CH$_2$Cl$_2$ (45 mL), was added triphenylbismuth carbonate [19] (6.33 g, 12.6 mmol). After being stirred under argon for 24 h at 40°C, the mixture was filtered and concentrated at reduced pressure. The crude was purified by CC (silica; Et$_2$O/n-hexane 1:3) to give the title compound as a yellow oil [20] (1.44 g, 61%): IR (NaCl) $\nu_{\text{max}}$ (cm$^{-1}$): 3063, 2983, 1745 (C = O, ester), 1721 (C = O, ketone). $^1$H NMR (400 MHz CDCl$_3$) $\delta_H$ (ppm): 1.18 (3H, t, $J = 7.2$ Hz, OCH$_2$CH$_3$), 1.85 (3H, s, CH$_3$CO), 4.23 (2H, m, OC$_2$H$_5$), 7.14 – 7.38 (5H, m, Ar–H), 13.13 (1H, s, OH); $^1$H NMR (400 MHz CDCl$_3$) $\delta_C$ (ppm): 3063, 2983, 1745 (C = O, ester), 1721 (C = O, ketone). $^1$H NMR (400 MHz CDCl$_3$) $\delta_H$ (ppm): 1.27 (3H, t, $J = 7.2$ Hz, OCH$_2$CH$_3$), 2.18 (3H, s, CH$_3$CO), 4.23 (2H, m, OCH$_2$CH$_3$), 4.69 (1H, s, PhCH), 7.14 – 7.38 (5H, m, Ar–H).
Ethyl 3-oxo-2,3-diphenyl-propanoate
To a solution of ethyl 3-oxo-3-phenyl-propionate (1.48 g, 7.7 mmol) in CH2Cl2 (25 mL), was added triphenylbismuth carbonate (4.22 g, 8.5 mmol). After being stirred under argon for 24 h at 40°C, the mixture was filtered and concentrated at reduced pressure. The crude was purified by CC (silica; Et2O/n-hexane 1:3) to give a viscous oil. Recrystallization from ethanol yielded the title compound (1.34 g, 65%): mp 88–89°C (ethanol) (lit.: [21] mp 89–90°C).

IR (KBr) νmax (cm⁻¹): 3063, 2985, 1741 (C = O, ester), 1674 (C = O, ketone).

1H NMR (400 MHz CDCl3)
keto-enol equilibrium, enol (12%): δ 1.25 (3H, t, J = 7.2 Hz, OCH2CMe3), 4.23 (2H, m, OCH2CH3), 7.11 – 7.99 (10 H, m, Ar–H), 13.66 (1H, s, OH), and ketone (88%): δ 1.25 (3H, t, J = 7.2 Hz, OCH2CMe3), 4.23 (2H, m, OCH2CH3), 5.62 (1H, s, PhCH), 7.11 – 7.99 (10 H, m, Ar–H).

Methyl-4-phenylisoxazolin-5-one
To a solution of ethyl 3-oxo-2-phenyl-butanoate (50 mg, 0.24 mmol) in EtOH (0.5 mL) and H2O (0.1 mL), was added hydroxylamine hydrochloride (32 mg, 0.46 mmol) and sodium acetate (6.4 mg, 0.078 mmol). The solution was refluxed with continuous stirring under argon for 3 h, 37% HCl (32 μL) was added and the mixture refluxed for further 30 min. The solvent was removed under reduced pressure and the crude diluted with distilled water (2 mL) and extracted with Et2O (3 × 5 mL). The organic extract was dried, filtered and concentrated under reduced pressure. Purification by CC (silica; AcOEt) yielded the title compound (32 mg, 66%): mp 138–140°C (ethyl acetate) (lit.: [22] mp 139–140°C). IR (KBr) νmax (cm⁻¹): 3322 (NH), 1669 (C = O).

1H NMR (400 MHz CDCl3) two distinct forms, isoxazol-5(2H)-one (A) and isoxazole-5(4H)-one (B) (A:B = 90:10) A, δ 2.35 (3H, s, CH3), 6.24 (1H, s, NH), 7.14 – 7.56 (5H, m, Ar–H); B, δ 2.04 (3H, s, CH3), 4.40 (1H, s, CH), 7.14 – 7.56 (5H, m, Ar–H).

Diphenylisoxazolin-5-one
To a solution of ethyl 3-oxo-2,3-diphenyl-propanoate (65 mg, 0.27 mmol) in EtOH (0.5 mL) and H2O (0.1 mL), was added hydroxylamine hydrochloride (32 mg, 0.46 mmol) and sodium acetate (6.4 mg, 0.078 mmol). The solution was refluxed with continuous stirring under argon for 3 h and processed as in the previous reaction to yield the title compound (40 mg, 61%) as a white powder: mp: 159°C (dec.) (benzene) (lit.: [23] mp
159°C). IR (KBr) ν max (cm⁻¹): 3297 (NH), 1680 (C = O).

1H NMR (400 MHz CDCl₃) δ 5.86 (1H, sl, NH), 7.01 – 7.79 (10H, m, Ar – H).

**General procedure for the synthesis of pyrazolinones**

To a stirred ethanolic solution (≈ 0.5 M) of ethyl 3-oxo-2,3-diphenylpropanoate [21] (1 eq.) in ethanol is added the desired hydrazine (1 eq.) and the reaction heated to reflux under argon. After total consumption of both starting materials (TLC control: silica, CH₂Cl₂:MeOH, 9:1), the solvent is evaporated under reduced pressure and the product is purified by hot recrystallization using AcOEt.

**Diphenyl-1-methyl-2-pyrazolin-5-one (3a)**

From methyl hydrazine, compound 3a obtained after 18 h as colourless crystals (50%): mp: 214–216°C (AcOEt). ¹H NMR (400 MHz CDCl₃) δ 7.72 – 7.20 (10H, m, Ar – H), 3.70 (3H, s, NCH₃). ¹³C NMR (100.62 MHz CDCl₃) δ 36.4 (NCH₃), 108.4, 124.9, 126.9, 127.2, 129.0, 131.8, 145.3, 165.8 (C = O). IR (KBr; cm⁻¹): 3235 (N-H), 1695 (C = O). EIMS (m/z, %): 250 (M+, 100), 178 (58), 77 (26). HRMS: calcd for C₁₆H₁₄N₂O: 250.11076; found: 250.11061.

**Triphenyl-2-pyrazolin-5-one (3b)**

From phenylhydrazine, compound 3b obtained after 24 h as colourless crystals (71%): mp 198–199°C (AcOEt). ¹H NMR (400 MHz DMSO-d₆ / CDCl₃, 1:2) δ 10.97 (1H, bs, OH), 7.84 – 7.25 (15H, m, Ar – H). IR (KBr, cm⁻¹): 3236 (N-H), 1697 (C = O). EIMS (m/z, %): 312 (M⁺, 78), 178 (100). HRMS: calcd for C₂₁H₁₆N₂O: 312.12626; found: 312.12661.

**Mitsunobu propargylation of pyrazolinones 3**

General procedure: To the desired pyrazolone (3a or 3b) (1.0 eq.) dissolved in dry THF (≈ 0.15 M) under argon, PPh₃ (1.2 eq.) and the required propargyl alcohol (1.0 eq.) are added. The reaction is cooled to 0°C and DIAD (1.2 eq.) in dry THF (≈ 1.5 M) is added dropwise. The
reaction is allowed to reach room temperature and after the reaction is finished (tlc control), the solvent is removed under vacuum. The products are purified by flash chromatography [AcOEt/n-hexane, (1:1) → AcOEt]. Following the general procedure, compounds (1a) and (2a) were obtained from 3a, and 1b and 2b from 3b.

Diphenyl-1-methyl-2-propargylypyrazolin-5-one (1a)
(65%), colourless crystals, mp 124°C (AcOEt). 1H NMR (400 MHz CDCl₃) δ 7.47 – 7.43 (2H, m, Ar–H), 7.34 – 7.22 (8H, m, Ar–H), 4.40 (2H, d, J = 2.4 Hz, OCH₂C = CH), 3.86 (3H, s, NCH₃), 2.49 (1H, t, J = 2.4 Hz, OCH₂C = CH). 13C NMR (100.62 MHz CDCl₃) δ 164.6 (C = O), 154.9 [N(Ph) = C(Ph)], 138.5 (Ar), 133.3 (Ar), 131.6 (Ar), 129.9 (Ar), 129.2 (Ar), 128.1 (Ar), 127.7 (Ar), 127.1 (Ar), 126.8 (Ar), 123.5 (Ar), 116.6 [N(Ph) = C(Ph)], 74.6 (NCH₂C = CH), 74.1 (NCH₂C = CH), 40.6 (NCH₂C = CH). IR (film, cm⁻¹): 3289, 2116, 1667 (C = O).

2-Propargyl-1,3,4-triphenyl-2-pyrazolin-5-one (1b)
(35%), yellowish oil. 1H NMR (400 MHz CDCl₃) δ 7.71 (2H, d, J = 7.0 Hz, Ar–H), 7.67 – 7.61 (13H, m, Ar–H), 4.68 (2H, d, J = 0.5 Hz, NCH₂C = CH), 3.45 (3H, s, NCH₃). I.R. (NaCl, cm⁻¹): 3287, 2125, 1748, 1651 (C = O). EIMS (m/z, %): 288 (M⁺, 50), 178 (50), 128 (35), 77 (100). HRMS: calcd for C₁₉H₁₆N₂O: 288.126263; found: 288.126259.

5-Propargyloxy-1,3,4-triphenyl-2-pyrazoline (2b)
(35%), yellowish oil. 1H NMR (400 MHz CDCl₃) δ 7.91 (2H, d, J = 7.8 Hz, Ar–H), 7.85 – 7.70 (13H, m, Ar–H), 4.40 (2H, d, J = 0.5 Hz, OCH₂C = CH), 2.36 (1H, t, J = 2.3 Hz, OCH₂C = CH). 13C NMR (100.62 MHz CDCl₃) δ 149.5 [N = C(Ph) = C(Ph)], 149.0 [N(Ph) = C(Ph)], 138.5 (Ar), 133.3 (Ar), 131.6 (Ar), 129.9 (Ar), 129.2 (Ar), 128.1 (Ar), 128.0 (Ar), 127.0 (Ar), 126.8 (Ar), 123.5 (Ar), 116.6 [N(Ph) = C(Ph)], 77.1 (OCH₂C = CH), 76.8 (OCH₂C = CH), 61.0 (OCH₂C = CH), 34.6 (NCH₃). I.R. (NaCl, cm⁻¹): 3289, 2125, 1748, 1651 (C = O). EIMS (m/z, %): 288 (M⁺, 40), 249 (C₁₆H₁₃N₂O⁺, 100), 211 (18), 178 (5), 115 (25), 91 (20). HRMS: calcd for C₁₉H₁₆N₂O: 288.126263; found: 288.126219.

General procedure for the thermal rearrangements of pyrazolinones and isomers
In a round bottom flask, the N-substituted pyrazoline or its O-substituted isomer dissolved in o-dichlorobenzene (ca. 0.04 – 0.05 M), are heated at 180°C until total consumption of the starting material (TLC control). After solvent evaporation the products are purified by flash chromatography [Et₂O/n-hexane (1:4)].

Pyrazoline 4a from 1a
Following the general procedure, heating 1a (30 mg) for 60 min afforded 3,4-diphenyl-1-methyl-4-(prop-1′,2′,3′-trienyl) pyrazoline-5-one (4a) (10.5 mg, 35%) as a colourless crystals: mp 146–147°C (Et₂O). 1H NMR (400 MHz CDCl₃) δ 7.56 (2H, d, J = 7.0 Hz, Ar–H), 7.57 – 7.60 (6H, m, Ar–H), 5.79 (1H, t, J = 6.6 Hz, (CH = C = CH₂), 4.90 (1H, dd, J = 11.6, 6.6 Hz, CH = C = CH₂), 4.74 (1H, dd, J = 11.6, 6.6 Hz, CH = C = CH₂), 3.45 (3H, s, NCH₃). 13C NMR (100.62 MHz CDCl₃) δ 208.9, 174.5, 158.8, 136.1, 129.9, 129.2, 128.4, 128.0, 127.0, 89.1, 79.1, 60.1, 31.8. IR (film, cm⁻¹): 3061, 2921, 1956 (C = C = C), 1714 (C = O), 1496. EIMS (m/z, %): 288 (M⁺, 60), 230 (40), 178 (20), 128 (65), 77 (100). HRMS: calcd for C₁₉H₁₆N₂O: 288.126263; found: 288.126455.
Pyrazolinone 4b from 1b
Following the general procedure, heating 1b (14 mg) for 10 min afforded 4-(prop-1′,2′-dienyl)-1,3,4-triphenylpyrazolin-5-one (4b) (10.1 mg, 72%) as a colourless oil. 1H NMR (400 MHz CDCl₃) δ 8.07 (2H, d, J = 7.8 Hz, Ar–H), 7.70 (2H, d, J = 7.8 Hz, Ar–H), 7.47–7.23 (11H, m, Ar–H), 5.90 (1H, t, J = 6.7 Hz, CH = C = CH₂), 4.94 (1H, dd, J = 11.7, 6.7 Hz, CH = C = CH₂), 4.77 (1H, dd, J = 11.7, 6.7 Hz, CH = C = CH₂). 13C NMR (100.62 MHz CDCl₃) δ 209.0 (C = C = C), 171.3 (C = O), 159.1 (N = C), 138.2, 136.0, 130.2, 130.1, 129.3, 128.9, 128.4, 127.4, 127.0, 125.3, 119.1, 89.1 (CH = C = CH₂), 79.5 (CH = C = CH₂), 61.6 (C–CH = C = CH₂). IR (film, cm⁻¹): 3063, 2921, 1954 (C = C = C), 1721 (C = O), 1596, 1494. EIMS (m/z, %): 275 (M+, 23), 178 (34), 105 (21), 77 (50). HRMS calcd for C₁₈H₁₃NO₂: 275.09463; found: 275.09405.

Pyrazolinone 4a from isomer 2a
Following the general procedure, heating 2a (20 mg) for 10 min afforded 3,4-diphenyl-1-methyl-4-(prop-1′,2′-dienyl)pyrazolin-5-one (4a) (18 mg, 90%) as a white solid with data identical with 4.4.1.

Pyrazolinone 4b from isomer 2b
Following the general procedure, heating 2b (24 mg) for 10 min afforded 4-(prop-1′,2′-dienyl)-1,3,4-triphenylpyrazolin-5-one (4b) (24 mg, 99%) as a white solid with data identical with 4.4.2.

Pyrazolinone 6a from 5a
Following the general procedure, heating 5a (10 mg) for 30 min afforded the pyrazolinone 6a (3 mg, 30%) as a glassy solid. 1H NMR (400 MHz CDCl₃) δ 7.52 (2H, d, J = 7.3 Hz, Ar–H), 7.38–7.22 (8H, m, Ar–H), 3.47 (3H, s, NCH₃), 3.43 (1H, dd, J = 16.0 Hz, 2.5 Hz, CH₂CH = C), 3.05 (1H, dd, J = 16.0, 2.5 Hz, CH₂CH = C), 1.91 (1H, t, J = 2.5 Hz, CH₂CH = C). IR (film, cm⁻¹): 3291 (C≡C-H), 2923, 1955 (C≡C-H), 1713 (C = O).

Pyrazolinone 6a from isomer 7a
Following the general procedure, heating 7a (10 mg) for 10 min afforded 6a (8 mg, 80%) with data identical with the previous reaction.

Reactions of pyrazolinones with base
In a round bottom flask, the propargylated pyrazolinone 1a or its isomer 2a is dissolved in dry THF (ca. 0.07 M) (1 eq.) under argon and 18-crown-6 ether (1 eq.) is added. After total dissolution of the reactants, EtOK (0.1 eq.) is added under anhydrous conditions. The reaction is left to react at room temperature. After consumption of the starting material (TLC control) the reaction is stopped by addition of a saturated solution of NH₄Cl and extraction with Et₂O (2x). The product is purified by flash chromatography [AcOEt / n-hexane (1:6)].

Pyrazolinone 6a from isomer 7a
Following the general procedure, 3,4-diphenyl-1-methyl-2-(prop-1′,2′-dienyl)pyrazolin-5-one (5a) was obtained from 1a after 16 h as a colourless oil (65%). 1H NMR (400 MHz CDCl₃) δ 7.69 – 7.64 (4H, m, Ar–H), 7.56 – 7.52 (2H, m, Ar–H), 7.47 – 7.43 (4H, m, Ar–H), 6.30 (1H, t, J = 6.2 Hz, N–CH = C = CH₂), 5.32 (2H, d, J = 6.2 Hz, NCH = C = CH₂), 3.49 (3H, s, NCH₃). IR (film, cm⁻¹): 3055, 2925, 1962 (C = C = C), 1659 (C = O), 1483.

Isomer 7a from 2a
Following the general procedure, 1-methyl-3,4-diphenyl-5-(prop-1′,2′-dienyloxy)pyrazole (7a) was obtained from 2a after 16 h as a colourless oil (74%). 1H NMR (400 MHz CDCl₃) δ 7.47 – 7.43 (2H, m, Ar–H), 7.34 – 7.24 (8H, m, Ar–H), 6.79 (1H, t, J = 5.9 Hz, OCH = C = CH₂), 5.36 (2H, d, J = 5.9 Hz, OCH = C = CH₂), 3.81 (3H, s, NCH₃). 13C NMR (100.62 MHz CDCl₃) δ 200.0 (OCH = C = CH₂), 147.7, 147.5, 133.5 (Ar), 131.6, 129.6, 129.2, 128.3, 128.2, 127.9, 127.6, 126.7, 121.7 (OCH = C = CH₂), 91.0 (OCH = C = CH₂), 34.7 (NCH₃). IR (film, cm⁻¹): 3059, 2940, 1972 (C = C = C), 1605, 1563.

Synthesis of isoxazolinones
Diphenyl-2-(prop-2′-yn-1′-yl)isoxazolin-5-one (8a)
To a solution of 3,4-diphenylisoxazolin-5-one (Section 4.2.4) (100 mg, 0.422 mmol), triphenylphosphine (121 mg, 0.46 mmol) and propargyl alcohol (21.5 mg, 0.384 mmol) in dry THF (1.5 mL) were added, dropwise, DIAD (93 mg, 0.46 mmol) and DIPEA (0.23 mL). After the addition was completed, the solvent was removed under reduced pressure and the crude purified by CC (silica; Et₂O / n-hexane 1:2) to yield the title compound 8a (22 mg, 21 %): mp 82–83°C (Et₂O / n-hexane). IR (KBr; cm⁻¹): 3291 (HC≡C), 2127 (C≡C), 1746 (C = O). 1H NMR (400 MHz CDCl₃) δ 2.64 (1H, s, HC≡C), 5.06 (2H, d, J = 2.1 Hz, NCH₃), 7.26 – 7.56 (10H, m, Ar–H), EIMS (m/z, %): 275 (M⁺, 23), 178 (34), 105 (100), 89 (60), 77 (50). HRMS calcd for C₁₃H₁₁NO₂: 275.09463; found: 275.09405.

Diphenyl-2-(2′-methylbut-3′-yn-2′-yl)isoxazolin-5-one (8b)
Following Nicholas protocol [24], to a stirred solution of 2-methylbut-3-yn-2-ol (25.2 mg, 0.3 mmol) in petroleum ether (2 mL) under nitrogen at RT, was added Co₂(CO)₈ (102.6 mg, 0.3 mmol) and MS 4 Å, followed by boron trifluoride diethyl etherate (42.5 mg, 0.3 mmol). After 10 min 3,4-diphenylisoxazolin-5-one (Section 4.2.4) (23.7 mg, 0.1 mmol) was added and the reaction monitored by TLC (silica; CH₂Cl₂ / AcOEt 4:1) until consumption of the starting isoxazoline. After 48 h water (5 mL) was added to the reaction mixture which was extracted with
Et₂O (2x5 mL) to yield the cobalt complex as a red oil, which was purified by PTLC (silica; n-hexane / AcOEt 4:1). To a solution of this red complex in acetone (2 mL) was added Et₂N (0.1 mmol) and (NH₄)₂Ce(NO₃)₆ (55 mg, 0.1 mmol) until formation of the required isoxazoline. Water was added (10 mL), followed by extraction of the mixture with Et₂O (3x5 mL) and purification by PTLC (silica; Et₂O / n-hexane 1:1) afforded the N-substituted isoxazoline 8b (17.6 mg, 58%); mp 113–115°C (Et₂O / n-hexane). IR (KBr, cm⁻¹): 3291 (HC≡C), 2113 (C≡N), 1711 (C = O), 1604 (C = C).1H NMR (400 MHz CDCl₃) δ 1.71 (10H, m, Ar), 128.5 (Ar), 129.4 (Ar), 129.6 (CH₂ = CH), 5.78 (1H, m, CH₂ = CH₂). 13C NMR (100.62 MHz CDCl₃) δ 215 (M+, 100), 130 (21), 116 (38), 115 (46), 89 (13), 77 (13). HRMS: calcd for C₁₉H₁₃NO₂: 303.12641; found: 303.12641.

**Allyl-3-methyl-4-phenylisoxazolin-5-one (8c)**

To 3-methyl-4-phenylisoxazolin-5-one (Section 4.2.3) (0.3 g, 1.71 mmol) was added a solution of Na (39 mg) in EtOH (1.7 mL). To this solution was added allyl bromide (0.207 mg, 1.71 mmol). The reaction mixture was magnetically stirred, under argon, while being heated under reflux (1.8 h). On completion of the reaction (TLC control: silica; 1) Et₂O / n-hexane 1:1; 2) AcOEt), the solvent was removed under reduced pressure. Purification by CC (silica; Et₂O / n-hexane 1:1) afforded the title compound 8c (171.6 mg, 66%) as a white solid: mp 50–51°C (Et₂O / n-hexane). IR (KBr, cm⁻¹): 3291 (HC≡C), 2113 (C≡N), 1711 (C = O), 1604 (C = C).1H NMR (400 MHz CDCl₃) δ 1.71 (10H, m, Ar), 128.5 (Ar), 129.4 (Ar), 129.6 (CH₂ = CH), 5.78 (1H, m, CH₂ = CH₂). 13C NMR (100.62 MHz CDCl₃) δ 215 (M+, 100), 130 (21), 116 (38), 115 (46), 89 (13), 77 (13). HRMS: calcd for C₁₉H₁₃NO₂: 303.12643; found: 303.12641.

**Allyl-3,4-diphenylisoxazolin-5-one (8d)**

3,4-Diphenylisoxazolin-5-one (Section 4.2.4) (0.406 g, 1.71 mmol), using the previous protocol, afforded the title compound (8d) (256 mg, 85%) as a white solid: mp 105–106°C (Et₂O / n-hexane). IR (KBr, cm⁻¹): 1720 (C = O), 1615 (C = C).1H NMR (400 MHz CDCl₃) δ 4.06 (2H, d, J = 6.0 Hz, NCH₂), 5.16 (1H, d, J = 17.2 Hz, CH₂ = CH), 5.25 (1H, d, J = 10.8 Hz, CH₂ = CH), 5.78 (1H, m, CH₂ = CH₂), 7.18 – 7.48 (10 H, m, Ar–H).13C NMR (100.62 MHz CDCl₃) δ 54.9 (N–CH₂), 105.2 [N–C(Ph) = C(Ph)], 121.0 (CH₂ = CH), 127.2 (Ar), 127.7 (Ar), 128.2 (Ar), 128.3 (Ar), 128.7 (Ar), 129.0 (Ar), 129.2 (Ar), 129.3 (Ar), 131.0 (CH₂ = CH), 162.8 [N–C(Ph)], 169.9 (C = O). EIMS (m/z, %): 277 (M⁺, 100), 236 (12), 192 (27), 178 (76), 133 (13), 117 (51), 89 (46), 77 (22). HRMS: calcd for C₁₇H₁₅NO₂: 277.11028; found: 277.11037.

**Synthesis of isoxazolidinone 8e**

Diethyl 2-[(allyl-(tert-butyldimethylsilyloxy)amino)methylene]malonate (10) To a stirred solution of N-(tert-butyldimethylsilyloxy)prop-2-en-1-amine [7] (0.58 g, 2.67 mmol) in chloroform (CHCl₃ / CH₃CN 1:3) (20 mL) under argon was added diethyl 2-(ethoxymethylene)malonate [5] (0.5 g, 2.67 mmol, 1 eq.). On completion of the reaction (TLC control: silica; Et₂O / n-hexane 1:1) (30 h), the solvent was removed under reduced pressure by CC (silica; Et₂O / n-hexane 1:1) to afford the title compound (10) (50%) as an oil (50%): IR (film, cm⁻¹) 1723 (C = O), 1707 (C = O), 1621 (C = C), 1262 (Si–O–N).1H NMR (400 MHz CDCl₃) δ 0.19 [6H, s, Si(CH₃)₂], 0.93 [9H, s, C(CH₃)₃], 1.23 (6H, m, OCH₂C₂H₅), 4.00 (2H, d, J = 6.0 Hz, NCH₂), 4.12 (4H, m, OCH₂CH₃), 5.26 (1H, d, J = 10.4 Hz, CH₂ = CH), 5.35 (1H, d, J = 17.3 Hz, CH₂ = CH), 5.90 (1H, m, CH₂ = CH₂), 7.88 (1H, s, N–C = C).13C NMR (100.62 MHz CDCl₃) δ -5.3 [Si(CH₃)₂], 14.1 (OCH₂CH₃), 17.8 [C(CH₃)₃], 25.8 [C(CH₂)₃], 59.9 (CH₂N), 60.3 (OCH₂CH₃), 60.6 (OCH₂CH₃), 61.4 (NCH = C), 119.6 (CH₂ = CH), 131.1 (CH₂ = CH), 149.5 (N–CH), 166.2 (C = O). EIMS (m/z, %): 357 (M⁺, 66), 312 ([M–C₂H₅OH]+, 86), 300 ([M–C₆H₄Ar]+, 100), 226 ([M–C₆H₄OSSi]+, 97), 198 (20), 57 (C₆H₄, 49). HRMS: calcd for C₁₉H₃₁NO₅Si: 357.19715; found: 357.19796.

Diethyl 2-[(allyl-(tert-butyldimethylsilyloxy)amino)methylene]malonate (10) To a magnetically stirred solution of 2-[(allyl-(tert-butyldimethylsilyloxy)amino)methylene]malonate [5] (10) (50 mg, 0.140 mmol) in CH₂CN [6 mL, 0.1% H₂O (m/v)], at RT under nitrogen, was added SbCl₅ (359 μL, from 0.039 M solution in CH₂CN, 0.1 eq.). On completion of the reaction (10 min), (TLC control: silica; Et₂O / n-hexane 1:1), the solvent was removed under reduced pressure. Purification by CC (silica; Et₂O / n-hexane 1:1) afforded diethyl 2-[(allyl
(hydroxyl)amino)methylene]malonate (11) (23 mg, 68%), and ethyl 2-allyl-5-oxo-2,5-dihydroisoxazole-4-carboxylate (8e) (3.3 mg, 12%). Compound 11 was unstable and lactonised spontaneously on standing to the 2-allyl-isoxazolinone 8e.

**Ethyl 2-allyl-5-oxo-2,5-dihydroisoxazole-4-carboxylate (8e)** Colourless crystals, mp 45–46°C (n-hexane). IR (film, cm⁻¹): 1784 (C = O, ester), 1698 (C = O), 1578 (C=C) (8e). Ethyl 2-allyl-5-oxo-2,5-dihydroisoxazole-4-carboxylate (8e) was purified by flash chromatography. **Rearrangement of 2-allyl-3-methyl-4-phenylisoxazolin-5-one (8d)** Following the general procedure, 2-allyl-3-methyl-4-phenylisoxazolin-5-one (8c) was obtained by heating 8d at 180°C for 7 h, followed by CC (silica; Et₂O / n-hexane 1:1), as a viscous oil (95%). ¹H NMR (400 MHz CDCl₃) δ 1.34 (3H, t, J = 6.6 Hz, CH₃), 5.89 (1H, m, CH₂ = CH), 7.86 (1H, s, N–CH = C), 13.11 (1H, s, H, exchange D₂O). Elemental analysis: calcd for C₁₃H₁₅NO₄ (%): C: 54.93, H: 5.66, N: 7.11. Found (%): C: 54.53, H: 5.66, N: 7.01.

**Rearrangement of 3,4-diphenyl-2-(2′-methylbut-3′-yn-1′-yl)isoxazolin-5-one (8b)** Following the general procedure, 3,4-diphenyl-4-(3′-methylbut-1′,2′-dien-1′-yl)isoxazolin-5-one (8b) was obtained by heating 8a at 60°C for 10 m, followed by CC (silica: Et₂O / n-hexane 1:1), as a colourless solid (85%): mp 77–80 (Et₂O / n-hexane). IR (KBr, cm⁻¹): 1699 (C = C = C), 1790 (C = O). ¹H NMR (400 MHz CDCl₃) δ 1.37 (3H, s, CH₃), 1.62 (3H, s, CH₃), 5.65 (1H, t, J = 2.6 Hz, HC = C), 7.28 – 7.54 (10H, Ar–H). ¹³C NMR (100.62 MHz CDCl₃) δ 19.3 (CH₃), 19.7 (CH₃), 58.5 [N = C(Ph)C], 86.6 [CH = C = C(CH₃)₂], 102.2 (CH = C = C(CH₃)₂), 127.0 (Ar), 127.7 (Ar), 128.1 (Ar), 128.5 (Ar), 128.9 (Ar), 129.4 (Ar), 129.7 (Ar), 131.2 (Ar), 132.2 (Ar), 134.7 (Ar), 167.2 (N = C), 177.5 (C = O), 203.5 (CH = C = C(CH₃)₂). EIMS (m/z, %) 303 (M⁺, 1), 288 ([M–CH₃]⁺, 29), 259 ([M–CO₂]⁺, 53), 244 (C₁₃H₁₄NO⁺, 50), 200 (C₁₁H₁₂O₂), 141 (C₁₁H₁₀₂, 71), 89 (C₆H₅, 20), 77 (C₅H₅, 76).

**Diethyl 2-[N-(allyl)(hydroxyl)amino)methylene]malonate (11)** Oil, IR (film, cm⁻¹): 3600 – 1800 (I, O-H), 1685 (C = O), 1629 (C = C). ¹H NMR (400 MHz CD₂CN) δ 1.26 (3H, t, J = 7.1 Hz, OCH₂CH₃), 1.33 (3H, t, J = 7.1 Hz, OCH₂CH₃), 4.16 (2H, q, J = 7.1 Hz, OCH₂CH₃), 4.25 (4H, m, OCH₂CH₃ + NCH₂), 5.39 (2H, m, CH₂ = CH), 5.96 (1H, m, CH₂ = CH), 7.86 (1H, s, N–CH = C), 13.11 (1H, s, H, exchange D₂O). ¹³C NMR (100.62 MHz CD₂CN) δ 14.1 (OCH₂CH₃), 30.2 (COCOEt), 60.0 (OCH₂CH₃), 61.5 (OCH₂CH₃), 61.6 (NCH₂), 120.8 (CH = CH₂), 129.9 (CH = CH₂), 147.3 (NCH = C), 166.2 (C = O), EIMS (m/z, %) 243 (M⁺, 2), 197 (C₉H₁₁NO₄, 100). HRMS: calcd for C₁₁H₁₅NO₄: 243.11067; found: 243.10985.

**General procedure for the thermal rearrangements of isoxazolines** In a round bottom flask, the isoxazolines (8a-e) dissolved in o-dichlorobenzene (ca. 0.04 – 0.05 M) are heated until total consumption of the starting material (TLC control). After solvent evaporation the products are purified by flash chromatography.

**Rearrangement of the 3,4-diphenyl-2-(prop-2′-yn-1′-yl)isoxazolin-5-one (8a)** Following the general procedure, 3,4-diphenyl-4-(prop-1′,2′-dien-1′-yl)isoxazolin-5-one (9a) was obtained by heating 8a (10 mg) at 60°C for 30 m, followed by CC (silica; Et₂O / n-hexane 1:1), as an oil (75%): IR (film, cm⁻¹): 1965 (C = C = C), 1798 (C = O). ¹H NMR (400 MHz CDCl₃) δ 4.88 (1H, dd, J = 6.6, 12.1 Hz, CH = C = CH₂), 5.04 (1H, dd, J = 6.6, 12.1 Hz, CH = C = CH₂), 5.80 (1H, t, J = 6.6 Hz, HC = C = CH₂), 7.30 – 7.58 (10H, Ar–H). ¹³C NMR (100.62 MHz CDCl₃) δ 57.8 [N = C(Ph)C], 80.6 (CH = C = CH₂), 88.0 (CH = C = CH₂), 126.9 (Ar), 127.1 (Ar), 127.7 (Ar), 128.8 (Ar), 129.2 (Ar), 129.6 (Ar), 131.6 (Ar), 134.3 (Ar), 166.6 (N = C), 175.1 (C = O), 203.0 [CH = C = C(CH₃)₂]. EIMS (m/z, %): 275 (M⁺, 19), 231 ([M–CO₂]⁺, 100), 172 (89), 128 (99), 102 (89), 77 (82). HRMS: calcd for C₁₅H₁₃NO₂: 275.09463; found: 275.09556.
reaction of isoxazolinones with base

**Reaction of 2-allyl-3,4-diphenylisoxazolin-5-one (8d)**

To a stirred solution of compound 8d (80 mg, 0.289 mmol) in dry 1,4-dioxane (2 mL) at RT under argon, potassium ethoxide (1.5 eq., 36.5 mg, 0.38 mmol) in dry 1,4-dioxane (1 mL) at RT under argon, was added potassium ethoxide (1.5 eq., 7.0 mmol). On completion of the reaction (10 min) (TLC control: silica; Et2O/H2O 3:1), the mixture was neutralized with aq. 0.5 N AcOH and the solvent removed under reduced pressure. The crude was diluted with Et2O (5 mL) and washed with distilled water (2 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Purification by CC (silica; Et2O/n-hexane 3:1) afforded 2-((2-ethoxyethyl)-4,5-diphenyl-2,3-dihydro-1,3-oxazin-6-one (14) (23.3 mg, 25%) as a yellow oil: IR (film, cm⁻¹): 3257 ν(OCH2), 1667 ν(C = O), 1603 ν(C = O). 1H NMR (400 MHz CDCl3) δ 1.05 (3H, t, J = 7.0 Hz, OCH2CH3), 2.22 (2H, m, CH2CH3), 3.44 (2H, m, OCH2CH3), 3.62 (1H, m, OCH2CH3), 3.77 (1H, m, OCH2CH3), 5.47 (1H, q, J = 4.9 Hz, CH2CH3), 6.46 (1H, d, J = 4.1 Hz, NH – exchange D2O), 7.02 – 7.24 (10H, m, Ar–H). 13C NMR (100.62 MHz CDCl3) δ 15.0 (OCH2CH3), 32.0 (OCH2CH3), 65.7 (OCH2CH3), 66.6 (OCH2CH3), 81.6 (N=CH–O), 103.9 (N=C=CH2), 126.1 (Ar), 126.7 (Ar), 128.2 (Ar), 129.8 (Ar), 130.2 (Ar), 131.4 (Ar), 133.9 (Ar), 155.5 (N=C=CH2), 166.3 (C=O). EIMS (m/z, %): 271 (M+, 10), 171 (M+ - CH3, 100), 155 (M+ - H2O, 43). HRMS: calcld for C20H20N3O3: 323.15254; and deoxybenzoin (15, R = D) (25.5 mg, 45%) as a colourless solid: mp 55–56°C (lit: 25 mp 55–56°C). IR (KBr, cm⁻¹): 1686 (C = O). 1H NMR (400 MHz CDCl3) δ 4.29 (2H, s, CH2), 7.24 – 8.04 (10 H, m, Ar–H). After the reaction in a parallel run was completed, glacial CH3COOD (3.0 eq.) was added to the reaction followed by H2O (2 mL). The reaction mixture was diluted with Et2O (5 mL) and washed with an aqueous solution of 1M NaHCO3. The aqueous layer was extracted with Et2O (3 × 5 mL), the combined organic extracts were dried over anhydrous sodium sulphate, filtered and concentrated. Purification by CC (silica; Et2O/n-hexane 3:1) afforded mono-deuterated deoxybenzoin (15, R = D) (37.5 mg, 66%): 1H NMR (400 MHz CDCl3) δ 4.29 (1H, s, CHD), 7.23 – 8.06 (10 H, m, Ar–H).

**Reaction of ethyl 2-allyl-5-oxo-2,5-dihydroisoxazole-4-carboxylate (8e)**

To a stirred solution of compound 8e (50 mg, 0.254 mmol) in dry 1,4-dioxane (1 mL) at RT under argon, was added potassium ethoxide (32 mg, 0.38 mmol, 1.5 eq.) and 18-crown-6 ether (100 mg, 0.38 mmol). On completion of the reaction (5 h, TLC control: silica; Et2O), the solvent was removed under reduced pressure and the crude purified by cc (silica; Et2O). N-Allylmalononic acid ethyl ester (13) was obtained as a white solid (34.7 mg, 80%): mp 40–41°C (Et2O). IR (KBr) νmax (cm⁻¹): 3299 (NH), 1740 (C = O ester), 1659 (C = O amide). 1H NMR (400 MHz CDCl3) δ 1.22 (3H, t, J = 7.1 Hz, OCH2CH3), 2.62 (2H, m, CH2CH3), 3.56 (1H, t, J = 6.8 Hz, NC–CH), 4.27 (2H, q, J = 7.1 Hz, OCH2CH3), 5.25 (2H, m, CH2 = CH2), 5.83 (1H, m, CH2 = CH2).

**Reactions of 2-(2′-methylbut-3′-yn-2′-yl)-3,4-diphenylisoxazolin-5-one (8b)**

With 1.5 eq. of EtOK

To a stirred solution of compound 8b (15 mg, 0.055 mmol) in dry 1,4-dioxane (0.25 mL), under argon, was added potassium ethoxide (1.5 eq., 7.0 mg, 0.083 mmol) and 18-crown-6 ether (21.8 mg, 0.083 mmol). On completion of the reaction (10 min) (TLC control: silica; Et2O/n-hexane 3:1), the mixture was neutralized with aq. AcOH 0.5 N and the solvent removed under reduced pressure. The crude was diluted with Et2O (5 mL) and washed with distilled H2O (2 mL). The organic layer was dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure. Purification by CC (silica; Et2O/n-hexane 3:1) afforded 4-(3′-methylbut-1′,2′-dienyl-1′-yl)-3,4-diphenylisoxazolin-5-one (9b) (4.5 mg, 30%). After 30 min of reaction, no rearrangement product could be still detected by TLC.

With 0.1 eq. of EtOK

Using the previous conditions with potassium ethoxide (0.1 eq.) and 18-crown-6 ether (0.1 eq.), the reaction after 5 days yielded 9b (55%).
With LDA To a stirred solution of 8b (1 eq.) in dry 1,4-dioxane, under argon, were added LDA (1.5 eq., from a 1.47 M solution) and 12-crown-4 ether (1 eq.). The reaction mixture was stirred for 48 h. TLC control (silica; Et₂O / n-hexane 3:1) showed no reaction and the starting material was recovered yield (5.4 mg, 90%).

With tert-BuLi To a stirred solution of 8b (1 eq.) in dry 1,4-dioxane, under argon, were added tert-BuLi (2 eq., from an hexane solution 0.8 M, 0.066 mmol) and 12-crown-4 ether (2 eq.). The reaction mixture was stirred for 70 h. TLC control (silica; Et₂O / n-hexane 3:1) showed no reaction and the starting material was recovered (9.5 mg, 95%).

Endnote
* Web Table (which contains energy profiles, molecular coordinates of intermediates and transition states as well as normal mode animations) is available via the HTML version of the article.

Additional file

Additional file 1: Table S1. Calculated relative energies for intermediates and transition states relating to Scheme 6.

Competing interests
The authors declare that they have no competing interest.

Authors’ contributions
AML, HSR and SP contributed equally to this work. LFVP, MJSG and PMCG carried out the experimental work. All authors read and approved the final manuscript.

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