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Intramolecular Diels–Alder reactions of N-substituted oxazolones

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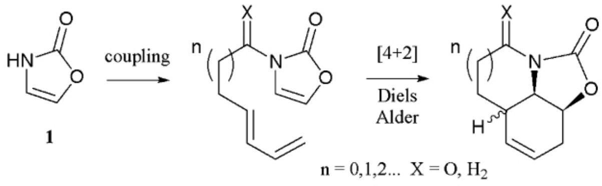
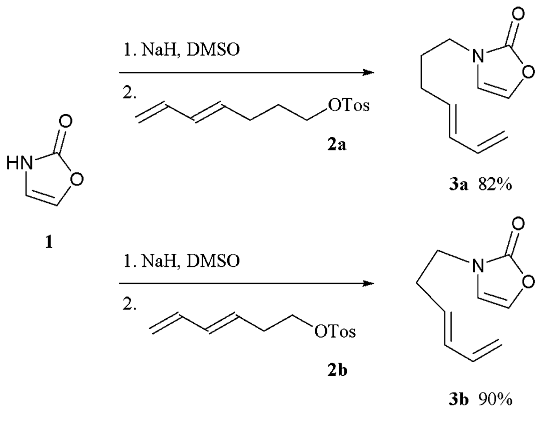
The first intramolecular Diels–Alder reactions of simple trienes featuring an N-substituted oxazolone as the dienophilic component have been investigated and are reported herein.

The intramolecular Diels–Alder reaction[1] has long proven an invaluable aid in the synthesis of complex natural products, particularly in approaches to alkaloids. We recently chose to examine the simple heterocycle oxazol-2(*3H*)-one **1** as a potential dienophilic component in reactions of this type. Indeed, N-substituted oxazolones have already proven willing participants in a variety of intermolecular reactions,[2,3] and the parent heterocycle itself is readily prepared.[4] We thereby sought to establish the efficacy of an intramolecular variant *via* a series of studies involving simplified parent triene systems, Scheme 1, the products of which themselves could prove pertinent to the construction of a wide variety of important alkaloidal motifs. We report our initial findings, to our knowledge the first of their kind, within this Communication.



Scheme 1

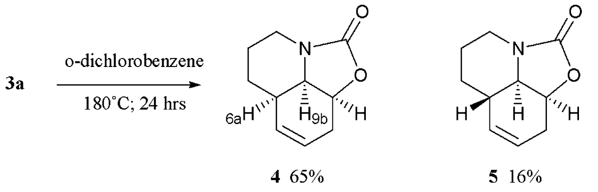
Investigation of the *N*-alkyl tether series presented the most direct line of pursuit. Construction of these precursors was readily effected by simple alkylation of the parent heterocycle **1** with the requisite diene fragments,[5] Scheme 2. Thus, treatment of oxazolone with a slight excess of sodium hydride in methyl sulfoxide, followed by dropwise addition of a solution of the tosylate **2a**[5a] afforded the heptadienyl triene system **3a** in 82% yield.[6] The hexadienyl triene **3b** was similarly obtained in 90% yield from diene **2b**.[5b]



Scheme 2

We initially chose to investigate the cycloaddition of these systems under standard thermal activation. A series of trial reactions at NMR scale disclosed conditions necessary to effect cycloaddition at both a reasonable rate and degree of conversion. Larger preparative scale reactions readily ensued.

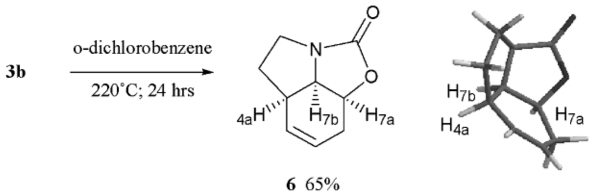
In the case of the heptadienyl triene system **3a** simply heating a dilute *ortho*-dichlorobenzene solution at 180 °C in a sealed tube for 24 h afforded a 4 : 1 mix of cycloadducts **4** and **5** in 81% combined yield, Scheme 3. Relative stereochemistry of each was assigned accordingly on the basis of key coupling constants, as determined from comprehensive ^{1}H NMR studies and closely supported by molecular modelling calculations.[7] The major *cis*-isomer **4** was readily identified after extensive decoupling experiments in CDCl$_3$ revealed a 3.8 Hz ^3J interaction between H$_{6a}$ and H$_{9b}$.[8] In contrast, the minor *trans*-isomer **5**, although partially occluded in CDCl$_3$, divulged a corresponding 9.8 Hz coupling upon detailed observation in C$_6$D$_6$.[9] These *cis*- and *trans*- products each arise from *endo* and *exo* modes of cycloaddition respectively, albeit presumably *via* minimization of unfavourable non-bonding interactions as opposed to any meaningful secondary orbital association.[1a]



Scheme 3

Unfortunately triene **3b** proved a less willing participant, requiring more forcing thermal conditions of 220 °C to induce cycloaddition; nevertheless, a single stereoisomer **6** was isolated in 65% yield.[10] The all *cis* stereochemistry was assigned on the basis of equivalent ring junction couplings of 7.7 Hz for H$_{4a}$–H$_{7b}$ and H$_{7a}$–H$_{7b}$. Calculated dihedral angles of 10.06 and 10.11° closely matched these observations, Scheme 4. Further confirmation was provided by subsequent NOE measurements. In this case the cycloaddition appears to proceed exclusively in overall *endo* fashion, though doubtless controlled by constraints of the tether.

To summarize, we have successfully demonstrated the first intramolecular Diels–Alder cycloadditions of N-substituted oxazolones. We are currently optimizing conditions for these novel reactions, as well as extrapolating the products to their logical ends, namely, as valuable synthons for the construction of various alkaloid skeletons. These and related results will be reported in due course.



Scheme 4

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Notes and references

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6 All new compounds were fully characterized by a wide range of analytical techniques, including ^{1}H and ^{13}C NMR, IR, MS, combustion analysis and/or HRMS AMM.

7 Modelled on PC Spartan Pro at the semi-empirical level, employing AM1 parameterization.

8 Selected data for **4**: δ_H (250 MHz; $CDCl_3$): 1.52 (2H, m), 1.72 (1H, m), 2.01 (1H, m), 2.07 (1H, m), 2.19 (1H, m), 2.60 (1H, ddd, *J* 16.5, 6.8 and 1.9), 2.80 (1H, ddd, *J* 13.3, 9.5 and 6.3), 3.83 (1H, dm, *J* 13.5), 3.97 (1H, dd, *J* 9.2 and 3.8), 4.90 (1H, dd, *J* 9.1 and 3.9), 5.68 (1H, dm, *J* 9.4), 5.94 (1H, m).

9 Selected data for **5**: δ_H (250 MHz; C_6D_6): 0.73 (1H, qd, *J* 12.4 and 3.7), 1.02 (2H, m), 1.36 (2H, bm), 1.89 (1H, dm, *J* 16.2), 2.14 (1H, dd, *J* 9.7 and 7.8), 2.24 (1H, m), 2.38 (1H, ddd, *J* 13.6, 12.2 and 4.6), 3.81 (1H, dbd, *J* 13.7 and 5.1), 3.98 (1H, dt, *J* 5.5 and 7.8), 5.27 (2H, m).

10 Selected data for **6**: δ_H (250 MHz; $CDCl_3$): 1.97 (1H, m), 2.13 (1H, dm, *J* 17.3), 2.26 (1H, m), 2.52 (1H, m), 2.55 (1H, ddd, *J* 17.0, 6.6 and 2.1), 3.16 (1H, ddd, *J* 11.1, 9.1 and 4.0), 3.55 (1H, dt, *J* 11.1 and 8.1), 4.15 (1H, t, *J* 7.7), 4.99 (1H, dm, *J* 8.2), 5.62 (1H, dm, *J* 10.3), 5.80 (1H, m).