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Reactivity of (*Z*)-4-arylidene-5(4*H*)-oxazolones: [4+2] cycloaddition versus [4+3] cycloaddition/nucleophilic trapping

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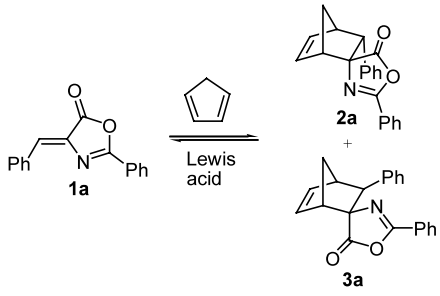
Abstract—The use of different aluminum derivatives in the reaction between cyclopentadiene and (*Z*)-2-phenyl-4-arylidene-5(4*H*)-oxazolones, and in particular the use of different equivalents of the reagent, allows the modulation of the synthesis of the norbornane skeleton by a [4+2] cycloaddition or the more interesting bicyclo[3.2.1]octane framework by a [4+3] cycloaddition followed by nucleophilic trapping of the ionic dipole cycloadduct with cyclopentadiene.

The value of 5(4*H*)-oxazolones as reagents in organic chemistry is well recognized. These compounds have been used to prepare other important heterocyclic derivatives and they are flexible reagents for the synthesis of α-keto and arylacetic acids, α-amino acids and peptides.[1–4] In particular, the chemistry of unsaturated 5(4*H*)-oxazolones has been studied in detail but, in spite of the importance and well known reactivity of the exocyclic double bond,[5–10] only very recently has it been reported by us that this double bond can operate as a dienophile in the Diels–Alder reaction. Further hydrolysis of adducts affords the subsequent amino acids and the aminolysis of adducts gives peptides.

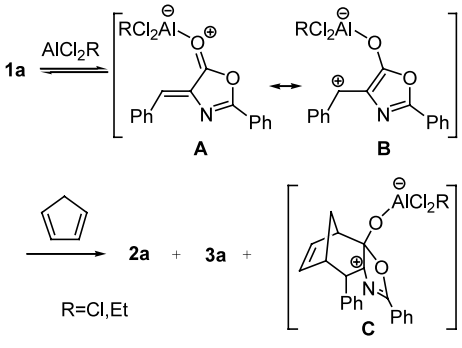
In this context, the (*Z*)-2-phenyl-4-benzylidene-5(4*H*)-oxazolone **1a** was the first azlactone to be reacted as a dienophile in the Diels–Alder cycloaddition with cyclopentadiene[11,12] using $AlCl_3$ as a Lewis acid (Scheme 1). This reaction has been extended to other dienes including 1,3-butadiene, 2,3-dimethyl-1,3-butadiene and Danishefsky's diene, with excellent results obtained in all cases.[13–16]

It is well-known that the activation of the carbonyl group of unsaturated oxazolones by a Lewis acid gives electrophilic character to the β-carbon,[1–4] which can in turn give rise to the key cationic intermediate **B** (Scheme 2).

On the other hand, a great deal of synthetic effort has been focused on methods for generating the less accessible three-atom component of the [4+3] cycloaddition,



Scheme 1. [4+2] Cycloaddition of oxazolone **1a** and cyclopentadiene.



Scheme 2. [4+2] Versus [4+3] cycloaddition of oxazolone **1a** and cyclopentadiene.

Keywords: oxazolones; Diels–Alder reactions; cycloadditions; polycyclic heterocyclic compounds; X-ray crystal structures.

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Table 1. Reaction conditions and ratio of [4+2] adducts **2a–e** and **3a–e** and [4+3] adduct **4a–e**[a]

Entry	Oxazolone	Lewis acid (equiv.)	T (°C)	Conversion[b] (%)	**2**/**3**/**4**[c]
1	**1a**	$AlCl_3$ (0.50)	−25	95	53/47/–
2	**1a**	$TiCl_4$ (0.75)	−25	60	54/46/–
3	**1a**	$AlClEt_2$ (0.75)	−25	100	37/63/–
4	**1a**	$AlMe_3$ (0.75)	−25	100	38/62/–
5[d]	**1a**	$SnCl_4$ (1.50)	−25	51	29/71/–
6[e]	**1a**	$AlCl_2Et$ (0.75)	−25	100	43/40/17
7	**1a**	$AlCl_3$ (0.75)	−25	100	22/34/44
8	**1a**	$AlCl_2Et$ (0.75)	−25	100	40/34/26
9	**1a**	$AlCl_2Et$ (1.50)	−25	100	19/12/69
10	**1a**	$AlCl_2Et$ (2.00)	−25	0	–
11	**1a**	$AlCl_2Et$ (1.50)	0	60	–/–/100
12	**1b**	$AlCl_2Et$ (0.75)	−25	100	30/34/36
13[d]	**1b**	$AlCl_2Et$ (0.75)	−25	100	29/35/36
14	**1c**	$AlCl_2Et$ (1.50)	−25	100	21/11/68
15	**1d**	$AlCl_2Et$ (1.50)	−25	100	–/11/89
16	**1e**	$AlCl_2Et$ (1.50)	−25	100	15/78/7

[a] The reaction time is 6 h with 3 equiv. of cyclopentadiene.
[b] Conversion from oxazolone to summation of adducts **2**, **3** and **4**.
[c] Measured by ^1H NMR at the vinylic protons.
[d] The reaction time is 21 h.
[e] 10 Equiv. of cyclopentadiene were used.

which can be regarded as the most attractive strategy for preparing seven-membered rings.[17–22] In particular, the oxyallyl cations are the most studied intermediates and they have participated as key derivatives in the synthesis of several natural products.[23–25]

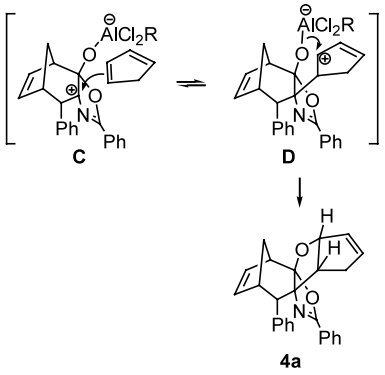
One of the most interesting methods to generate oxyallyl cation derivatives starts from 2-(trimethylsilyloxy)acrolein and its derivatives by treatment with a Lewis acid. When generated in the presence of a diene they can give the [4+3] cycloaddition.[26–29]

Taking into account this fact and the similarities between 2-(trimethylsilyloxy)acrolein derivatives and the (*Z*)-2-phenyl-4-benzylidene-5(4*H*)-oxazolone **1a**, it seemed reasonable to believe that the aromatic cation intermediate **B** could give cycloaddition with dienes as a three-atom component rather than as a two-atom dienophile, leading to the corresponding [4+3] cycloadduct **C** (Scheme 2).

In an effort to explore this possibility and the novel reactivity of unsaturated 5(4*H*)-oxazolone **1a** in the [4+3] cycloaddition with cyclopentadiene to generate the bicyclo[3.2.1]octane skeleton, we used several Lewis acids and different sets of conditions (Scheme 2, Table 1). When $AlClEt_2$, $AlMe_3$, $SnCl_4$ or $TiCl_4$ were used as Lewis acids only the [4+2] cycloadducts **2a** and **3a** were observed.

However, the use of more than 1 equiv. of $AlCl_3$ or $AlCl_2Et$ (up to 1.50 equiv.) led to the formation of a new major product. When we employed 1.50 equiv. of $AlCl_2Et$ and the reaction was carried out at –25°C, we obtained total conversion and a high yield of the new compound **4a**. The use of a higher temperature (0°C) gave rise to compound **4a** exclusively. Other Lewis acids were tested in this reaction (Yamamoto's catalyst and $BF_3{\cdot}Et_2O$) but there was no evidence for any reaction (Table 1).

We performed several experiments including COSY, HETCOR, NOESY, mass spectrometry (FAB+) and elemental analysis to elucidate the structure of the new compound **4a**. The results provided evidence for a highly functionalized bicyclo[3.2.1]octane incorporating condensed rings. The formation of this product could be explained by a highly regioselective and stereoselective nucleophilic trapping of the cationic [4+3] cycloadduct **C** with the excess cyclopentadiene. Such a process would give the intermediate **D**, which would be quickly transformed into compound **4a**. Not surprisingly,[29,30] under all conditions only the *endo* [4+3] cycloadduct is observed (Scheme 3).



Scheme 3. Nucleophilic trapping of [4+3] cycloadduct **C** with cyclopentadiene.

Moreover, we were able to confirm this structure using X-ray diffraction[†] (Fig. 1). We wish to point out the importance of this skeleton, since it is the basic scaffold of many essential biologically active natural compounds and has attracted of a great deal of interest worldwide.[31]

In order to confirm the proposed mechanism, i.e. [4+3] cycloaddition followed by nucleophilic trapping with cyclopentadiene, and to discard a possible rearrangement of the [4+2] cycloadducts followed by trapping with cyclopentadiene, we carried out the reaction between cyclopentadiene and adducts **2a** and **3a**, respectively, obtaining in both cases the starting material (conditions from entry 11, Table 1).

Moreover, when the reaction of oxazolone **1a** (entry 9, Table 1) was carried out in an NMR tube and the spectra were recorded at intervals, we observed that the progress in the formation of the three compounds **2a**, **3a** and **4a** is identical in all cases. We suppose that the driving force of the reaction is the capture of the unstable ionic [4+3] cycloadduct **C** by cyclopentadiene, with the subsequent formation of compound **4a**.

With the aim of exploring the scope of this new reaction, we tried it with other (*Z*)-4-arylidene-2-phenyl-5(4*H*)-oxazolones. The reaction of substituted-phenyl systems such as *para*-chloro, -nitro, -bromo or *ortho*-nitro allows the corresponding bicyclo[3.2.1]octane to be obtained. In the case of oxazolone **1d** an excellent yield of [4+3] cycloadduct was obtained. The NMR spectra of the new compounds **4b–e** are similar to the that of compound **4a** and are consistent with the expected structure (Scheme 4, Table 1).

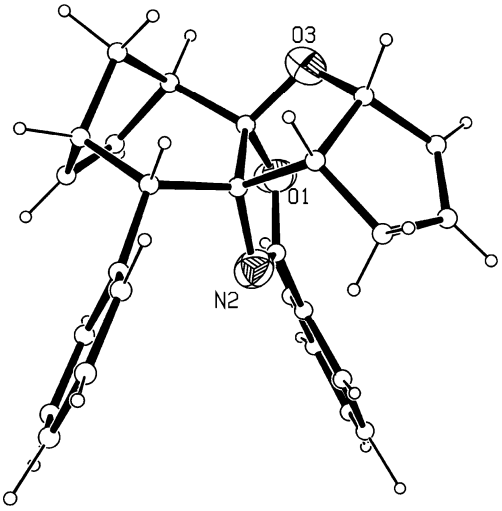
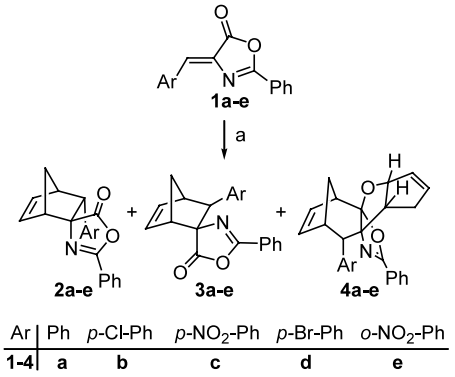


Figure 1. ORTEP diagram of compound **4a**.

The extension of this reactivity to other, less reactive dienes, such as 2,3-dimethyl-1,3-butadiene or 1,3-cyclohexadiene, has been examined and only [4+2] cycloaddition was observed in these cases. Reaction did not occur on using furan. We also investigated the cycloaddition of (*Z*)-2-methyl-4-benzylidene-5(4*H*)-oxazolone with cyclopentadiene but, in this case, only the corresponding [4+2] cycloadducts were observed under all conditions tested.

In conclusion, we have studied the significant reaction between cyclopentadiene and 2-phenyl-4-arylidene-5(4*H*)-oxazolones. These oxazolones can behave as much as a three-atom component in a [4+3] cycloaddition as a two-atom dienophile in a [4+2] cycloaddition,[32] depending on the number of equivalents of the aluminum derivative used as a Lewis acid. The corresponding [4+3] cycloadduct is captured by the excess cyclopentadiene as nucleophile, giving a highly functionalized bicyclo[3.2.1]octane framework incorporating condensed rings. This novel reactivity of unsaturated 5(4*H*)-oxazolones will be explored further in order to assess its applicability in the synthesis of interesting, highly functionalized molecules.



Scheme 4. Reaction between (*Z*)-4-arylidene-2-phenyl-5(4*H*)-oxazolones and cyclopentadiene.

[†] Crystal data: (a) $C_{26}H_{24}NO_2$, $M_w = 382.46$, colorless prism, $T = 298$ K, tetragonal, space group $P42/n$, $Z = 8$, $a = 18.6599(7)$ Å, $b = 18.6599(7)$ Å, $c = 11.2144(5)$ Å, $V = 3904.8(3)$ Å^3, $D_{calcd} = 1.301$ g cm^{-3}, $F(000) = 1624$, $\lambda = 0.71073$ Å (Mo Kα), $\mu = 0.082$ mm^{-1}, Nonius kappa CCD diffractometer, θ range 4.38–27.48°, 4443 unique reflections, full-matrix least-squares (SHELXL97[b]), $R_1 = 0.0660$, $wR_2 = 0.1389$, ($R_1 = 0.1515$, $wR_2 = 0.1713$ all data), goodness of fit = 1.013, residual electron density between 0.183 and −0.457 e Å^{-3}. Hydrogen atoms were located from mixed methods (electron-density maps and theoretical positions). Further details on the crystal structure are available on request from Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, UK on quoting the depository number 182371. (b) Sheldrick, G. M. SHELXL97. Program for the refinement of crystal structures. University of Göttingen, Germany, 1997.

Acknowledgements

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