

# Diels–Alder chemistry of 2-cyanoalk-2-enones. A convenient general approach to angularly substituted polycyclic systems

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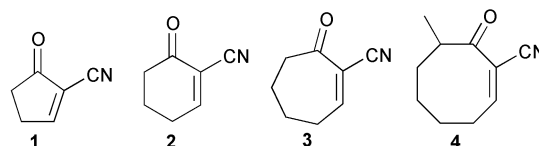
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Under zinc chloride catalysis, a number of 2-cyanoalk-2-enones representing various ring sizes were found to undergo facile cycloaddition with several selected conjugated dienes; sequential treatment of the adducts with lithium naphthalenide and an alkylating agent resulted in the direct replacement of the angular cyano group with an alkyl group, providing easy access to angularly substituted polycyclic systems.

The Diels–Alder reaction has long played an important role in synthetic organic chemistry. One of the most important features of its application is to build fused polycyclic skeletons, a process requiring only a straightforward addition of a cyclic dienophile to an appropriately substituted buta-1,3-diene. However, early investigations have demonstrated that under thermal conditions, the cycloaddition of dienes to cyclic dienophiles, such as cyclohex-2-enone is a poor process, often resulting in low yields of products.<sup>1</sup> Over the years, there have been extensive studies directed towards the enhancement of the dienophilicity of cycloalkenones, resulting in the development of two general solutions. One makes use of Lewis acid catalysis and the other involves the incorporation of an additional electron-withdrawing group to the dienophilic carbon–carbon double bond. In 1977, we showed that the introduction of a methoxycarbonyl group to C-2 of 4,4-dimethylcyclohexa-2,5-dien-1-one vastly improved the Diels–Alder reactivity of an otherwise poor dienophile.<sup>2</sup> This strategy proved to be useful for the activation of the dienophilic double bond in systems where the conjugated enone functionality could not undergo enolization towards the C-4 carbon and has been successfully applied in facilitating the total synthesis of various polycyclic natural products.<sup>3</sup> This strategy, however, was found to be less effective when the cycloalk-2-enone contains an enolizable hydrogen at C-4, as the placement of an ester group onto the C-2 carbon makes the compound extremely labile. For instance, although 2-methoxycarbonylcyclohex-2-enone can be applied as a dienophile,<sup>4</sup> the efficiency of its Diels–Alder reaction is much lower than that of its 4,4-dimethyl derivative because of the poor stability associated with the former compound. Another drawback of using an ester as an activating group is the multi-step operation required for its subsequent conversion to an alkyl group, which is often necessary in natural product synthesis. In continuation of our investigations on the activation of cycloalk-2-enones as dienophiles, we have observed that the placement of a cyano group at C-2 induces a high degree of enhancement of the dienophilicity of the parent molecule. Interestingly, the enolizable 2-cyanocyclohex-2-enones, unlike the corresponding 2-alkoxycarbonyl compounds, are rather stable.<sup>†</sup> Also the cyano group in the adducts can be directly replaced by an alkyl group *via* a reductive alkylation process.

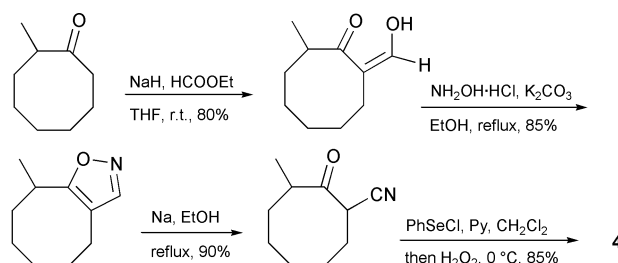
Four 2-cyanocycloalk-2-enones **1–4** representing various ring sizes were examined. Compound **4** was readily prepared from 2-methylcyclooctanone *via* a four-step synthetic sequence (Scheme 1), involving formylation,<sup>6</sup> isoxazole formation and its subsequent rearrangement,<sup>7</sup> and phenylselenenylation–oxidative elimination.<sup>8</sup> Compounds **1–3** were easily accessible by



Thorpe–Ziegler condensation of the corresponding alkanedinitriles followed by phenylselenenylation–oxidative elimination. In sharp contrast to the instability associated with the corresponding 2-alkoxycarbonylcycloalk-2-enones, cyano compounds **1–4** were shown to be rather stable and could be distilled, chromatographed and stored at 0 °C over a long period of time without apparent decomposition. Under Lewis acid catalysis, zinc chloride in particular, the Diels–Alder reaction of these compounds occurred readily at room temperature with a variety of dienes to give adducts in high yields.<sup>§</sup> As shown in Table 1, which summarizes the results obtained for the present studies, the regioselectivity strictly follows the general rules governing the Diels–Alder reaction; 1-substituted and 2-substituted buta-1,3-dienes gave *ortho*- and *para*-adducts, respectively. In terms of stereochemistry, all of the reactions, where applicable (Entries 3, 6 and 7), gave the *endo*-to-ketone addition products. Interestingly, the addition of 2-cyano-8-methylcyclooct-2-enone (**4**) to two selected dienes (Entries 6 and 7) occurred with a complete face-selectivity from what appears to be the sterically less hindered face to give adducts **10** and **11**, respectively.

The cyano group present in each of the adducts could be readily replaced by a proton or an alkyl group *via* reductive removal of the cyano group using lithium naphthalenide (LN) followed by trapping of the ensuing enolate ion with a proton source or an appropriate electrophile.<sup>9</sup> As an example, treatment of adduct **6** with a stock solution of LN (6 eq.) in THF<sup>10</sup> at –25 °C for 30 min resulted in the reductive elimination of the cyano group. Protonation of the enolate thus formed with MeOH gave ketone **12** (80% yield), whereas treatment with allyl bromide (20 °C, 20 h) gave the angularly substituted ketone **13** (75% yield). The reductive alkylation process is apparently general and highly stereoselective. In all of the cases examined (Table 2), only the *cis*-fused alkylation product was observed.

In conclusion, 2-cyanoalk-2-enones, which are surprisingly stable, have proved to be useful dienophiles. Their Diels–Alder reaction coupled with the ease of replacement of the cyano

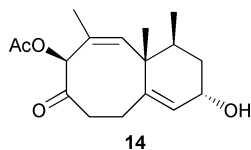


Scheme 1

**Table 1** Diels–Alder reactions of 2-cyanocycloalk-2-enones

Entry	Dieno- phile	Diene	Time/ h	Product(s)	Yield (%)
1	1		28		80
2	2		24		85
3	2		24		75
4	2		18		90
5	3		40		75
6	4		26		78
7	4		16		70

group with an alkyl group provides convenient access to various angularly substituted, *cis*-fused bicyclic systems. This newly developed process is expected to have broad synthetic utility, particularly towards polycyclic natural products of structural complexity. For instance, the complete carbon framework of neolemnane (**14**)<sup>11</sup>¶ could be rapidly constructed by two simple operations. Addition of cyano enone **4** to 2-*tert*-butyldimethylsilyloxy-penta-1,3-diene (Table 1, Entry 7) gave adduct **11**. Sequential treatment of **11** with LN and methyl iodide (Table 2, Entry 11) completed the carbon skeleton of neolemnane (**14**). Modification of the existing functionalities to effect the total synthesis of **14** is under active investigation.



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## Notes and references

† The same observation has been made previously by Fleming *et al.*<sup>5</sup>

‡ For an alternative synthetic approach to compounds **2** and **3**, see ref. 5.

§ Satisfactory spectral and elemental or HRMS analytical data were obtained for all new compounds. The structure of several compounds was further confirmed by X-ray crystallography.

¶ The IUPAC name for neolemnane is 2-hydroxy-4,4a,6-trimethyl-8-oxo-2,3,4,4a,7,8,9,10-octahydrobenzocycloocten-7-yl acetate.

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**Table 2** Reductive decyanation and alkylation of the Diels–Alder adducts

Entry	Adduct	RX or CH <sub>3</sub> OH	Time/ h	Product(s)	Yield (%)
1	5	benzyl bromide	12		60
2	6	CH <sub>3</sub> OH	0.5		80
3	6	allyl bromide	20		75
4	6	benzyl bromide	40 <sup>a</sup>		65
5	7	CH <sub>3</sub> OH	0.5		80
6	7	CH <sub>3</sub> I	12		70
7	7	benzyl bromide	12		80
8	8	allyl bromide	12		70
9	9	CH <sub>3</sub> I	13		80
10	10	CH <sub>3</sub> I	14		70
11	11	CH <sub>3</sub> I	14		70

<sup>a</sup> This alkylation was carried out at 20 °C.

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