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Unexpected Addition and Cycloaddition Products from the Reaction of 2-Alkenyl-4*H*-1,3,4-Oxadiazines with Dienophiles and Dienes.

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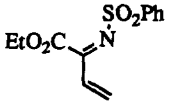
Abstract: Reaction of 2-Alkenyl-4*H*-1,3,4-oxadiazines 3 with electron deficient dienophiles gave linear addition products rather than cycloaddition products. When reacted with an electron-deficient diene, cycloaddition occurred across the olefin and not the imine.

The use of 1-aza-1,3-dienes in Hetero Diels-Alder reactions as precursors for functionalised piperidines and pyridines has been studied over the past few years[1]. In order to enhance the reactivity of 1-azadienes towards Diels-Alder cycloadditions strategic placement of substituents with 'strong' electron demands is employed. For example, 1-azadienes bearing strongly electron-withdrawing groups on the imino nitrogen and possibly a second electron-withdrawing group on the 2-position e.g. **1** readily undergo [4+2] cycloaddition reactions by an inverse electron demand mechanism.[2] Similarly, 1-azadienes with electron-donating groups on the 1-aza position, such as the *N,N*-dimethyl-aminohydrazine of methacrolein **2**, give Diels-Alder products with electron-deficient olefins.[3] Conversely, α,β-unsaturated imines have been shown to act as dienophiles with electron-rich dienes, giving substituted piperidines with good regiospecificity.[4] We were interested in developing this dual role of α,β-unsaturated imines as diene/dienophile and wanted to study the effects that addition of an electron-donating group at the C-2 position and insertion of a chiral auxilliary within the molecule would have on their reactivity in cycloaddition reactions. We would now report our initial findings on the use of 2-alkenyl-4*H*-1,3,4-oxadiazines **3** as possible chiral cyclic 1-aza-1,3-dienes or as chiral dienophiles.



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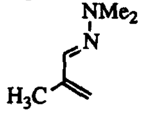

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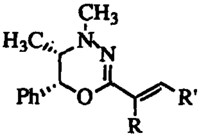
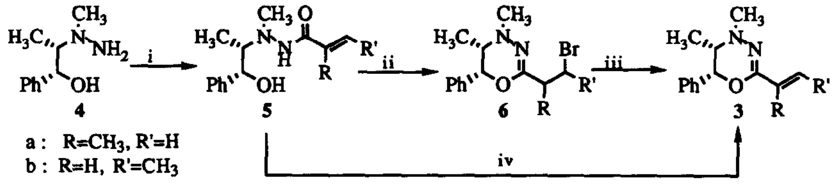


3a : R=CH_3, R'=H
3b : R=H, R'=CH_3

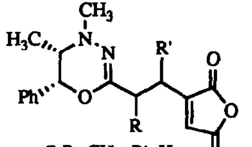
The 2-alkenyl oxadiazines **3a,b** were prepared by a modification of the procedure for the preparation of 2-aryl oxadiazines.[5] Thus, aminoephedrine **4**, prepared in two steps from *l*-ephedrine hydrochloride, was *N*-acylated with either methacryloyl chloride or crotonyl chloride to give the hydrazides **5a,b** in good yield (Scheme 1).[6] Cyclisation of the ephedrine hydrazide **5** was effected by passing gaseous hydrogen bromide through glacial acetic acid, to give the bromoalkyl oxadiazine **6** in high yield. Dehydrobromination with DBU in acetonitrile gave the expected alkenyl oxadiazine **3** in good yield. An alternative one step cyclisation of **5** using phosphoric acid gave only poor yields of oxadiazine **3**.[7]



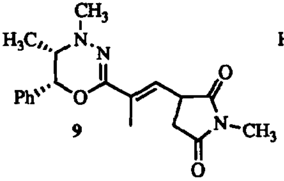
Conditions: i) R'CH=CHRCOCl, Na_2CO_3, H_2O, CH_2Cl_2 : **5a** 82 %; **5b** 85%. ii) HBr, CH_3COOH: **6a** 76 %; **6b** 82 %. iii) DBU, CH_3CN; **3a** 61 %; **3b** 69 %. iv) H_3PO_4 : **3a** 10 %; **3b** 41 %.

Scheme 1

Treatment of oxadiazines **3** with various electron-deficient acyclic dienophiles e.g. dimethyl fumarate, dimethyl acetylenedicarboxylate, acrylonitrile, under a variety of forcing reaction conditions gave no reaction. Reaction of **3a** or **3b** with maleic anhydride and *N*-methylmaleimide in refluxing toluene gave the unstable linear addition products **7**, **8**, **9** and **10** (see Table) and not the expected [4+2] cycloaddition products. Similarly, reaction of **3a** with triethyl ethylenetricarboxylate **11**[8] or reaction of **3b** with phenylthiomaleic anhydride **13**[9], gave only the linear addition products **12** and **14** respectively, with no cycloaddition product detected.



7 R=CH3, R'=H
8 R=H, R'=CH3



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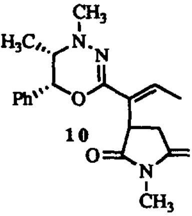

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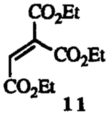

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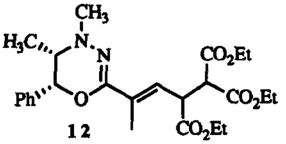

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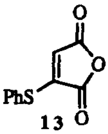

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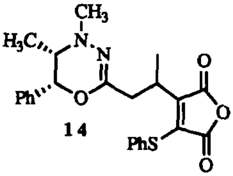

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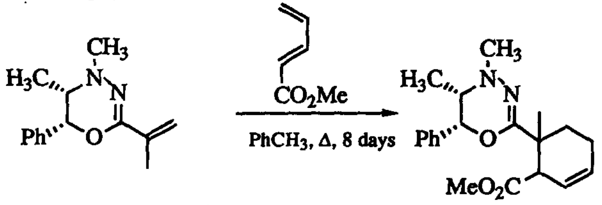
These results show that the reaction is faster with the 1,1-disubstituted olefin of **3a** than for the 1,2-disubstituted olefin of **3b** (Entries 1 and 2), and that the addition reaction is quicker for maleic anhydride than for *N*-methylmaleimide (Entries 1 and 3). Polarization of the dienophile with electron-withdrawing groups, as in **11**, or with electron-donating group, as in **13** decreases the rate of reaction[10-11] (entries 5 and 6). The low yields of the addition products **7-10** and **14** would appear to be due to the the instability of the maleic and succinimide rings towards silica gel chromatography. Adducts stable to silica gel such as **12** can be isolated in better yields.

ENTRY	OXADIAZINE	DIENOPHILE[a] (TIME)[b]	PRODUCT (YIELD)[c]
1	**3a**	MA (12 h)	**7** (46%, 1:1)
2	**3b**	MA (30 h)	**8** (21 %, 4:1)
3	**3a**	NMM (4 days)	**9** (14 %)
4	**3b**	NMM (7 days)	**10** (15 %)
5	**3a**	**11** (3 days)	**13** (19 %, 1:1)
6	**3b**	**12** (3 days)	**14** (65 %, 1:1)

[a] MA= maleic anhydride; NMM = *N*-methylmaleimide. [b] Typical reaction procedure: The oxadiazine (0.5 mmol) and dienophile (1.0 mmol) were refluxed in toluene (5 ml) under argon. The reaction was monitored by loss of starting material (tlc) and the reaction mixture was purified by silica gel column chromatography (pentane-ether). [c] Yields refer to isolated yields after chromatography. Ratios of diastereomers were measured by ^{1}H nmr integration.

The mechanism for these reactions is unclear, but reaction in which **3a** or **3b** acts as a vinyloguous azaenamine[12] giving rise to a cyclobutane derivative intermediate would seem likely.[13] Turning now to the use of 2-alkenyl-oxadiazines as dienophiles, reaction of oxadiazine **3a** or **3b** with 1-methoxy-3-(trimethylsilyloxy)-butadiene, with or without a Lewis acid present, gave no cycloadduct. However, an unexpected cycloaddition was observed for the reaction of **3a** with electron-deficient methyl pentadienoate, giving 44 % of cycloadduct **15** as a mixture of diastereomers, along with 24 % recovered starting oxadiazine (Scheme 2). A single diastereomer of **15** was isolated in 30 % yield by careful column chromatography.



3a **15**

Scheme 2

The addition of the diene across the exocyclic C=C double bond rather than the imine C=N bond is unusual, indicating that the presence of the oxygen substitutant on the C-2 carbon has an unusual effect on the unsaturated system. Once again, a vinylogous azaenamine can be envisaged to be directing stepwise cycloaddition via the C-4 position of the unsaturated system.

In conclusion, we have found that 2-alkenyl 4*H*-1,3,4-oxadiazines do not react as 1-aza-1,3-dienes, but do react with very electron-deficient and/or polar dienophiles to give linear addition products and that reaction with electron-deficient dienes occurs to give an unexpected cycloaddition across the exocyclic vinyl moiety with good regioselectivity. Work is currently in progress in extending the scope of these reactions.

Acknowledgements

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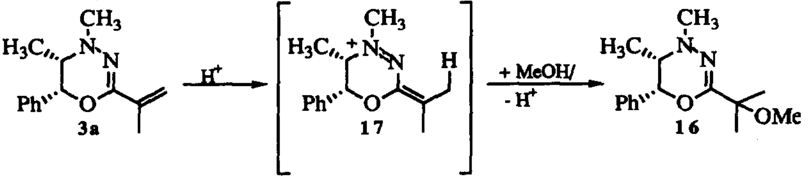
12. Treatment of oxadiazine **3a** overnight in acidified methanol gave the methoxypropyl oxadiazine **16**, presumably via the intermediate **17**.



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