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Control of electron demand in the cycloadditions of 2(*H*)-1,4-oxazin-2-ones

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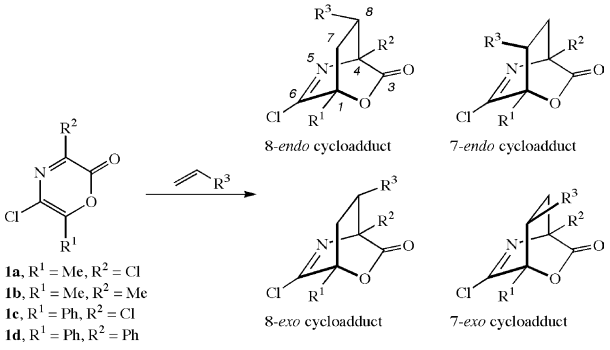
Abstract—3-Methoxy-5-chloro-6-methyl-2(*H*)-1,4-oxazin-2-one **4**, 3-methoxy-5-chloro-6-phenyl-2(*H*)-1,4-oxazin-2-one **5**, 3-phenylsulfenyl-5-chloro-6-methyl-2(*H*)-1,4-oxazin-2-one **6**, and 3-phenylsulfenyl-5-chloro-6-phenyl-2(*H*)-1,4-oxazin-2-one **7**, are ambident dienes and undergo Diels–Alder cycloadditions with electron neutral, rich and deficient dienophiles.

5-Chloro-2(*H*)-1,4-oxazin-2-ones bearing an alkyl or phenyl substituent at their 6-position and a chloro, alkyl or phenyl substituent at their 3-position, for example, **1a–d**, are ambident azadienes and undergo Diels–Alder cycloadditions with electron neutral, rich and deficient dienophiles (Scheme 1).[1–7] These cycloadditions are highly efficient, but with the exception of those for **1d**, are poorly regio- and stereoselective (Table 1). Although the cycloadditions of 5-chloro-2(*H*)-1,4-oxazin-2-ones have proved to be very useful synthetically,[8–10] the lack of selectivity in the reactions is a major obstacle in the development of new methodologies based around them. Therefore, methods which allow improved selectivity in these cycloadditions are highly desirable.

Although the ambident nature of 2(*H*)-1,4-oxazin-2-ones is unique amongst azadienes, it is paralleled in the chemistry of substituted 2(*H*)-pyran-2-ones.[11–17] Pyrone dienes bearing electronically neutral substituents also undergo poorly selective cycloadditions with dienophiles. However, the efficiency, as well as the regio- and stereoselectivity, of these cycloadditions improves significantly if the 2(*H*)-pyran-2-one diene is electronically matched with the dienophile by means of ring substitution. Hence, 3-phenylsulfenyl-2(*H*)-pyran-2-one **2**[18,19] and 3-phenylsulfonyl-2(*H*)-pyran-2-one **3**[20–23] react with electron deficient and electron-rich dienophiles, respectively, with excellent regio- and stereocontrol (Scheme 2).



Scheme 1. Cycloadditions of 2(*H*)-1,4-oxazin-2-ones with non-polar substituents.[1–4]

We expected that introduction of electronically biased groups onto the 2(*H*)-1,4-oxazin-2-one ring should

Table 1.

R^1	R^2	R^3	8-*endo*	7-*endo*	8-*exo*	7-*exo*
Me	Cl	CO_2Me	35	33	32	0
	Cl	OEt	73	0	27	0
	Me	CO_2Me	55	18	27	0
	Me	OBu	60	0	40	0
Ph	Cl	CO_2Me	30	20	30	20
	Cl	OBu	30	20	30	20
	Ph	CO_2Me	80	10	10	0
	Ph	$4\text{-}BrC_6H_4$	>98	Trace	Trace	0
	Ph	OBu	>98	0	Trace	0

Keywords: 2(*H*)-1,4-Oxazin-2-ones; Diels–Alder; Cycloaddition.
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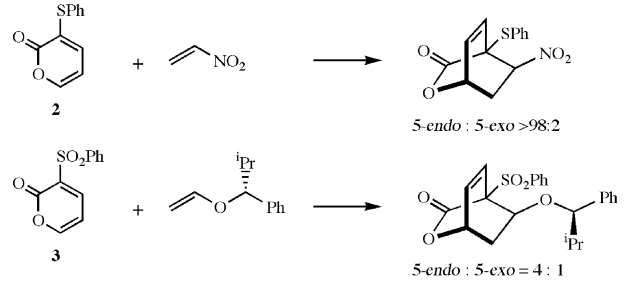
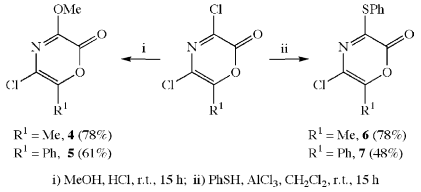


Scheme 2. Cycloadditions of 2(*H*)-pyran-2-ones.[18–23]



Scheme 3. Preparation of 2(*H*)-1,4-oxazin-2-ones.

similarly improve the regio- and stereoselectivity in their cyclo- addition reactions. Therefore, we decided to investigate the cycloaddition chemistry of 5-chloro-2(*H*)-1,4-oxazin-2-ones bearing electron donating (OMe, SPh) substituents at their 3-position. 5-Chloro-3-methoxy-6-methyl-2(*H*)-1,4-oxazin-2-one **4**, and 5-chloro-3-methoxy-6-phenyl-2(*H*)-1,4-oxazin-2-one **5**, were prepared by treatment of **1a** and **1c** with methanolic hydrogen chloride. 5-Chloro-3-phenylsulfenyl-6-methyl-2(*H*)-1,4-oxazin-2-one **6**, and 5-chloro-3-phenylsulfenyl-6-phenyl- 2(*H*)-1,4-oxazin-2-one **7**, were prepared by treatment of **1a** and **1c** with thiophenol and aluminium trichloride (Scheme 3).[4]

The 2(*H*)-1,4-oxazin-2-ones were treated with a range of electron rich and electron deficient dienophiles (**8**–**13**, Fig. 1) at room temperature or at 70 °C, and the crude reaction mixtures were analysed by NMR. In all cases, clean conversion was observed with only the cycloadducts and traces of starting materials present in the crude reaction mixtures. However, when chromatography was used to isolate the cycloadduct products, this resulted in partial or complete decomposition of the cycloadducts in some cases and loss of yield. The results are shown in Scheme 4 and Table 2, and Scheme 5 and Table 3. Assignments of the relative configurations of isolated cycloadducts were based on NOE (nuclear Overhauser enhancement) data,[1] and by comparison of the chemical shifts with those of analogous compounds.[1,6,10]

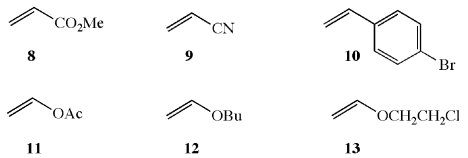
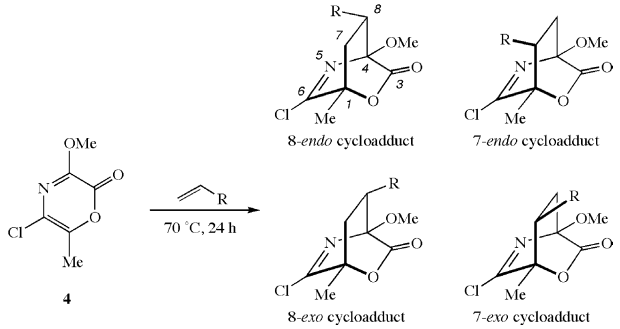


Figure 1.

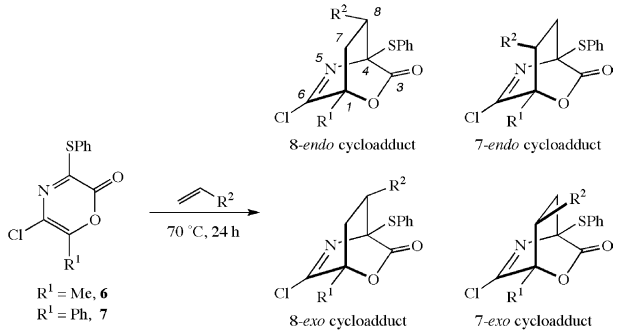


Scheme 4. Cycloadditions of **4**.

Table 2.

R	Ratio of cycloadducts[a] (yield %)[b]			
	8-*endo*	7-*endo*	8-*exo*	7-*exo*
CO_2Me	67 (53)	0	33 (26)	0
CN	50 (46)	0	50 (44)	0
4-BrC_6H_4	57 (46)	0	43 (34)	0
OAc	54[c]	Trace	46[c]	Trace
OBu	50 (38)	24 (18)	25 (19)	Trace

[a] Ratios of cycloadducts are normalised.
[b] Yields after purification by chromatography.
[c] Cycloadducts decomposed during chromatography.



Scheme 5. Cycloadditions of **6** and **7** with mono-substituted dienophiles.

Table 3.

R^1	R^2	Ratio of cycloadducts[a] (yield %)[b]			
		8-*endo*	7-*endo*	8-*exo*	7-*exo*
Me	CO_2Me	50 (35)	0	50 (25)	0
	4-BrC_6H_4	75 (69)	0	25 (15)	0
	OCH_2CH_2Cl	50 (18)[c]	12.5[c]	25 (10)[c]	12.5[c]
Ph	CO_2Me	32 (27)	18 (15)	44 (38)	6 (1)
	CN	50 (30)[c]	16 (4)[c]	34 (5)[c]	0
	4-BrC_6H_4	58 (57)	18 (12)	14 (3)	10 (10)
	OAc	33[d]	26[d]	33[d]	8[d]
	OCH_2CH_2Cl	48 (33)[c]	17 (13)[c]	35 (27)[c]	0

[a] Ratios of cycloadducts are normalised.
[b] Yields after purification by silica gel chromatography.
[c] Cycloadducts partially decomposed during chromatography.
[d] Cycloadducts decomposed during chromatography.

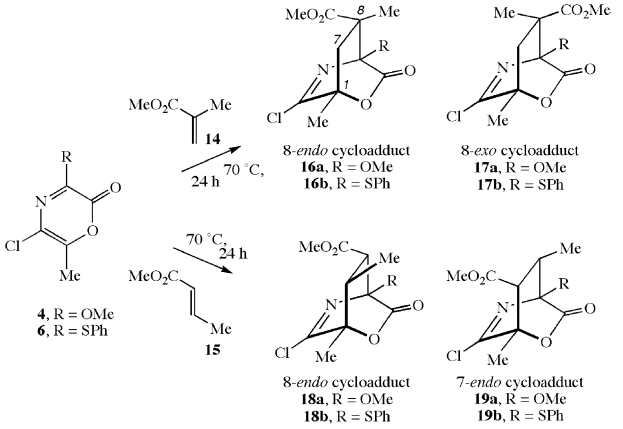
5-Chloro-3-methoxy-6-methyl-2(*H*)-1,4-oxazin-2-one **4**, underwent highly efficient cycloadditions with dienophiles **8**–**12** (Scheme 4, Table 2). In the reactions with electron-neutral and electron-rich dienophiles, all four possible cycloadducts were seen in the crude NMR. However, in the reactions with electron-deficient dienophiles, only the 8-*endo* and 8-*exo* cycloadducts were seen in the crude NMR.

The results from the cycloadditions of **4** with electron-deficient and electron-neutral dienophiles were entirely consistent with our expectations of the electron demand of this compound. Having an electron donating methoxy substituent at its 3-position, compound **4** should be an electron-rich diene and favour normal electron demand cycloadditions with electron-deficient dienophiles. The regioselectivity in favour of the formation of the 8-substituted cycloadducts is expected from Alder's rules, even though the stereoselectivity in favour of the *endo* cycloadducts is disappointingly low. Surprisingly, we also obtained cycloadducts with electron-rich dienophiles. These reactions are neither regio- nor stereoselective as might be expected from the mis-match from the electronic demand of the diene and dienophile.

The results from the cycloadditions of compounds **6** and **7** with mono-substituted dienophiles mirrored those obtained from the cycloadditions of compound **4** (Scheme 5, Table 3) Again, the results were consistent with our expectations of the electron demand of these compounds. Having an electron donating phenylsulfenyl substituent at their 3-position, compounds **6** and **7** are electron-rich dienes and favour normal electron demand cycloadditions with electron deficient dienophiles. Exclusive formation of 8-substituted cycloadducts in reactions with electron-deficient dienophiles is expected although we again obtained poor stereoselectivity as was observed in the cycloadditions of compound **4**. Again we obtained cycloadducts with electron-rich dienophiles in reactions that were neither regio- nor stereoselective.

It is clear from these results that the 5-chloro-2(*H*)-1,4-oxazin-2-ones bearing electron-donating groups at their 3-positions remain ambident dienophiles and are still capable of reacting with electron-rich, electron-neutral and electron-deficient dienophiles. The advantage gained from introducing electron-donating substituents at the 3-position of 5-chloro-2(*H*)-1,4-oxazin-2-ones is that cycloadditions with their electronically matched dienophiles (i.e., electron deficient or electron 'neutral' alkenes) become regioselective.

Cycloadditions of 2(*H*)-1,4-oxazin-2-ones with di-substituted dienophiles provided more intriguing results (Scheme 6 and Table 4). Compounds **4** and **6** undergo cycloaddition with both methyl methacrylate **14** and methyl crotonate **15**. However, although the reaction with *gem*-substituted **14** affords a mixture of the 8-*endo* and the 8-*exo* cycloadducts **16** and **17**, reaction with *vic*-substituted **15** affords a mixture of the 8-*endo* and the 7-*endo* cycloadducts **18** and **19**. No traces of the other regioisomeric cycloadducts were observed in the crude



Scheme 6. Cycloadditions of **4** and **6** with disubstituted dienophiles.

Table 4.

Dienophile	Diene	Ratio of cycloadducts[a] (yield %)[b]			
		8-*endo*	7-*endo*	8-*exo*	7-*exo*
14	**4**	50 (16)	0	50 (5)	0
14	**6**	75 (20)	0	25 (10)	0
15	**4**	50 (15)	50 (25)	0	0
15	**6**	20 (13)	80 (38)	0	0

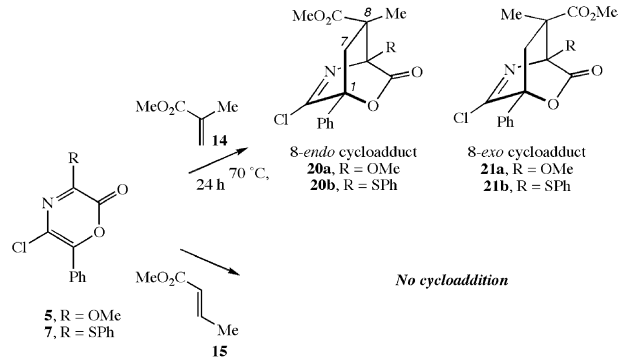
[a] Ratios of cycloadducts are normalised.
[b] Yields after purification by silica gel chromatography.

NMR spectra in any of the cases. The regiochemistry of the cycloadducts were confirmed by NOESY. For instance, the regiochemistry of the cycloadducts **16a** and **17a** were confirmed by an NOE between the signals of H-7 at 1.90 and 2.66 ppm for **16a**, and 2.05 and 2.75 ppm for **17a**, with the methyl substituent at C-1. Similarly, the regiochemistry of the cycloadducts **18a** and **19a** were confirmed by an NOE between the signals of H-7 at 2.49 and 2.67 ppm, respectively, with the methyl substituent at C-1.

The observed regiochemical preference in the cycloadditions of **4** and **6** with **14** are in line with that observed in the cycloaddditions with methyl acrylate **8**. However, the outcome of the cycloadditions of **4** and **6** with **15** are unexpected. The dominance of the 7-substituted cycloadducts in these reactions indicates that the regiochemical preferences in the cycloadditions are not exclusively determined by the electronic demand of the dienes.

Another unusual feature of the cycloadditions of these unprecedented ambident dienophiles is that 5-chloro-6-phenyl-2(*H*)-1,4-oxazin-2-ones, **5** and **7**, are considerably less reactive than the corresponding 5-chloro-6-methyl-2(*H*)-1,4-oxazin-2-ones, **4** and **6**. For instance, 2(*H*)-1,4-oxazin-2-ones, **5** and **7**, do not afford any cycloadducts with **15** although they do undergo efficient cycloaddition with **14** to afford 8-substituted cycloadducts **20** and **21** (Scheme 7 and Table 5).

We speculate that the differences between the reactivity of the 6-methyl and the 6-phenyl substituted 2(*H*)-1,



Scheme 7. Cycloadditions of **5** and **7** with disubstituted dienophiles.

Table 5.

Dienophile	Diene	Ratio of cycloadducts[a] (yield %)[b]			
		8-*endo*	7-*endo*	8-*exo*	7-*exo*
14	**5**	90 (32)	0	10 (3)	0
14	**7**	64 (50)[c]	0	36 (16)[c]	0

[a] Ratios of cycloadducts are normalised.
[b] Yields after purification by silica gel chromatography.
[c] 33% of unreacted starting material was also isolated.

4-oxazin-2-ones with di-substituted dienophiles **14** and **15** may be due to the influence of steric factors. Thus, the lack of reactivity between **15** and **5** or **7** can be attributed to the repulsion between the sterically demanding phenyl substituent at the 6-position of 2(*H*)-1,4-oxazin-2-one azadiene with the β-methyl substituent in methyl crotonate. Similarly, the preference for formation of the 7-*endo* cycloadduct in the cycloadditions between **15** and **4**, or **6**, can be attributed to the greater repulsion between the C-1 and C-7_{endo} methyl groups, which would have arisen in the 8-*exo* cycloadduct.

These results also show that although the pattern of reactivity of 2(*H*)-1,4-oxazin-2-ones broadly follows those of 2(*H*)-pyran-2-ones, there are subtle but significant differences between them. In particular, although 2(*H*)-1,4-oxazin-2-ones can be considered as the 2-azadiene analogues of 2(*H*)-pyran-2-one dienes, they are significantly more versatile and reactive species than 2(*H*)-pyran-2-ones.

In summary, we have demonstrated that 2(*H*)-1,4-oxazin-2-ones are highly reactive azadienes that undergo efficient regio- and stereoselective cycloadditions with mono-substituted dienophiles. The presence of electron-donating groups at the 3-position on the 2(*H*)-1,4-oxazin-2-one rings improves the regioselectivity of the cycloadditions with electronically matched (i.e., electron deficient) dienophiles, however, it does not preclude cycloadditions with electronically mis-matched (i.e., electron rich) dienophiles. Furthermore, cycloadditions of electron rich 2(*H*)-1,4-oxazin-2-ones with disubstituted dienophiles **14** and **15**, do not follow the same pattern, indicating that the regiochemical preferences in the cycloadditions are not exclusively determined by the electronic demand of the dienes.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.07.105.

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