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2(*H*)-1,4-Oxazin-2-ones as ambident azadienes

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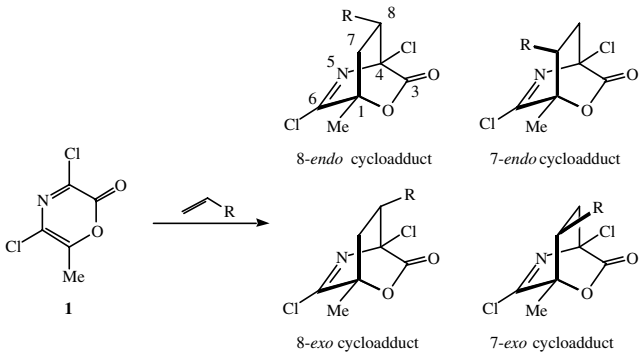
Abstract—3,5-Dichloro-6-phenyl-2(*H*)-1,4-oxazin-2-one **3**, 5-chloro-3,6-dimethyl-2(*H*)-1,4-oxazin-2-one **4**, 5-chloro-6-methyl-3-phenyl-2(*H*)-1,4-oxazin-2-one **5** and 5-chloro-3,6-diphenyl-2(*H*)-1,4-oxazin-2-one **7**, are ambident azadienes reacting efficiently and selectively with both electron rich and electron poor dienophiles.

The Diels–Alder reaction of azadienes is a well established and useful method in organic synthesis.[1] In particular, the azadiene components of many aromatic nitrogen-containing heterocycles have been utilised in [4+2] cycloadditions.[2] These include 1,2,4-triazines,[3] oxazoles,[4] thiazoles,[5] pyrimidines,[6] 1,3-oxazin-2-ones,[7] 1,3-oxazin-6-ones[8] and 1,4-oxazin-2-ones.[9]

During an investigation of the use of 2(*H*)-1,4-oxazin-2-ones in the synthesis of azasugars,[10] we became interested in an unusual feature of the Diels–Alder cycloadditions of 3,5-dichloro-6-methyl-2(*H*)-1,4-oxazin-2-one **1**, which were originally reported by Hoornaert.[9a,b] This compound was reported to undergo cycloadditions with examples of electron deficient (methyl acrylate), electron neutral (styrene), and electron rich (ethyl vinyl ether) dienophiles (Scheme 1, Table 1). Although the reactions were not regio- and stereoselective, to our knowledge this was the only example of an 'ambident' 2-azadiene, that is one which is capable of both normal and inverse electron demand Diels–Alder cycloadditions. Curiously, the only other known ambident dienes are derived from 2(*H*)-pyran-2-ones, for example, 3-bromo-2(*H*)-pyran-2-one,[11a] 5-bromo-2(*H*)-pyran-2-one **2**,[11b,c] and 3,5-dibromo-2(*H*)-pyran-2-one,[12] (Scheme 2, Table 2). Therefore, it appears that 2(*H*)-1,4-oxazine-2-ones are 2-azadiene counterparts of the well-investigated 2(*H*)-pyran-2-one dienes. To complement our long standing interest in the cycloaddition reactions of 2(*H*)-pyran-2-ones[11] and their synthetic applications,[13] we decided to evaluate the cycloaddition reactions of several 1,4-oxazin-2-ones with the aim of exploring their potential for synthesis.



Scheme 1. Cycloadditions of 3,5-dichloro-6-methyl-2(*H*)-1,4-oxazin-2-one.[9]

Table 1

R	Conditions[a]	Ratio of cycloadducts			
		8-*endo*	7-*endo*	8-*exo*	7-*exo*
CO_2Me	A	35	33	32	0
C_6H_5	B	53	20	18	9
OEt	C	73	0	27	0

[a] Conditions: A: 70 °C, 3 d; B: 70 °C,18 h; C: rt, 4 h.

3,5-Dichloro-6-methyl-2(*H*)-1,4-oxazin-2-one **1**, and 3,5-dichloro-6-phenyl-2(*H*)-1,4-oxazin-2-one **3**, were prepared according to the method reported by Hoornaert.[14] 5-Chloro-3,6-dimethyl-2(*H*)-1,4-oxazin-2-one **4**, and 5-chloro-6-methyl-3-phenyl-2(*H*)-1,4-oxazin-2-one

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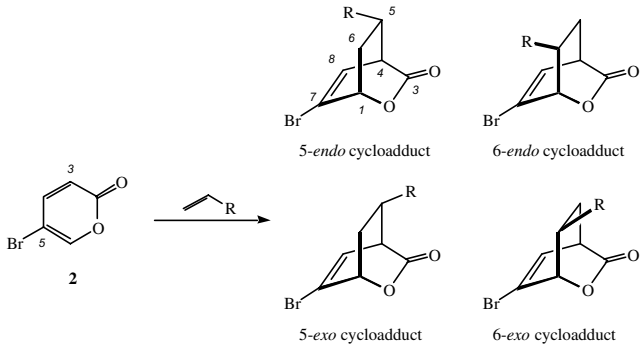
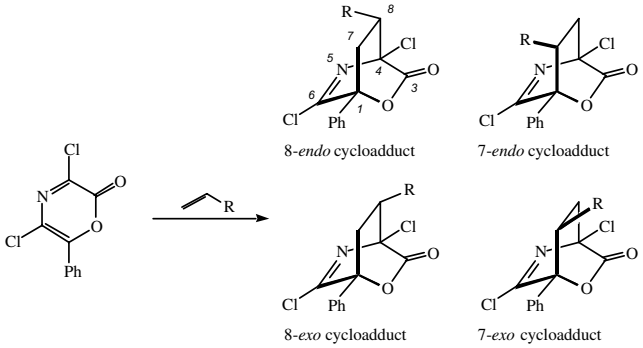


Scheme 2. Cycloadditions of 5-bromo-2(*H*)-pyran-2-one.[11b,c]



Scheme 4. Cycloadditions of 3,5-dichloro-6-phenyl-2(*H*)-1,4-oxazin-2-one.

Table 2

R	Conditions[a]	Ratio of cycloadducts			
		5-*endo*	6-*endo*	5-*exo*	6-*exo*
CO_2Me	A	66	20	14	0
4-BrC_6H_4	B	80	20	0	0
OCH_2CH_2Cl	B	67	0	33	0

[a] Conditions A: rt, 4 d; B: 100 °C, 2 d.

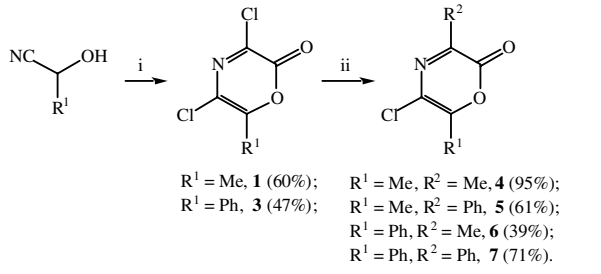
Table 3

R	Conditions[a]	Ratio of cycloadducts			
		8-*endo*	7-*endo*	8-*exo*	7-*exo*
OBu	A	30	20	30	20
	B	30	20	30	20
CO_2Me	A	30	20	30	20
4-BrC_6H_4	A	40	20	30	10
OAc	A	40	20	30	10

[a] Conditions A: 70 °C, 2 d; B: rt, 4 d.

5, were prepared by the Stille coupling of **1** with tetramethyltin and trimethylphenyltin, respectively (Scheme 3). 5-Chloro-3-methyl-6-phenyl-2(*H*)-1,4-oxazin-2-one **6**, and 5-chloro-3,6-diphenyl-2(*H*)-1,4-oxazin-2-one **7**, were prepared by the Stille coupling of **3** with tetramethyltin and trimethylphenyltin, respectively (Scheme 3).

The oxazinones were treated with a range of electron rich and electron deficient dienophiles (**8**–**12**, Fig. 1) at room temperature or at 70 °C and the crude reaction mixtures were analysed by NMR. The yields of the cycloadditions were taken to be quantitative as no starting material or impurity could be detected in the unpurified reaction mixtures. Where possible, the cycloadduct products from each reaction were isolated by chromatography, recrystallisation or a combination of both.



Scheme 3. Preparation of 2(*H*)-1,4-oxazin-2-ones. (i) ($COCl_2$), toluene, reflux, 24 h; (ii) R^2SnMe_3, $Pd(PPh_3)_4$, toluene, reflux, 24 h.

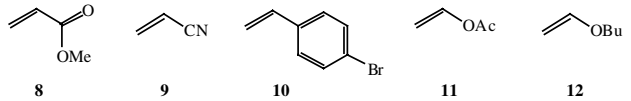


Figure 1.

3,5-Dichloro-6-phenyl-2(*H*)-1,4-oxazin-2-one **3**, underwent a highly efficient but poorly selective cycloaddition with methyl acrylate **8**, 4-bromostyrene **10**, vinylacetate **11** and butyl vinyl ether **12** (Scheme 4, Table 3). This parallels the results obtained by Hoornaert for the cycloadditions of the methyl analogue **1**.[9] Indeed, in these cycloadditions all four possible cycloadducts were seen in the crude NMR.

To test that the ratios of products obtained were not the results of a thermodynamic equilibrium, we carried out the reaction between **3** and butyl vinyl ether **12**, at both reflux and room temperatures. The proportions of the cycloadducts were identical in both reactions. Furthermore, the ratio of cycloadducts remained unchanged over a period of time beyond that required for the completion of the cycloaddition reaction, confirming that the cycloadditions were not reversible and that these ratios are not thermodynamically derived.

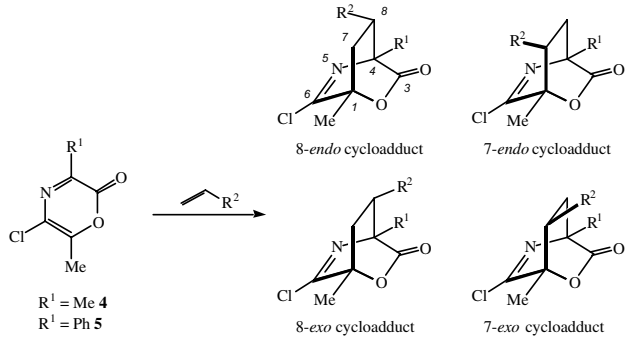
Although the cycloadditions of 3,5-dichloro-6-phenyl-2(*H*)-1,4-oxazin-2-one **3** were poorly stereoselective, in each case two of the four possible isomers predominated slightly. These were deduced to be the 8-*endo* and 8-*exo* substituted cycloadducts based on NOE (nuclear Overhauser enhancement) data, and a comparison of the chemical shifts with those of analogous reference compounds.[11d,15]

This is demonstrated by the cycloadducts from the reaction between **3** and butyl vinyl ether (Scheme 4,

R = OBu). In the cycloadduct assigned the 8-*endo* configuration, we observed no NOE between H-8 (appearing distinctly at 4.25 ppm) and any of the aromatic protons. However, we did observe an NOE between H-7_{endo} (appearing at 2.33 ppm) and one of the aromatic protons. Interestingly, H-7_{exo} (appearing at 2.78 ppm) showed a considerably weaker NOE with the same aromatic proton. Similarly, in the cycloadduct assigned the 8-*exo* configuration, we observed no NOE between H-8 (appearing distinctly at 4.08 ppm) and any of the aromatic protons. However, we did observe an NOE between H-7_{exo} (appearing at 2.43 ppm) and one of the aromatic protons. Interestingly, H-7_{endo} (appearing at 2.87 ppm) showed a considerably weaker NOE with the same aromatic proton. The lower chemical shift of the H-8 (4.08 ppm) in the compound assigned the 8-*exo* configuration, compared to that of the H-8 (4.25 ppm) in the compound assigned the 8-*endo* configuration is fully consistent with the previously established literature precedent.[11d,15] For the cycloadducts assigned the 7-*endo* and 7-*exo* configurations the H-7 signals appearing at 4.27 and 4.37, respectively, showed NOEs to an aromatic proton. The assignments of the cycloadducts from the reaction between **3** and methyl acrylate **8**, and bromostyrene **10**, were carried out in a similar fashion.

The configurations (*endo*/*exo*) of the two 8-substituted isomers in the cycloaddition of bromostyrene, and vinyl acetate where partial stereoselectivity was observed, were deduced from the expectation of the predominance of the *endo* isomer in the Diels–Alder cycloaddition, and from the results obtained for the cycloadditions of 5-chloro-3,6-diphenyl-2(*H*)-1,4-oxazin-2-one **7** (see later).

The results of the cycloadditions with oxazines **4** and **5** are reported in Scheme 5 and Table 4. Again, it was possible to assign the relative regiochemistry of the cycloadducts based on NOE data. The configurational (*endo*/*exo*) assignment of the two 8-substituted isomers was deduced from the expectation of the predominance of the *endo* isomer in the Diels–Alder cycloaddition. As can be seen, the reactions were more selective than the ones for **1** and **3**, affording the 8-*endo* cycloadduct as the major product followed typically by the 8-*exo* product. The 7-*exo* product was only observed in trace quantities in one reaction.



Scheme 5. Cycloadditions of 5-chloro-3,6-dimethyl-2(*H*)-1,4-oxazin-2-one and 5-chloro-6-methyl-3-phenyl-2(*H*)-1,4-oxazin-2-one.

Table 4

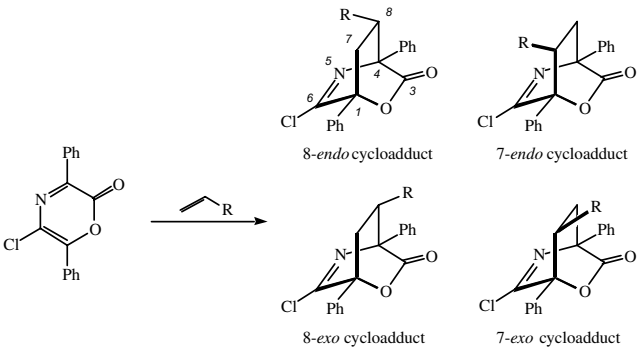
R^1	R^2	Conditions[a]	Ratio of cycloadducts			
			8-*endo*	7-*endo*	8-*exo*	**7**-*exo*
Me	CO_2Me	B	55	18	27	0
	CN	A	67	0	33	0
	4-BrC_6H_4	A	38	16	38	8
	OAc	A	64	14	22	0
	OBu	A	60	0	40	0
Ph	CO_2Me	B	68	16	16	0
	CN	A	40	7	53	0
	4-BrC_6H_4	A	80	0	20	0
	OAc	A	55	18	27	0
	OBu	A	71	0	29	0

[a] Conditions A: 70 °C, 2 d; B: rt, 4 d.

In contrast, we were unable to obtain pure cycloadducts from the reactions of **6** with any of the dienophiles **8**–**12**. This heterocycle was found to be sensitive and decomposed significantly during the attempted cycloaddition reactions.

We next turned our attention to the cycloadditions of 5-chloro-3,6-diphenyl-2(*H*)-1,4-oxazin-2-one **7** (Scheme 6, Table 5). This azadiene underwent facile and selective cycloadditions to the dienophiles shown in Figure 1.

Since in the cycloadducts obtained in these reaction both bridgehead substituents are phenyl, assignments of the relative configurations of the cycloadducts based on NOE data is not possible. Fortunately, however, the major products in each of the cycloadditions to acrylonitrile **9**, 4-bromostyrene **10**, and butyl vinyl ether **12**, were all crystalline and the relative configurations of all



Scheme 6. Cycloadditions of 5-chloro-3,6-diphenyl-2(*H*)-1,4-oxazin-2-one.

Table 5

R	Conditions[a]	Ratio of cycloadducts			
		8-*endo*	7-*endo*	8-*exo*	**7**-*exo*
CO_2Me	B	80	10	10	0
CN	A	77	8	15	0
4-BrC_6H_4	A	>98	Trace	Trace	0
OAc	A	45	22	22	11
OBu	A	>98	0	Trace	0

[a] Conditions A: 70 °C, 2 d; B: rt, 4 d.

three could be confirmed by X-ray crystallography. The configurations of all three of the major cycloadducts from the reaction between *7* and these three dienophiles were found to be 8-*endo*. In other words, cycloadditions between **7** and electron deficient, electron neutral or electron rich dienophiles (Scheme 5, R = CN, 4-BrC_6H_4, and OBu) all afforded selectively the same configuration of cycloadduct.

The results for the cycloadditions of 2(*H*)-1,4-oxazin-2-ones **3**–**5** and **7** demonstrate that the ambident nature of **1** is not unique and that the introduction of methyl and phenyl substituents to the 3- and 6-positions of the 2(*H*)-1,4-oxazin-2-one nucleus affords ambident azadienes which react with both electron deficient dienophiles (e.g., methyl acrylate **8**, and acrylonitrile **9**) and electron rich dienophiles (e.g., butyl vinyl ether **12**), as well as weakly activated dienophiles (e.g., 4-bromostyrene **10**, and vinyl acetate **11**). Furthermore, the cycloadditions can be very selective, but the selectivity depends on the substituents present on the oxazinone ring. For example, in most cases, oxazinone **7** affords only one major cycloadduct. Finally and most importantly, the cycloadditions of these 2(*H*)-1,4-oxazin-2-ones always afford an 8-*endo* cycloadduct either exclusively or as the major product *regardless of the electronic demand of the dienophile*. This configuration is similar to the major one obtained in the cycloadditions of 3- and 5-bromo-2(*H*)-pyran-2-ones, the regio- and stereoselectivity of which are also independent of the electronic demand of the dienophile. Therefore, there appears to be a strong parallel between the cycloaddition chemistry of 3- and 5-bromo-2(*H*)-pyran-2-ones and 5-chloro-2(*H*)-1,4-oxazinones.

Acknowledgements

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