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Unusual Stereoselectivity in Diels-Alder Cycloadditions of 5-Bromopyrone

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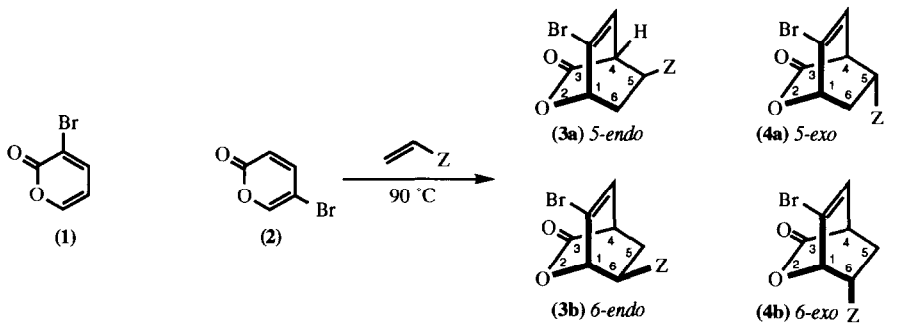
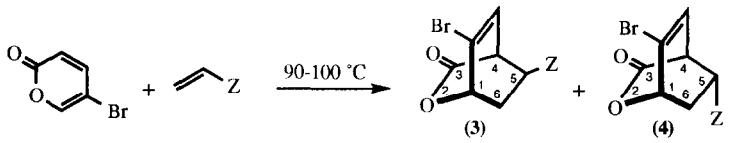
Abstract: 5-Bromopyrone undergoes cycloaddition to poorly activated or unactivated alkenes to afford high yields of cycloadducts. The regiochemistry of the cycloaddition is excellent. The stereoselectivity of cycloaddition depends on both electronic and steric factors in the dienophile but can be controlled to give predominantly *endo* or predominantly *exo* cycloadducts. © 1997 Elsevier Science Ltd.

It has been shown by Posner that easily prepared[1] 3- and 5-bromopyrone, **(1)** and **(2)**, take part as diene components in Diels-Alder cycloadditions, with **both** electron rich and electron deficient alkenes, to afford excellent yields of bicyclic lactones **(3)** and **(4)**.[2,3,4] These functionally rich bicyclic lactones can be chemically manipulated and thus, are a convenient springboard for the synthesis of densely substituted cyclohexane structural motifs present in many natural products. For instance, Posner *et al.* have used this methodology for the synthesis of ring A analogues of the biologically important steroidal hormone, calcitriol (Vitamin D_3).[3,5]



It has been established previously that cycloadditions of 5-bromopyrone with electronically biased alkene dienophiles can be highly regio- and stereoselective, affording the 5-endo cycloadduct **(3a)** as the major product, regardless of the electron demand of the alkene substituent. The regio- and stereoselectivity observed in the cycloadditions of 5-bromopyrone is similar to that of 3-bromopyrone and until now, the latter was believed not to have any advantages over the former, except that it reacts faster. In this paper, we report two unprecedented features of 5-bromopyrone cycloadditions: Firstly, the cycloaddition of 5-bromopyrone with *unactivated* mono-substituted alkenes which is unparalleled for 3-bromopyrone. Secondly, direct formation of *exo* cycloadducts with *sterically demanding* alkenes.

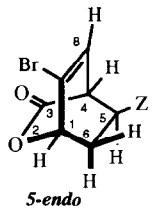


Z	Yield (%)	*endo : exo*	Z	Yield (%)	*endo : exo*
$OSiPh_2Me$	47	70:25	OCO[redacted]	61	50:50
$4\text{-}BrC_6H_4$	89	80:20	[redacted]	73	55:45
CH_2Br	62	50:50	OCHO	49	40:60
C_4H_{10}	84	50:50	OCOMe	88	30:70
CH_2CHMe_2	86	50:50	N-Pyrroli[redacted]	79	<10:90
$CH(Me)C_2H_5$	33	45:55	NPhth	90	<10:90

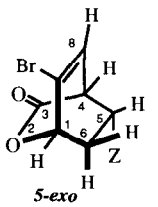
Scheme 1

The yields and the diasteromeric ratio of the products of the cycloadditions of 5-bromopyrone to a range of mono substituted alkenes of different electronic demand is outlined above (Scheme 1). The ratio of the regio- and stereoisomers of the cycloadducts was determined from analysis of the crude reaction mixture by high field nmr prior to purification. The products were isolated by silica gel chromatography. In some instances, isomeric cycloadducts were separable by chromatography, occasionally however, the product itself was obtained as an inseparable mixture of stereoisomers (*endo* and *exo*). Generally speaking, the regioselectivity of the reaction is very good, typically >95:5 in favour of the 5-substituted cycloadducts.

	5-*endo* Cycloadduct			**5-*exo* Cycloadduct**		
Z	δH_5	$J_{4,5}$	$J_{4,8}$	δH_5	$J_{4,5}$	$J_{4,8}$
CO_2Me	3.09	2.7	6.3	2.81	2.3	7.1
$OSiPh_2Me$	4.40	3.3	6.5	4.21	3.3	6.9
$4\text{-}BrC_6H_4$	3.39	2.4	6.6	3.16	2.3	6.8
OAc	5.40	3.4	6.4	5.05	3.2	7.0
OCOPh	2.87	3.7	6.5	2.58	3.4	7.0
N-Pyrrolidinone	3.63	2.6	6.6	3.51	2.4	7.0
NPhth	4.80	2.6	6.5	4.59	2.2	6.9



5-endo



5-exo

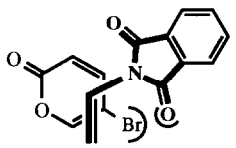
Scheme 2

The stereochemistry and regiochemistry of cycloadducts was established from the coupling constants in high field (360 MHz) nmr according to the empirical rules set previously by us and others.[4,6] Thus, the regioisomerism of the cycloadducts was determined by the multiplicity of the H-1 and H-4 protons which are distinguished by their distinctive chemical shifts at 5.0-5.2 ppm and 3.6-4.1 ppm respectively. In 5-substituted cycloadducts, the H-1 proton appears as a multiplet, usually unresolved whereas H-4 appears as a clear dd. In 6-substituted cycloadducts, the H-4 proton appears as an unresolved multiplet whereas H-1 appears as a clear ddd or dt. The stereochemistry at the 5-position of the cycloadduct is easily assigned from the size of $J_{4,5}$ and

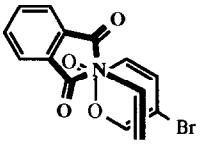
$J_{4,8}$ couplings (Scheme 2). The $J_{4,5}$ is larger in the *endo* cycloadduct than in the *exo* cycloadduct, whereas $J_{4,8}$ is smaller in the *endo* cycloadduct than in the *exo* cycloadduct. It should also be noted that H-5 in *exo* cycloadducts has a lower chemical shift than its counterpart in the *endo* cycloadduct. This is due to deshielding of $H\text{-}5_{endo}$ by the magnetic anisotropic effect of the alkene in the cycloadducts.[7]

As can be seen (Scheme 1), 5-bromopyrone undergoes thermal cycloadditions to poorly activated alkenes (vinylacetate) and even some unactivated alkenes (1-hexene). Although the reactivity of 5-bromopyrone with weakly activated alkenes should be expected from its well-established "chameleon" nature, it is unparalleled in 3-bromopyrone and can only be attributed to its higher reactivity as a diene.[8]

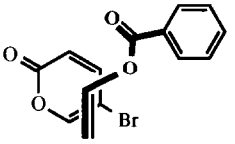
Cycloadditions of 5-bromopyrone with unactivated, non-sterically demanding alkenes are regioselective, however, the stereoselectivity of the cycloadditions is quite interesting. It is generally accepted that the product of the cycloaddition of pyrones (and pyridones) are the kinetically favoured *endo* cycloadduct.[4] *Exo* cycloadducts, which are thermodynamically favoured, are usually obtained at higher temperatures where the cycloaddition is reversible.[9] Since cycloadducts are prone to loss of CO_2 (ultimately resulting in aromatic compounds) at elevated temperatures, this means that practically, *exo* cycloadducts are not obtainable by cycloaddition. Indeed, cycloadditions of many substituted pyrones and pyridones are highly *endo* selective. The promotion of the *endo* cycloaddition is attributed to the secondary orbital interactions and therefore, it is not unexpected that cycloaddition to 1-hexene gives *endo : exo* ratio of nearly one.[10] A similar result is obtained if the dienophile is sterically demanding but the steric bulk is not very close to the alkene dienophile. Thus the same *endo.: exo* ratio is obtained for 4-methylpent-1-ene. On the other hand, cycloaddition to 3-methylpent-1-ene where the steric congestion is closer to the reaction centre, affords very slighlty more of the *exo* isomer (*endo : exo* = 45 : 55). We subsequently demonstrated that the *exo* cycloadduct is formed kinetically under reaction conditions by showing that the *endo : exo* ratio of the product at time intervals is constant. This is the first example in the cycloaddition chemistry of pyrones where steric factors alone have influenced the stereoselectivity of the cycloaddition. Since all strongly activated dienophiles are known to afford endo cycloadducts regardless of their steric bulk, it is clear that the overriding factor deciding the stereoselectivity of cycloaddition is secondary orbital interaction.



(5)



(6)



(7)

Scheme 3

However, we obtained a surprising result from the cycloaddition of vinylbenzoate. Although this dienophile is weakly activated, we still expected the major cycloadduct to have the *endo* configuration due to the possible secondary orbital interaction. Contrary to our expectation, the reaction is not stereoselective and indeed affords very slightly more of the *exo* isomer. Interestingly, the *endo : exo* ratio is quite similar to that obtained in the cycloadditions of vinylformate and vinylacetate. The lack of stereoselectivity, which presumably arises from the lack of strong secondary orbital interaction, suggested to us that cycloaddition to these weakly activated dienophiles may be much more susceptible to steric interaction. This is confirmed from the results of the cycloadditions of N-vinylpyrrolidinone and N-vinylphthalimide, where the reactions are highly *exo* selective. Here, the steric congestion arises directly from an unfavoured steric interaction in the transition state leading to the *endo* cycloadduct **(5)** between the second nitrogen substituent and the bromine atom. Therefore, transition state **(6)** leading to the *exo* cycloadduct is favoured. This does not arise in the transition state for the *endo* cycloadduct of vinylbenzoate, **(7)** since the benzoate group can swing away from the bromine in transition state (Scheme 3).

In summary, we have shown that 5-bromopyrone undergoes cycloaddition to a very wide range of activated and unactivated mono-substituted alkenes. The reactions proceed with excellent yield and with the correct choice of dienophile can afford either predominantly *endo* or predominantly *exo* cycloadducts. Being a more promiscuous diene than 3-bromopyrone, 5-bromopyrone clearly has more advantages as a starting point for total synthesis. We are currently investigating the cycloadditions of symmetrical and unsymmetrically disubstituted dienophiles and will report on their regio- and stereoselectivity in due course.

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10. *Typical experimental procedure:* 5-bromopyrone (80 mg, 0.46 mmol) was dissolved in hexene (2.0 mL) containing few drops of dichloromethane and the solution was transferred into an ACE pressure tube (purchased from Aldrich Chemical Co. Cat No Z18,109-9) containing a small magnetic stirrer bar (optional). The pressure tube was sealed and then immersed in an oil bath maintained at 95 °C. After 5 days, the tube was cooled and opened. The solution was transferred into a roundbottomed flask and solvent was removed. The crude sample was analysed by nmr prior to silica gel chromatography using 20% v/v diethylether in petroleum ether (60-80 °C bp fraction). Removal of solvent from appropriate fractions afforded the desired products as gums (100 mg, 84%); δ_H (360 MHz, $CDCl_3$): Exo cycloadduct 0.90 (3H, t, J = 6.7 Hz, CH_3), 1.25-1.50 (7H, m, 3 x CH_2), 1.66 (1H, ddd, J = 13.4 Hz, 4.8 Hz, 3.6 Hz, H-6_{exo}), 1.87 (1H, m, H-5), 2.09 (1 H, ddd, J = 13.4 Hz, 9.9 Hz, 1.7 Hz, H-6_{endo}), 3.40 (1 H, dd, J = 6.8 Hz , 2.3 Hz, H-4), 5.07 (1 H, m, H-1), 6.61 (1 H, dd, J = 6.8 Hz, 2.5 Hz, H-8) Endo cycloadduct 0.89 (3H, t, J = 6.5 Hz, CH_3), 1.2-1.3 (6H, m, 3 x CH_2), 1.38 (1H, ddd, J = 13.6 Hz, 4.0 Hz, 1.4 Hz, H-6_{endo}), 2.10 (1 H, m, H-5), 2.40 (1H, ddd, J = 13.6 Hz, 9.0 Hz, 4.4 Hz, H-6_{exo}), 3.49 (1 H, dd, J = 6.7 Hz , 2.5 Hz, H-4), 5.07 (1 H, m, H-1), 6.48 (1 H, dd, J = 6.7 Hz, 2.5 Hz, H-8); δ_C (90 MHz, $CDCl_3$) Exo cycloadduct 14.0 (CH_3), 22.5 (CH_2), 29.8 (CH_2), 32.5 (C-5), 34.0 (C-6), 35.0 (CH_2), 48.4 (C-4), 81.3 (C-1), 120.8 (CBr=), 131.6 (CH=), 171.3 (C=O) Endo cycloadduct 14.0 (CH_3), 22.5 (CH_2), 29.4 (CH_2), 32.5 (C-5), 32.7 (C-6), 34.5 (CH_2), 47.7 (C-4), 80.9 (C-1), 120.5(CBr=), 128.8 (CH=), 172.4 (C=O); IR ($CHCl_3$) 1740 (C=O) cm^{-1}; HRMS Calcd for $C_{11}H_{16}O_2{}^{79}Br^+$ (MH^+) 259.0334, found 259.0319.

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