CONCENTRATION EFFECT ON THE STEREOSELECTIVITY OF [4+2] CYCLOADDITION REACTIONS OF 3-CYANO-γ-BENZOPYRONE DERIVATIVES WITH ELECTRON RICH DIENES

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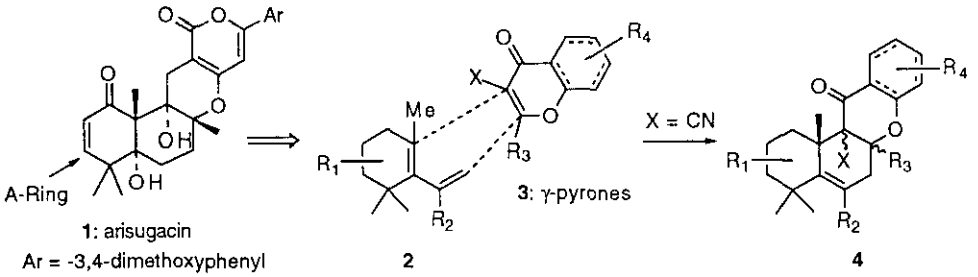
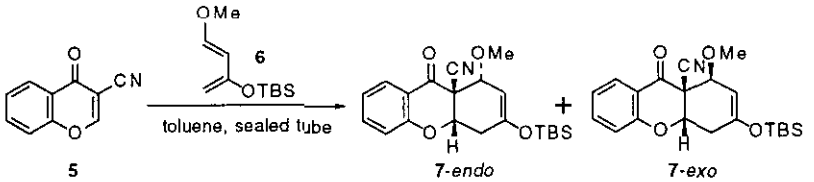
Abstract - The stereoselectivity of [4+2] cycloaddition reactions of 3-cyano-γ-benzopyrone derivatives with electron rich dienes was found to be influenced by the reaction concentrations of γ-benzopyrone derivatives.

[4+2] Cycloaddition reactions employing γ-pyrones (**3**) as dienophiles with electron rich dienes such as **2** offer a unique approach to the synthesis of natural products such as arisugacin (**1**). Arisugacin (**1**), a novel and selective inhibitor of acetylcholinesterase, was first isolated from penicillium Sp. FO-4259 in 1995.[1] Given the potential significance of arisugacin in the therapeutic treatment of Alzheimer's disease,[2,3] this



synthetic strategy could provide a convergent approach to a wide range of useful structural analogs. We recently reported the first highly stereoselective [4+2] cycloaddition reactions of 3-cyano-γ-benzopyrone derivatives (**3**) with electron rich dienes, and a synthesis of the ABC tricyclic core (**4**) of arisugacin using this methodology.[4] We report here our observations of an interesting stereochemical dependence of cycloaddition reactions of 3-cyano-γ-benzopyrone derivatives on reaction concentrations of γ-pyrones.

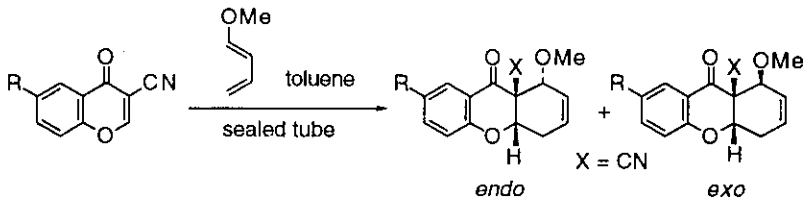
Scheme 1



Conc. of 5	Temp.	Time	Yield	*endo* : *exo* Ratio
0.1 *M*	200 °C	72 h	80 %	57 : 43
0.1	300	96	90	33 : 67
0.5	300	24	95	48 : 52

It was initially observed that reactions of 3-cyano-γ-benzopyrone (**5**) with the TBS protected Danishefsky's diene provided opposing stereoselectivities at 200 °C and 300 °C[5] (**Scheme 1**), and that the stereoselectivity of these reactions appeared to depend on the reaction concentration of **5**. Since dienophilic reactivities of γ-pyrones have received rather limited attention,[6-8] these observations were further examined using a series of γ-benzopyrones reacting with 1-methoxy-1,3-butadiene.

Table 1: Effect of the γ-Benzopyrone Concentration on Stereoselectivity.



endo *exo*

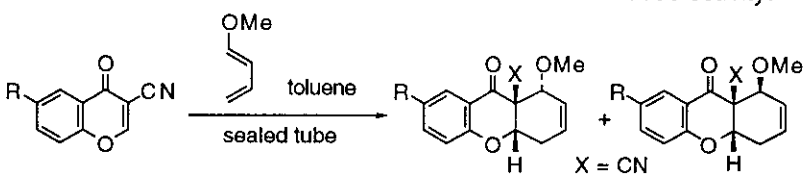
Entry	γ-Pyrone	R	γ-Pyrone Concentration[a]	Temperature[b]	Time	Product	Yield[c]	*endo* : *exo* [d]
1	**5**	H	0.10 *M*	300 °C	96 h	**8**	83 %	11 : 1
2	**5**	H	0.20	300	48	**8**	74	6.5 : 1
3	**5**	H	0.45[e]	300	60	**8**	83	3.5 : 1
4	**9**	Br	0.10	300	30	**10**	74	9 : 1
5	**9**	Br	0.45[e]	300	48	**10**	79	1 : 1
6	**9**	Br	0.10	200	40	**10**	80	≥25 : 1
7	**9**	Br	0.45[e]	200	24	**10**	78	11 : 1
8	**11**	Cl	0.10	300	32	**12**	58	1 : 1
9	**11**	Cl	0.45[e]	300	38	**12**	75	1 : 3
10	**11**	Cl	1.43[e]	300	20	**12**	86	1 : 1
11	**11**	Cl	0.10	200	20	**12**	87	22 : 1
12	**11**	Cl	0.45[e]	200	24	**12**	89	19 : 1

[a] In all reactions, 2.0 eq of dienes were used. Reactions were carried out in toluene using a sealed tube. [b]The reaction temperatures indicated were measured at the bottom of a sand bath. [c]All yields were isolated yields. [d] Ratios were obtained using ^{1}H NMR, and the stereochemistry was assigned according to nOe experiments. [e]Concentrations of γ-pyrones here were calculated based on the total volume which included toluene and the volume contributed by the addition of larger amounts of the diene.

When reactions were carried out at 300 °C, the stereoselectivity was found to be very sensitive to concentrations of 3-cyano-γ-benzopyrone derivatives (**5**, **9**, and **11**). For all three γ-benzopyrones, the *endo* selectivity decreased noticeably when concentrations of γ-pyrones were increased from 0.10 *M* to 0.45 *M* (**Table 1**, Entries 1-5 and 8-9). This trend is particularly interesting in the case of γ-benzopyrone (**11**). The reaction of **11** with 1-methoxy-1,3-butadiene was completely stereorandom when the concentration of **11** was 0.1 *M*, while provided the highest *exo* selectivity at 0.45 *M* (**Table 1**, Entry 9). At an even higher concentration (1.43 *M*), the reaction of **11** was again not stereoselective (**Table 1**, Entry 10). The *endo*:*exo* ratios of these reactions were determined by using ^{1}H NMR, and the stereochemical assignment was carried out by using nOe experiments.[9] This concentration effect was also observed for reactions of γ-

benzopyrones (**9**) and (**11**) at 200 °C. The *endo* : *exo* ratio clearly decreased from ≥25:1 to 11:1 when the concentration of **9** was raised from 0.10 *M* to 0.45 *M* (**Table 1**, Entries 6 and 7). However, the concentration effect was less apparent for the γ-benzopyrone **11** at 200 °C since the *endo* : *exo* ratio was only reduced slightly from 22:1 to 19:1 with the respective change in the reaction concentration (**Table 1**, Entries 11 and 12). It is worthy to note that γ-benzopyrones **9** and **11** behaved quite differently under the same reaction conditions. It implies that bromine and chlorine substituents at the C-6 position of **9** an **11** exert different electronic influence to the dienophilicity of these γ-benzopyrones.

Table 2: Effect of the Diene Concentration on Stereoselectivity.



Entry	γ-Pyrone	R	Eq of Diene[a]	Temperature[b]	Time	Product	Yield[c]	*endo* : *exo*[d]
					endo		*exo*	
1	**9**	Br	2.00 eq	200 °C	40 h	**10**	80 %	≥25 : 1
2	**9**	Br	17.0	200	36	**10**	86	15 : 1
3	**9**	Br	29.0	200	36	**10**	60	18 : 1
4	**9**	Br	2.00	300	30	**10**	74	9 : 1
5	**9**	Br	17.0	300	24	**10**	71	22 : 1
6	**9**	Br	29.0	300	26	**10**	67	19 : 1
7	**11**	Cl	2.00	200	20	**12**	87	22 : 1
8	**11**	Cl	17.0	200	30	**12**	70	20 : 1
9	**11**	Cl	29.0	200	30	**12**	50	≥25 : 1
10	**11**	Cl	2.00	300	32	**12**	58	1 : 1
11	**11**	Cl	17.0	300	24	**12**	48	8 : 1
12	**11**	Cl	29.0	300	26	**12**	48	17 : 1

[a] In all reactions, γ-benzopyrone concentration was 0.1 *M* (see Reference 10).
[b] Reactions were carried out in toluene using a sealed tube and the temperatures indicated were measured at the bottom of a sand bath. [c] All yields were isolated yields.
[d] Ratios were obtained by using ^{1}H NMR, and the stereochemistry was assigned according to nOe experiments.

Since 2 eq of the diene were used in the studies described in **Table 1**, the diene concentration was also varied with γ-benzopyrone concentrations. Hence, it became necessary to distinguish whether the observed stereochemical dependence in these reactions is solely due to the variation of γ-benzopyrone concentrations or also due to the corresponding change in diene concentrations. A series of reactions were carried out in which the diene concentration was varied, while the concentration of the γ-benzopyrone was maintained at 0.1 *M* [10] (**Table 2**). At 200 °C, the excess of diene appeared to disfavor the *endo* selectivity for the γ-benzopyrone **9** (**Table 2**, Entries 1-3) but favor the *endo* selectivity for the γ-benzopyrone (**11**) (**Table 2**, Entries 7-9). The more compelling observations would be from those reactions carried out at 300 °C.

Higher diene concentrations favored the *endo* selectivity for both γ-benzopyrones (**9**) and (**11**) (**Table 2**, Entries 4-6 and 10-12). Given the stereochemical dependence (especially at 300 °C) shown in **Table 1**, results here in **Table 2** suggest that the observed loss of *endo* selectivity is likely due to the change in the concentration of γ-benzopyrones but not the diene.

In an effort to further understand the observed stereochemical dependence on reaction concentrations, the following control experiments were carried out. A 0.1 *M* solution of the cycloadduct (**12**) with an *endo* : *exo* ratio of 22:1 was resubjected to the same reaction condition (without adding any **11**) either in the absence of diene or the presence of 2.0 eq of the diene. In the absence of diene, **12** was recovered in 65% yield with a ratio of 20:1 in favor of the *endo* product after 24 h at 300 °C, and the corresponding γ-benzopyrone (**11**) was also isolated in 15% yield. In the presence of 2.0 eq of the diene, **12** was recovered in 85% yield with a ratio of 20:1 in favor of the *endo* product after 24 h at 300 °C, and the γ-benzopyrone (**11**) was not observed. The presence of **11** in the first experiment indicated the occurrence of retrocycloaddition which is not surprising at high temperatures. Therefore, an equilibration between the *endo* and *exo* products could take place. Although such an equilibration at high temperatures could be responsible for the loss of *endo* selectivity, that *endo* : *exo* ratios remained relatively the same in both of these control studies suggests that equilibration alone cannot account for the drastic loss of the *endo* selectivity shown in **Table 1**, and that the reaction concentration of γ-benzopyrone derivatives is in part responsible for the observed stereochemical dependence in **Table 1**. This intriguing concentration effect on stereochemistry is rather uncommon for Diels-Alder cycloaddition reactions,[11] and has not been previously reported for [4+2] cycloadditions using γ-pyrone derivatives as dienophiles. We are currently exploring the mechanistic details of this interesting concentration effect.

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9. NOe enhancement was observed only for the tertiary allylic hydrogen on the newly formed ring upon irradiation of the β-hydrogen on the γ-pyrone ring in *endo*-**7**. On the other hand, nOe enhancement was observed only for methyl hydrogens upon irradiation of the same β-hydrogen in *exo*-**7**.
10. Reaction concentrations of γ-benzopyrone derivatives were maintained at 0.1 *M* by adjusting the amount of the γ-benzopyrone used to the increased volume caused by the addition of excess of diene. Specifically, for reactions using 17 eq of the diene, 0.12 mmol of **9** and **11** were used to maintain the concentration at 0.1 *M* since volume increased by 0.2 mL when 17 eq of the diene were added. For reactions using 29 eq of the diene, 0.14 mmol of **9** and **11** were used to maintain the concentration of the γ-benzopyrone at 0.1 *M* since the reaction volume increased by 0.4 mL when 29 eq of the diene were added.
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