First Stereoselective [4 + 2] Cycloaddition Reactions of 3-Cyanochromone Derivatives with Electron-Rich Dienes: An Approach to the ABC Tricyclic Frame of Arisugacin[1]

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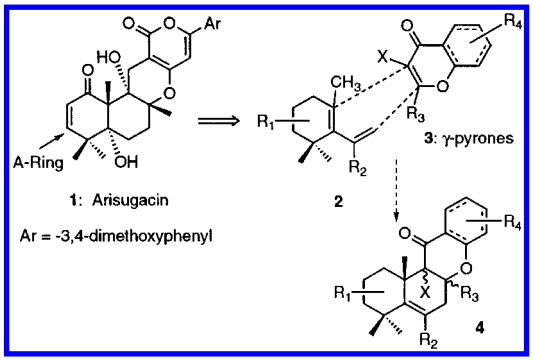
Our interest in arisugacin (**1**), a novel and selective inhibitor of acetylcholine esterase that was isolated from penicillium sp. Fo-4259,[2] has led us to explore the synthetic potential of γ-pyrones as dienophiles in [4 + 2] cycloaddition reactions. Particularly, we envisioned that if dienes such as **2** could be used, then such a cycloaddition would lead to a convergent approach for constructing not only the tetracyclic frame of arisugacin, but also of other structurally analogous natural products such as pyripyropenes[3] and forskolin.[4] Given the significant therapeutic potential of arisugacin in the treatment of Alzheimer's disease,[2,5] this strategy could serve as a useful entry to a wide range of structural analogues with unique biological activities.



It was surprising to find that there have been very few reports on [4 + 2] cycloaddition reactions using γ-pyrones as dienophiles.[6,7] We have focused our interest on 3-cyanochromone derivatives because to the best of our knowledge, the dienophilic reactivity of these compounds have gone unnoticed,[8] and they could be excellent systems for exploring the potential of our strategy as well as for investigating the scope (i.e., regio- and stereoselectivity) of γ-pyrones in [4 + 2] cycloadditions. In addition, the aromatic ring of cyanochromone derivatives, when appropriately substituted, could serve as a precursor for constructing the D-ring of arisugacin, and more importantly, analogues of arisugacin containing aromatic D-rings could offer interesting biological activities. We report here our initial success in achieving high stereoselectivities in the first [4 + 2] cycloaddition reactions using 3-cyanochromone derivatives as dienophiles and in demonstrating the synthetic application of this reaction for constructing the ABC tricyclic core of arisugacin.

The reaction of 3-cyanochromone (**5**) with TBS-protected Danishefsky's diene (**6**) in toluene proceeded well at 200 °C in a sealed tube for 72 h to give the desired cycloadduct **7** in 80% yield (Scheme 1) without observing any inverse-electron demand [4 + 2] cycloadducts.[9] However, the *endo*:*exo* ratio was only 1.3:1 as determined from ^{1}H NMR, and the stereochemistry was assigned according to NOE experiments.[10] A strong electron-withdrawing group at the C-3 position was essential and the most effective in adjusting the electron density of the γ-pyrone system of chromone derivatives and enhancing the dienophilic reactivity. For examples, 3-bromochromone (**8**)[11] was found to be reactive only with 1,3-cyclohexadiene giving the adduct **10** in <16% yield with an isomeric ratio of 2:1 (stereochemistry not vigorously assigned) after heating at 300 °C for 120 h. An acyl group at the C-2 position rendered the compound **9** more reactive providing **11** (1:1 *endo*:*exo*) in 25% yield after 120 h at 270 °C, but the regioselectivity suffered in this case since regioisomers were isolated in an equal amount.

The reactions of **5** with 1-methoxy-1,3-butadiene provided a much different stereochemical outlook giving the cycloadduct **12** in 83% yield with an *endo*:*exo* ratio of 92:8 (entry 1 in Table 1). This represents the first example of a highly diastereoselective [4 + 2] cycloaddition reaction involving a γ-benzopyrone dienophile.[6b] Subsequent reactions of **5** with all other less oxygenated dienes were found to be highly *endo* selective (Table 1, entries 2−4). However, the rate of reaction was noticeably slower when the electron density of the diene decreased. For nonoxygenated dienes, reactions had to be promoted by the use of a Lewis acid (Table 1, entries 4 and 5). After screening a variety of Lewis acids, $TiCl_4$ (1.0 equiv) was found to be most suitable, and the stereoselectivity in these reactions remained in favor of the *endo* products (Table 1, entry 4). When the diene **16**, which bears an electron-withdrawing group was used, no cycloadducts were isolated under any conditions (Table 1, entry 6). In comparison, the diene **16** reacted well with 2-cyclohexenone and methyl vinyl ketone under Lewis acid conditions.[12] This suggests that the lack of reactivity observed here with 3-cyanochromone (**5**) is likely not due to the steric nature (being 1,1-disubstituted) but rather the

(1) The preliminary results of this work were carried out at Columbia University.

(2) For isolation of arisugacin see: (a) Omura, S.; Kuno, F.; Otoguro, K.; Sunazuka, T.; Shiomi, K.; Masuma, R.; Iwai, Y. *J. Antibiot.* **1995**, *48*, 745. For biological activities of arisugacin see: (b) Kuno, F.; Otoguro, K.; Shiomi, K.; Iwai, Y.; Omura, S. *J. Antibiot.* **1996**, *49*, 742. (c) Kuno, F.; Shiomi, K.; Otoguro, K.; Sunazuka, T.; Omura, S. *J. Antibiot.* **1996**, *49*, 748.

(3) (a) Tomoda, H.; Tabata, N.; Yang, D. J.; Namatame, I.; Tanaka, H.; Omura, S.; Kaneko, T. *J. Antibiot.* **1996**, *49*, 292. (b) Smith, A. B., III; Kinsho, T.; Sunazuka, T.; Omura, S. *Tetrahedron Lett.* **1996**, 6461.

(4) (a) Corey, E. J.; Jardine, P. D. S.; Rohloff, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 3672. (b) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *Ibid.* **1987**, *109*, 8115.

(5) (a) Alzheimer, A. *Gesamte Psych.* **1907**, *64*, 1264. Arisugacin's therapeutic potential was found on the basis of the cholinergic hypothesis since it is a potent inhibitor of acetylcholine esterase (AChE). For a leading reference see: (b) Jaén, J. C.; Gregor, V. E.; Lee, C.; Davis, R.; Emmerling, M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 737. For a leading reference on another potent inhibitor huperzine see: (c) Kozikowski, A. P.; Ding, Q. J.; Saxena, A.; Doctor, B. P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 259.

(6) (a) Cremins, P. J.; Saengchantara, S. T.; Wallace, T. W. *Tetrahedron* **1987**, *13*, 3075. (b) Ohkata, K.; Kubo, T.; Miyamoto, K.; Ono, M.; Yamamoto, J.; Akiba, K. *Heterocycles* **1994**, *38*, 1483.

(7) (a) Groundwater, P. W.; Hibbs, D. E.; Hursthouse, M. B.; Nyerges, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 163. (b) Chen, D.; Totah, N. I. *Abstracts of Papers*, 213th National Meeting of the American Chemical Society, San Francisco, CA, Spring 1997; American Chemical Society: Washington, DC, 1997; ORGN-173.

(8) 3-Cyano-4*H*-benzopyran-4-thione was reported to give xanthione upon reacting with 1-(dimethylamino)-1,3-butadiene. An initial [4 + 2] cycloadduct, albeit never isolated, was postulated as the intermediate involved in providing xanthione after dehydroamination and dehydrocyanation. See: Sain, B.; Prajapati, D.; Mahajan, A. R.; Sandhu, J. S. *Bull. Soc. Chim. Fr.* **1994**, *131*, 313.

(9) Wallace, T. W.; Wardell, I.; Li, K.-D.; Leeming, P.; Redhouse, A. D.; Chanlland, S. R. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2293.

(10) 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**, whereas NOE enhancement was observed only for methyl hydrogens upon irradiation of the same β-hydrogen in *exo*-**7**.

(11) Gammill, R. B. *Synthesis* **1979**, 901.

(12) Stork, G.; Hsung, R. P. Unpublished results.

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Scheme 1

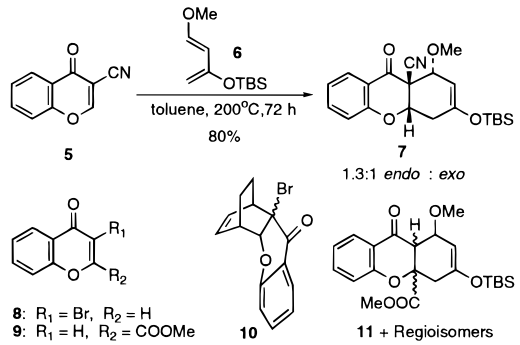


Table 1. [4 + 2] Cycloaddition Reactions of 3-Cyanochromone Derivatives

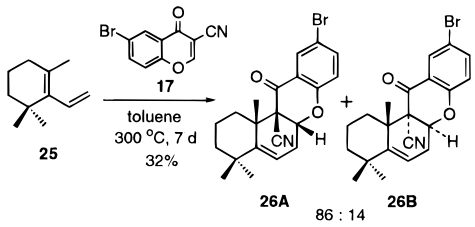
Entry	γ-Pyrones	Dienes[a]	Product	Temp/LewisAcid, Time[b]	endo:exo[c]	Yield (%)[d]
1	5	OMe	12	300 °C, 72 h	92 : 8	83
2[e]		OMe	13	300 °C, 96 h	75 : 25	62
3			14	300 °C, 120 h	94 : 6	18
4				$TiCl_4$(1.0 eq), 10 h	≥96 : 4	84
5			15	$TiCl_4$(1.0 eq), 10 h		76
6		OEt 16		No products were observed under the thermal or Lewis acid conditions.		
7	17	OMe	18	180 °C, 40 h	≥96 : 4	80
8			19	300 °C, 60 h	93 : 7	50
9	20	OMe	21	180 °C, 20 h	95 : 5	87
10			22	300 °C, 48 h	93 : 7	44
11	23	OMe	24	300 °C, 60 h	43 : 57	60

[a] Concentrations of γ-pyrones were 0.1 M in thermal reactions and 0.2 M in Lewis acid-promoted reactions. In all cases, 2.0 equiv of dienes was used. [b] Thermal reactions were carried out in toluene using a sealed tube, and the temperature indicated here was measured at the bottom of a sand bath. Methylene chloride was the solvent for Lewis acid-promoted reactions, and these reactions were carried at room temperature. [c] Ratios were obtained by using ^{1}H NMR, and the stereochemistry was assigned according to NOE experiments. [d] All yields were isolated yields. [e] The source of this diene came from 1-methoxy-1,3-cyclohexadiene via a 1,5-hydrogen shift under the high temperature.

electronic nature of the diene **16**. This suggests that **16** sets a lower limit for the electron density of dienes that would be reactive toward γ-benzopyrones.

The most intriguing results are shown in entries 7−11 of Table 1, where substituents at the C-6 position on the benzene ring of chromone derivatives significantly effect the rate of reactions as well as the stereoselectivity. Both bromine and chlorine substituents (inductively electron withdrawing) at the C-6 position rendered the cyanochromone derivatives **17** and **20** more reactive toward both oxygenated (entries 7 and 9) and nonoxygenated (Table 1, entries 8 and 10) dienes as indicated by the shorter reaction time and/or lower reaction temperature.

Scheme 2



The levels of *endo*-selectivity remained very high in all cases, and the thermal reactions of **17** and **20** with 1,3-cyclohexadiene were far more efficient (Table 1, entries 8 and 10) than that of **5** (Table 1, entry 3). Reactions of **17** and **20** are of synthetic significance since halogen substituents are potential precursors for functionalizing the aromatic ring and constructing the D-ring in arisugacin. An electron-donating methyl group at the C-6 position of the cyanochromone **23**, on the other hand, reduced the level of selectivity to essentially stereo random (Table 1, entry 11). At this point, it is not clear why the stereoselectivity dropped so dramatically in this reaction, given that the Alder's *endo* rule so far can be applied to all other reactions. These results, however, do suggest that the dienophilicity of the γ-benzopyrones can be adjusted via appropriate substitutions at the C-6 position and perhaps other positions as well on the aromatic ring. We are currently exploring these substituent effects in detail.

Finally, to examine the potential of this reaction in developing our convergent strategy for constructing the ABC tricyclic frame of arisugacin, the diene **25**[13] was reacted with 2.0 equiv of 6-bromo-3-cyanochromone (**17**) at 300 °C in toluene for 7 d to give the desired adduct **26** in 32% yield with an *endo*:*exo* ratio of 86:14 (Scheme 2). The stereochemistry here was assigned according to NOE experiments. The moderate yield observed here is encouraging given the fact that with the exception of highly reactive dienophiles such as benzoquinone[14] and acetylenedicarboxylic acid derivatives[4,15] essentially no other examples of dienophiles are known to react with the diene **25** without the usage of extreme high pressure or Lewis acids.[14b]

We have shown here the first highly stereoselective [4 + 2] cycloaddition reactions using cyanochromones as dienophiles and demonstrated the potential of this reaction in constructing the tricyclic core of arisugacin in a convergent manner. We are currently exploring this approach for syntheses of arisugacin and other analogues.

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Supporting Information Available: Experimental procedures as well as ^{1}H NMR spectral and characterization data are given for all new compounds (27 pages).

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(13) The diene **25** was prepared in 85% yield via a Stille coupling involving (*n*-Bu)$_3$(vinyl)Sn and 2,2,6-trimethyl-1-cyclohexenetriflate in THF at 65 °C. For a reference see: Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630.

(14) For leading references see: (a) Engler, T. A.; Sampath, U.-S.; Vander Velde, D.; Takusagawa, F. *Synth. Commun.* **1992**, *22*, 2031. (b) Engler, T. A.; Sampath, U.-S.; Vander Velde, D.; Takusagawa, F. *Tetrahedron* **1992**, *48*, 9399.

(15) For some examples see: (a) Brieger, G. *Tetrahedron Lett.* **1965**, 4429. (b) He, J.-F.; Wu, Y.-L. *Tetrahedron* **1988**, *44*, 1933.