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Use of 4-Cyanocoumarins as Dienophiles in a Facile Synthesis of Highly Substituted Dibenzopyranones

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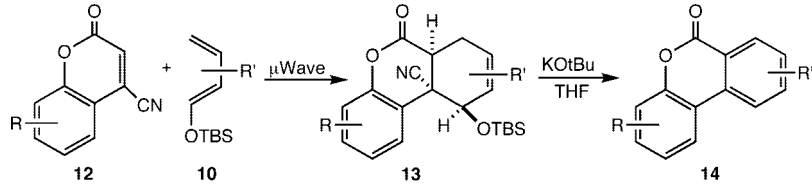
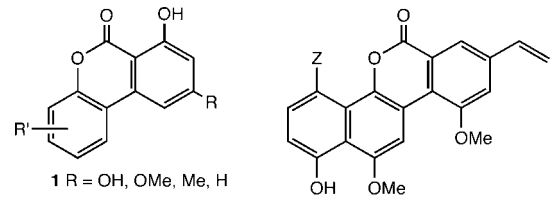
ABSTRACT



A new synthesis of dibenzopyranones 14 is reported via the Diels−Alder cycloaddition of 4-cyanocoumarins 12 with 1-silyloxydienes 10 to give the adducts 13 which are then converted into 14 in one step via treatment with base and loss of the cyano and silyloxy groups.

Dibenzopyranones serve as the structural core for many natural products including the structurally similar compounds autumnariol, autumnariniol, altenuisol, and alternariol (Scheme 1, **1**).[1] They also occur in a number of natural antitumor and antibiotic agents such as the gilvocarcins, ravidomycins, and chrysomycins (Scheme 1, **2**).[2] In addition, dibenzopyranones have been used as intermediates in the syntheses of several pharmaceutically interesting compounds including progesterone, androgen, and glucocorticoid receptor agonists[3] and endothelial cell proliferation inhibitors.[4] There are several methods for the synthesis of dibenzopyranones, with most involving a Suzuki cross-coupling reaction followed by metal or Lewis acid mediated lactonization.[5] More recently the *tert*-butyl-lithium-mediated cyclization of bromobenzylfluorophe-

Scheme 1



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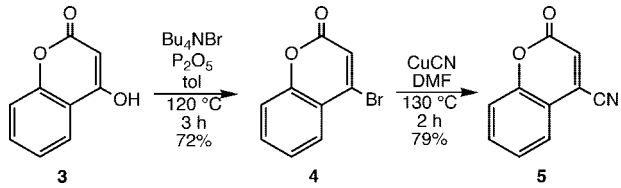
nyl ethers[6] and the ruthenium-catalyzed cyclotrimerization of aryl diynes[7] have been reported. Such existing methods, however, require the use of palladium catalysts, aryl fluorides and iodides, and ionic liquids. Finally the synthesis of 7-hydroxydibenzopyranones via addition of bissilyl enol ethers to chromones has been reported.[8] In this paper, we present a simple, general, palladium-free method for the synthesis of highly substituted dibenzopyranones using a Diels−Alder reaction between 4-cyanocoumarins and 1-oxygenated dienes followed by elimination−aromatization with potassium *tert*-butoxide. Diels−Alder reactions of 3-nitrocoumarins[9] and 4-cyanoquinolones[10] are known. However, to the best of our knowledge, this is the first report of the use of a 4-substituted coumarin as the dienophile in a [4 + 2] cycloaddition process.

The 4-cyanocoumarin **5** was prepared in two steps without purification from the commercially available 4-hydroxycoumarin **3** (Scheme 2). Bromination with Bu_4NBr/P_2O_5[11]

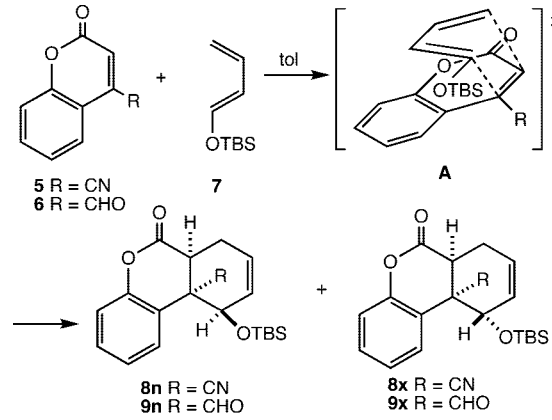
Scheme 2



followed by cyanation with CuCN gave the 4-cyanocoumarin in 57% yield over two steps. Many other substituted 4-hydroxycoumarins are commercially available but are generally expensive. However, they can be made from inexpensive staring materials in three simple steps without purification (see Supporting Information).

Initially various 4-substituted coumarins were screened as dienophiles by treatment with excess cyclopentadiene. Among the 4-substituted coumarins screened (R = H, Cl, Br, I, N_3, OH, OTs, CN, and CHO), only the 4-cyanocoumarin **5** and the 4-formylcoumarin **6** afforded the Diels−Alder products. Presumably, the additional electron-withdrawing group, cyano or formyl, is needed to activate the coumarin sufficiently for the Diels−Alder reaction, even with cyclopentadiene. The regioselectivity of the reaction was then investigated, and the results are shown in Scheme 3. Treatment of 4-cyanocoumarin **5** with the 1-silyloxydiene **7** in toluene at 120 °C for 2 days gave the Diels−Alder adduct in 92% yield as a single regioisomer as observed by ^{1}H NMR spectroscopy. We presume that the cyano group exclusively

Scheme 3

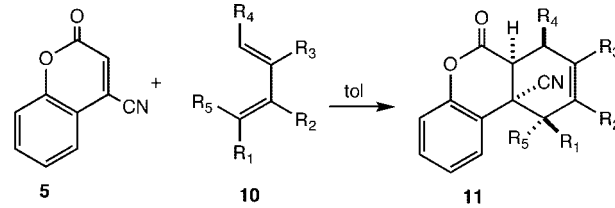


compd	R	temp (°C)	time	yield (%)	endo/exo
5	CN	120	2 d	92	5:1
5	CN	120	0.5 h (μW)	94	5:1
6	CHO	60	0.5 h (μW)	93	1:1

directs the regiochemistry over the lactone because the lactone is slightly cup-shaped and consequently partially out of conjugation with the olefin. In addition, the Diels−Alder adduct was isolated as an ca. 5:1 mixture of endo to exo stereoisomers **8n** and **8x** which was then recrystallized to afford the pure endo isomer **8n**[12] in 70% yield. However, the stereochemistry is of little consequence in this case because it is destroyed in the subsequent elimination step. The reaction time can be decreased significantly from 2 days to 0.5 h by conducting the reaction in the microwave without the loss of either regio- or stereocontrol. Finally, the 4-formylcoumarin **6** was treated with the silyloxydiene **7** at only 60 °C and afforded the Diels−Alder adduct in 93% yield, again with complete regiocontrol but as a 1:1 mixture of endo and exo stereoisomers, **9n** and **9x**.

The effect of substitution on the diene on the Diels−Alder reaction was then tested by treating the 4-cyanocoumarin **5** with a number of oxygenated dienes **10a**−**f** (Scheme 4).

Scheme 4



diene	R_1	R_2	R_3	R_4	R_5	time	prod.	yield (%)	endo/exo
7/10a	OTBS	H	H	H	H	0.5 h	**11a**	94	5:1
10b	OTBS	allyl	H	H	H	0.5 h	**11b**	96	5:1
10c	OTBS	Me	H	Me	H	0.5 h	**11c**	95	5:1
10d	OMe	H	OTMS	H	H	0.5 h	**11d**	97	2:1
10e	OMe	H	OTBS	H	H	1 h	**11e**	91	2:1
10f	Me	H	OTBS	H	Me	2 h	**11f**	89	NA

Overall, the Diels−Alder adducts were isolated in excellent yields as single regioisomers. The 2-allyl-1-silyloxydiene **10b**

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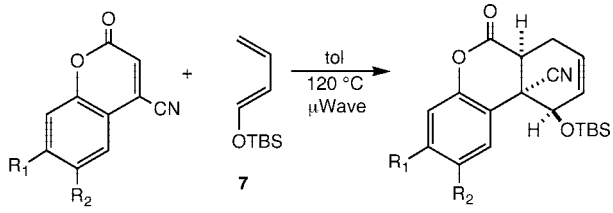
and the 2,4-dimethyl-1-silyloxydiene **10c** gave the Diels−Alder adducts **11b** and **11c**, respectively, both as 5:1 mixtures of endo and exo stereoisomers. Reaction with Danishefsky's diene **10d** or its OTBS analogue **10e** resulted in a slight decrease in stereoselectivity from 5:1 to 2:1 endo:exo but still with complete regioselectivity, compounds **11d** and **11e**. Lastly, treatment with the very hindered 4,4-dimethyl-2-silyloxydiene **10f** afforded the expected product **11f** in 89% yield but after 2 h rather than 0.5 h.

The effect of substitution on the coumarin was also explored by treating a number of analogues with the 1-silyloxydiene **7** (Scheme 5). The 6-chloro-7-methyl ana-

Scheme 5



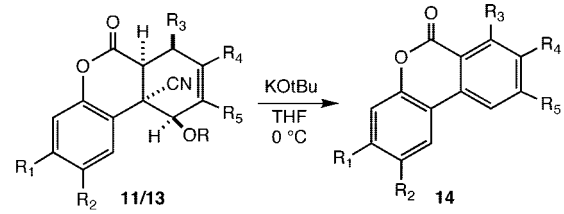
12 7 13

dienophile	R_1	R_2	time	prod.	yield (%)	endo/exo
5/12a	H	H	0.5 h	**13a**	94	5:1
12b	Me	Cl	0.5 h	**13b**	82	4:1
12c	Me	Me	4 h	**13c**	89	4:1
12d	OMe	H	4 h	**13d**	84	4:1

logue **12b** gave the Diels−Alder adduct **13b** in 82% yield as a 4:1 mixture of endo and exo stereoisomers. The electron-rich 6,7-dimethyl analogue **12c** and the 7-methoxy analogue **12d** afforded the Diels−Alder adducts **13c** and **13d** in 89% and 84% yield, respectively, again as 4:1 mixtures of endo and exo stereoisomers. Initially, we were afraid that electron-rich 4-cyanocoumarins might require higher reaction temperatures which would likely result in lower yields. However, the reactions proceeded smoothly at 120 °C simply by increasing the reaction time from 0.5 to 4 h.

The Diels−Alder adduct **11a** was treated with several bases in an attempt to induce elimination of both the cyano and silyloxy groups. Although both of these are only moderately good leaving groups, we believed that aromatization of the ring would provide a strong driving force for the reaction. Treatment with various carbonate bases in methanol or THF gave either low conversion of starting material, even upon heating to reflux, or yields less than 50%. However, treatment of **11a** with 2.5 equiv of potassium *tert*-butoxide in THF at 0 °C for 15 min provided the dibenzopyranone **14a** in 92% yield (Scheme 6). Treatment of each of the Diels−Alder adducts with potassium *tert*-butoxide led to the aromatized products **14b**−**14g** in 85−95% yield. Compound **14c** was isolated as the phenol (R_4 = OH) rather than the silyl ether (R_4 = OTBS) in 88% yield. Interestingly, the complete conversion of the Diels−Alder adduct **11c** to the dibenzopyranone **14g** required 60 min at 23 °C, rather than at 0 °C, as did the other examples. In fact, quenching the reaction after 15 min at 0 °C revealed complete conversion of the starting material to a 1.0:1.8 mixture of

Scheme 6

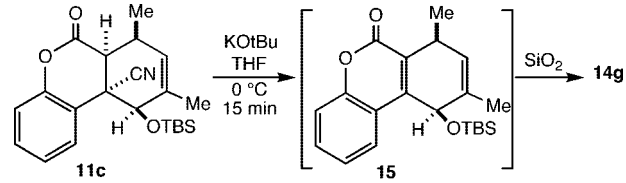


11/13 14

compd	R_1	R_2	R_3	R_4	R_5	R	time (min)	prod.	yield (%)
11a	H	H	H	H	H	TBS	15	**14a**	92
11b	H	H	H	H	allyl	TBS	15	**14b**	94
11e	H	H	H	OTBS	H	Me	15	**14c**	88
13c	Me	Me	H	H	H	TBS	15	**14d**	90
13d	OMe	H	H	H	H	TBS	15	**14e**	95
13b	Me	Cl	H	H	H	TBS	15	**14f**	85
11c	H	H	Me	H	Me	TBS	60	**14g**	93

the intermediate **15** and the product **14g** by crude ^{1}H NMR spectroscopy (Scheme 7). Attempts to purify the intermediate

Scheme 7

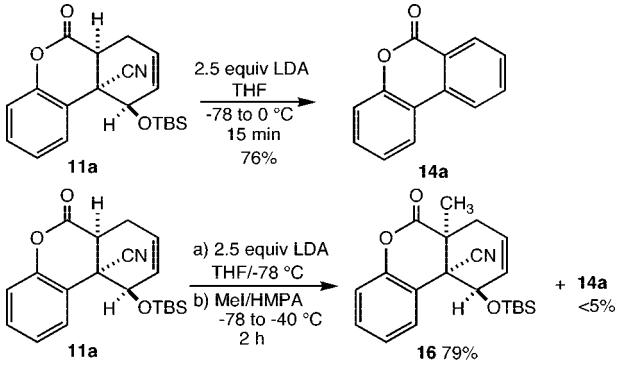


11c 15

15 by silica gel chromatography led to elimination of the silanol to give the product **14g**. There are two possible mechanisms for the aromatization process, either initial β-elimination of cyanide to the diene followed by loss of TBSOH or initial elimination of the silanol followed by loss of cyanide. Our observation of the intermediate **15** implies the reaction must proceed, at least to some extent, through the first mechanism, but does not completely rule out the possibility that the reaction occurs simultaneously through the second mechanism as well. The mechanism of the elimination was further explored by methylation of the Diels−Alder adduct **11a** at low temperature. As expected, treatment of the adduct **11a** with 2.5 equiv of LDA at −78 °C and warming to 0 °C afforded the dibenzopyranone **14a** in 76% yield. However, deprotonation of **11a** with 2.5 equiv of LDA at −78 °C followed by sequential addition of HMPA and MeI and warming to −40 °C gave the methylated product **16** in 79% yield with less than 5% of the dibenzopyranone **14a** being isolated (Scheme 8). These results suggest that the elimination proceeds through an E1cb-type mechanism; namely, treatment of the Diels−Alder adduct with base leads to rapid deprotonation of the acidic proton α to the lactone. However, at low temperatures, the ring is in a conformation such that the carbanion orbital does not align well with the σ^* orbital of the carbon−cyano bond.

(12) The stereochemistry was confirmed through an X-ray crystal structure analysis of the product **16** of methylation of **8n**.

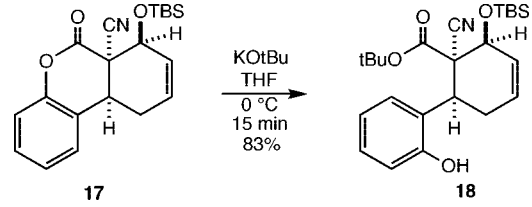
Scheme 8



Only on warming the reaction to above −40 °C does the ring adopt a conformation which allows for facile β-elimination. Further support for the E1cb mechanism was obtained from the regioisomeric Diels−Alder adduct **17**, prepared in good yield from the reaction of 3-cyanocoumarin and the 1-silyloxybutadiene **7**. Treatment of **17** with potassium *tert*-butoxide afforded none of the elimination product, but rather the hindered *tert*-butoxide acted as a nucleophile and opened the lactone with displacement of phenoxide to afford cleanly the substitution product **18** in 83% yield (Scheme 9).

In summary, we have developed a novel route for the preparation of highly substituted dibenzopyranones in excellent yield through the Diels−Alder reaction of 4-cyanocoumarins and 1-oxygenated dienes followed by elimination/aromatization with base. 4-Cyanocoumarins are excellent

Scheme 9



dienophiles since they are stable and can be synthesized in only a few steps from inexpensive, commercially available starting materials in high yields without column chromatography. Their cycloaddition to 1-silyloxydienes is highly regioselective and proceeds in excellent yields. The mechanism of the elimination/aromatization is likely an E1cb-type process, namely, formation of the anion α to the nitrile followed by elimination of cyanide and then aromatization via loss of the silanol to give the aromatic products.

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Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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