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). They also occur in a number of natural antitumor and antibiotic agents such as the gilvocarcins, ravidomycins, and chrysomycins (Scheme 1, 2). In addition, dibenzopyranones have been used as intermediates in the syntheses of several pharmaceutically interesting compounds including progesterone, androgen, and glucocorticoid receptor agonists and endothelial cell proliferation inhibitors. 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. More recently the tert-butyl-lithium-mediated cyclization of bromobenzylfluorophenol.

Scheme 1


nly ethers and the ruthenium-catalyzed cyclotrimerization of aryl diynes 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 bis-silyl enol ethers to chromones has been reported. 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 and 4-cyanoquinolones 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 Bu4NBr/P2O5 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 starting 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, N3, 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 1H NMR spectroscopy. We presume that the cyano group exclusively 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 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). Overall, the Diels–Alder adducts were isolated in excellent yields as single regioisomers. The 2-allyl-1-silyloxydiene 10b
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 12b. The Diels–Alder adducts 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 THF gave either low conversion of starting material, even upon heating to reflux, or yields less than 50%. 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 (R4 = OH) rather than the silyl ether (R4 = 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 the intermediate 15 and the product 14g by crude 1H NMR spectroscopy (Scheme 7). Attempts to purify the intermediate 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.

**Scheme 6**

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<td>H</td>
<td>H</td>
<td>TBS</td>
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<tr>
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<td>14g 93</td>
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**Scheme 7**

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