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Synthesis of 2-substituted chromenes via ring-closing metathesis and stable 1-benzopyrylium ions

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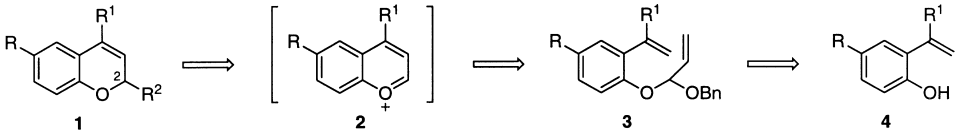
Abstract

2-Substituted chromenes were obtained via combination of ring-closing metathesis of allylic acetals to the corresponding cyclic acetals, followed by Lewis acid-mediated functionalization of the resulting stable 1-benzopyrylium ion with suitable nucleophiles.

Keywords: benzyloxy-1,2-propadiene; ring-closing metathesis; 1-benzopyrylium ions; chromenes.

Chromenes (2*H*-1-benzopyran derivatives, viz. **1**) are important intermediates in the synthesis of many natural products and medicinal agents.[1] Their basic structural framework for example is a common feature of many tannins and polyphenols[2] found in teas, fruits, vegetables and red wines and these compounds have become increasingly important as a result of their health-promoting effects. As a result of these interesting properties, a number of methods for their preparation have been developed, such as the Claisen rearrangement of propargyl phenol ethers,[3] Pd-catalyzed ring closure of 2-isoprenyl phenols,[4] Ru-catalyzed ring closing metathesis of 2-styrenyl allyl ethers[5] and *O*-alkylation of reduced coumarin.[6] In all of these methods, the substituent at the 2-position is introduced in the early stages of the synthesis. Herein, we report a new and flexible route for the synthesis of different 2-substituted-2*H*-chromenes **1** via selective functionalization of the 1-benzopyrylium ions **2**, where the 2-substituent is introduced in the final stages (Eq. (1)).



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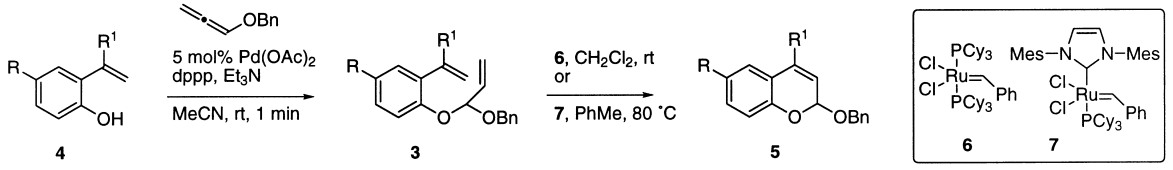
This sequence, which involves the formation of the allylic acetals **3** from the corresponding phenols **4**, follows a pathway that combines oxypalladation of benzyloxy-1,2-propadiene and Ru-catalyzed ring-closing metathesis, which was previously developed in our group for the synthesis of six- and seven-membered ring ethers.[7–9]

Thus, the chromene skeleton was constructed starting with the readily available vinyl-substituted phenols **4**,[10] which were reacted with benzyloxy-1,2-propadiene[11] using a Pd^{2+}-catalyst in the presence of triethylamine and 1,3-bis(diphenylphosphino)propane (dppp) at room temperature (Table 1). This led to the corresponding allylic acetals **3** in a remarkably selective and fast reaction, with reaction times in the order of minutes.[12,13] Although in all cases the ^{1}H NMR spectra of the crude reaction mixtures indicated that the reactions proceeded without side reactions, the isolated yields were relatively moderate. This was probably due to partial hydrolysis of the acetals on the silica gel during column chromatography, despite the fact that a small amount of Et_3N was added to the eluent.

Table 1



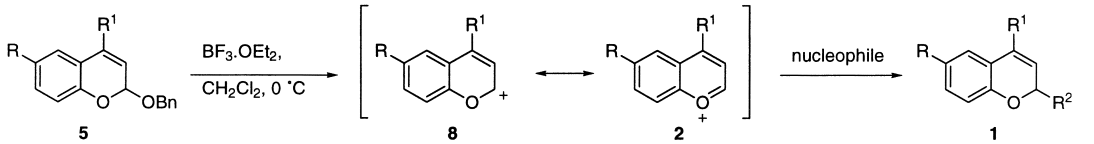
entry	substrate	diolefin (yield)[a]	catalyst	equiv (mol%)	time (h)	yield (%)[a]
1	**a**: R = H, R^1 = H	**3a** (62%)	**6**	10	4	**5a** (77%)
			7	4	1	**5a** (78%)
2	**b**: R = OMe, R^1 = H	**3b** (75%)	**6**	8	7	**5b** (85%)
			7	3	4	**5b** (87%)[b]
3	**c**: R = Br, R^1 = H	**3c** (35%)	**6**	15	15	**5c** (60%)
			7	10	4	**5c** (60%)
4	**d**: R = H, R^1 = Me	**3d** (63%)	**6**	9	8	**5d** (87%)
			7	6	4	**5d** (84%)

[a]Isolated yields after column chromatography. [b]Yield corrected for recovered starting material.

The linear acetals **3** appeared as suitable precursors for ring-closing metathesis (RCM) using the Grubbs' Ru-catalysts **6**[14] and **7**[15] (Table 1). Initially, the reactions were conducted using the well-established catalyst **6** in CH_2Cl_2 at room temperature under argon. As an example, reaction of **3a** in the presence of catalyst **6** yielded chromene **5a** after 4 h in 77% yield. It was necessary to add the catalyst (10 mol%) portionwise over this period to drive the reaction to completion (entry 1). Unfortunately, this problem of catalyst decomposition could not be overcome by running the reaction at higher temperatures. Recently however, Grubbs and co-workers[15] reported the more active and stable Ru-catalyst **7**, which also seemed to be the catalyst of choice for this system. Indeed, reaction of diolefin **3a** with catalyst **7** (4%) in toluene at 80°C yielded chromene **5a** in 1 h in 78% yield (entry 1). Next, acetals **3b–d** were subjected to similar metathesis conditions in order to arrive at the desired products. Application to **3b**—having an electron-donating group in the aromatic ring (entry 2)—showed virtually no difference in reactivity towards both catalysts. In both cases, the catalyst had to be added portionwise to complete the reaction. On the other hand, substrate **3c**, containing an electron-withdrawing group in the aromatic ring (entry 3) showed similar behavior to the parent compound. Both reactions gave the same yield of **5c**, but the

process was more efficiently carried out with catalyst **7**. The same applied to the disubstituted olefin (**3d**, entry 4) affording the trisubstituted olefin **5d** in good yield with both catalysts.

Table 2



5 **8** **2** **1**

entry	substrate	nucleophile	product (yield)[a]	entry	substrate	nucleophile	product (yield)[a]
1	**5a**	$SiMe_3$ (**9**)	**1a**: R^2 = allyl (100%)	6	**5b**	**10**	**1b**: R^2 = CN (83%)
				7	**5b**	**11**	**1b**: R^2 = propargyl (60%)
2	**5a**	Me_3SiCN (**10**)	**1a**: R^2 = CN (75%)	8	**5c**	**9**	**1c**: R^2 = allyl (88%)
3	**5a**	$SnBu_3$ (**11**)	**1a**: R^2 = propargyl (35%)	9	**5c**	**11**	**1c**: R^2 = propargyl (42%)
				10	**5c**	**12**	**1c**: R^2 = phenacetyl (45%)
4	**5a**	Ph, $OSiMe_3$ (**12**)	**1a**: R^2 = phenacetyl (63%)	11	**5d**	**9**	**1d**: R^2 = allyl (65%)
				12	**5d**	**10**	**1d**: R^2 = CN (68%)
5	**5b**	**9**	**1b**: R^2 = allyl (97%)	13	**5d**	**11**	**1d**: R^2 = propargyl (70%)

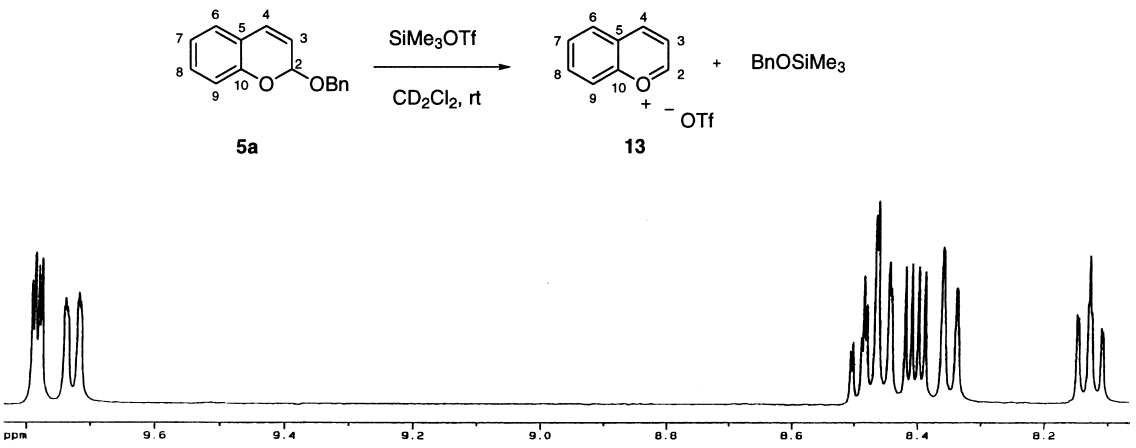
[a]Isolated yields after column chromatography.

The chromene acetals **5a–d** were then evaluated as precursors for functionalization at the 2-position via 1-benzopyrylium ion chemistry. To this end, the acetals **5** were treated with a mild Lewis acid to generate the corresponding strongly colored 1-benzopyrylium ions **2**.[16] Trapping of these intermediates with different π-nucleophiles provided a variety of 2-substituted chromenes (Table 2). Reaction of **5a** in the presence of the Lewis acid $BF_3{\cdot}OEt_2$ (2 equiv.) gave the dark red colored 1-benzopyrylium ion **2**, which reacted with allyltrimethylsilane (**9**, 2 equiv.) to yield **1a** (R^2 = allyl) in quantitative yield (entry 1). Other nucleophiles were also successfully used in this reaction, such as trimethylsilyl cyanide (**10**), allenyl tributyltin (**11**) and the silyl enol ether derived from acetophenone (**12**) giving the targeted products in moderate to good yields (entries 2–4). Similarly, acetals **5b–d** were subjected to identical conditions and nucleophiles providing the expected products without surprises. In all cases, incorporation of the nucleophile took place selectively at the more electrophilic 2-position.

Interestingly, the 1-benzopyrylium ions **2** appeared sufficiently stable to be characterized by NMR spectroscopy so that ^1H and ^{13}C NMR of these cations were recorded.[17] The aromatic character was clearly observed in the proton spectra, where all the aromatic signals shifted downfield to values between 8 and 10 ppm. A typical example is shown in Scheme 1.

Treatment of **5a** with TMSOTf in CD_2Cl_2 led to the formation of the triflate salt of the 1-benzopyrylium ion **13** with concomitant formation of trimethylsilyl-protected benzyl alcohol.[18] In the ^1H spectrum of **13**, the α-proton shifted from 6.4 to 9.87 ppm, while the proton at the 4-position shifted from 5.6 to 9.72 ppm. Recording the same spectrum after storage of the reaction mixture for 1 week led to an identical and clean spectrum, thus proving the stability of the 1-benzopyrylium ion species.

In conclusion, we have developed a general and flexible transition metal-mediated route for the synthesis of 2-substituted chromenes. This sequence provides ample possibilities for the introduction of functional groups at different positions of the skeleton without affecting the efficiency of the procedure. In this way, a versatile heterocyclic scaffold has been created which could be useful in combinatorial chemistry approaches during the search for biologically active chromene derivatives.



Scheme 1. Spectrum of the benzopyrylium salt **13**

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18. Characterization of compound **5a**: ^{1}H NMR (400 MHz, C_6D_6): $\delta = 7.16$–7.21 (m, 2H), 7.05–7.11 (m, 3H), 6.98–7.03 (m, 2H), 6.85 (br.d, $J = 7.2$ Hz, 1H), 6.74–6.78 (m, 1H), 6.36 (d, $J = 9.2$ Hz, 1H, H4), 5.52–5.57 (m, 2H, H2,3), 4.74 (d, $J = 12.1$ Hz, 1H, CH_2Ph), 4.50 (d, $J = 12.1$ Hz, 1H, CH_2Ph). Characterization of compound **13**: ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta = 9.87$ (dd, $J = 1.8$, 4.1 Hz, 1H, H2), 9.72 (dt, $J = 0.7$, 8.3 Hz, 1H, H4), 8.44–8.51 (m, 2H), 8.39 (dd, $J = 4.1$, 8.3 Hz, 1H, H3), 8.34 (dd, $J = 0.4$, 8.8 Hz, 1H), 8.13 (dt, $J = 0.9$, 7.2 1H).