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Unexpected Tandem Ylide Annulation Reaction for Controllable Synthesis of 2*H*-Chromenes and 4*H*-Chromenes

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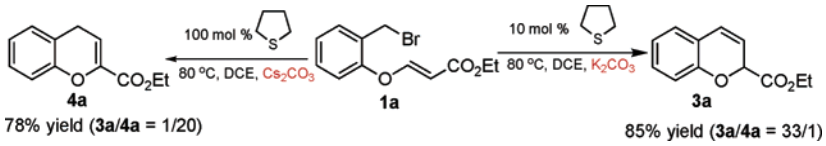
ABSTRACT



An unexpected tetrahydrothiophene-catalyzed ylide annulation reaction, via tandem Michael addition/elimination/substitution, for the controllable synthesis of 2*H*-chromenes and 4*H*-chromenes has been developed.

The occurrence of the 1-benzopyran subunits such as chromane,[1] 2*H*-chromene,[2] and 4*H*-chromene[3] in many biologically active compounds, as well as their utility as key intermediates in the synthesis of numerous natural products and medicinal reagents,[4] has promoted several strategies for their construction.[5,6] In our study on ylide chemistry in organic synthesis,[7] unexpectedly, we found that reaction of ester **1a** in the presence of 10 mol % of tetrahydrothiophene (THT) and K_2CO_3 did not afford the desired product **2a**[8] and that 2*H*-chromene **3a** was obtained in 85% yield.

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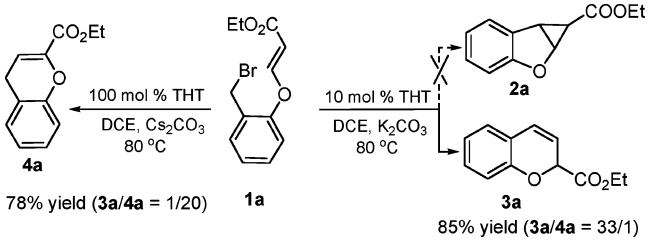
Interestingly, using Cs_2CO_3 instead of K_2CO_3 in the reaction gave 4*H*-chromene **4a** as a major product (Scheme 1). Thus,

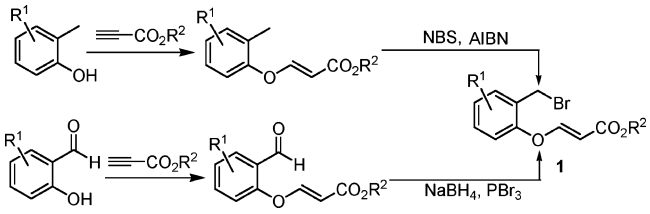
Scheme 1. Base Effect on the Ylide Annulation of **1a**



2*H*-chromenes and 4*H*-chromenes could be synthesized controllably from the same starting material just by choice of base. In this communication, we wish to report the preliminary results.

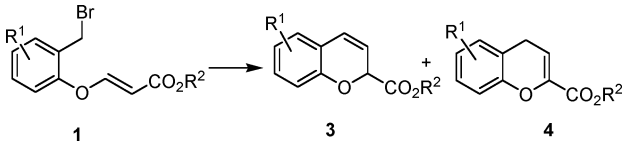
The benzyl bromides **1** are readily available from the corresponding 2-methyl phenols or salicylaldehydes (Scheme 2) in gram scale in good yields.[9] It was found that chromenes

Scheme 2. Synthesis of Benzyl Bromides **1**



3a and **4a** were not observed when **1a** was treated with K_2CO_3 in the absence of THT. However, in the presence of stoichiometric THT, 92% yield of the chromenes was obtained (**3a**:**4a** = 35:1, entry 2, Table 1) under the same conditions. Further studies showed that 10 mol % of THT gave 85% yield of the desired product (**3a**:**4a** = 33:1, entry 1, Table 1).[10]

Table 1. Intramolecular Tandem Annulation for 2*H*-Chromenes Catalyzed by THT[a]



entry	1	time (h)	R^1	R^2	3 (3:4)	yield[b] (%)
1	**1a**	41	H	Et	**3a** (33:1)	85
2[c]	**1a**	22	H	Et	**3a** (35:1)	92
3	**1b**	35	H	Me	**3b** (8:1)	88
4	**1c**	41	H	^{i}Pr	**3c** (34:1)	83
5[d]	**1d**	58	H	Bn	**3d** (57:1)	87
6	**1e**	38	1-naphthyl	Et	**3e** (37:1)	88
7	**1f**	37	6-^{t}Bu	Et	**3f** (>99:1)	99
8[e]	**1f**	96	6-^{t}Bu	Et	**3f** (>99:1)	97
9	**1g**	36	4-CH_3	Et	**3g** (20:1)	85
10[d]	**1h**	52	4-Cl	Et	**3h** (14:1)	75
11	**1i**	36	5-Cl	Et	**3i** (45:1)	76
12[d]	**1j**	50	4-Br	Et	**3j** (20:1)	81

[a] Reaction conditions: 10 mol % of THT, 2.0 equiv of K_2CO_3, 80 °C. [b] Isolated yield. [c] 1 equiv of THT. [d] 1.3 equiv of K_2CO_3. [e] 0.01 equiv of THT.

To study the generality of the present reaction, a variety of unsaturated esters with different structures were investigated. As shown in Table 1, using K_2CO_3 as a base under the optimal conditions (10 mol % of THT, 2.0 equiv of K_2CO_3, 80 °C),[11] various substituted acrylates were good substrates for this reaction. Methyl, ethyl, isopropyl, and benzyl esters gave the desired products **3a**−**e** in high yields, demonstrating that ester groups had almost no effect on this annulation reaction (entries 1−5, Table 1). Neither electronic nor sterically hindered variations on aryl groups resulted in obvious changes in yields (entries 6−12, Table 1). Noticeably, in some cases, 4*H*-chromenes were obtained as minor products. The ratio of 2*H*-chromene and 4*H*-chromene proved substrate-dependent. For example, compound **1f** bearing a *tert*-butyl group at the 6-position of the aryl group gave 2*H*-chromene as a single product but the methyl ester **1b** gave these two products with an 8:1 ratio (entry 7 vs 3, Table 1). It is worth noting that, even if the catalyst (THT) loading was lowered to 1 mol % in the case that **1f** was used as a substrate, the reaction also afforded 2*H*-chromene **3f** in almost quantitative yield (entry 9, Table 1).

Interestingly, using Cs_2CO_3 instead of K_2CO_3, the reaction of compound **1a** gave 4*H*-chromene **4a** as a major product. The generality of the reaction was examined by employing a variety of acrylates under one-pot reaction conditions (1 equiv of THT, 2.0 equiv of Cs_2CO_3, 80 °C). As shown in Scheme 3, in the presence of stoichiometric THT, 4*H*-chromene could be obtained in good yields and the ratios of 4*H*-chromenes and 2*H*-chromenes were higher than 20:1.

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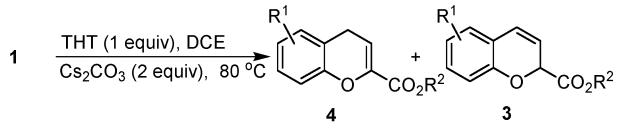
(10) Under this condition (reaction time of 24 h), only 24% conversion was obtained even when 20 mol % of dimethyl sulfide was used instead of 10 mol % of THT.

(11) For details, please see the Supporting Information.

Scheme 3. Intramolecular Annulation for 4*H*-Chromene



1	4 (4:3)	yield (%)[a]
1a	**4a** (20:1)	78(83[b])
1b	**4b** (38:1)	67
1c	**4c** (50:1)	74[b]
1e	**4e** (>99:1)	75(85[b])
1f	**4f** (20:1)	87(75[c])
1g	**4g** (25:1)	85

[a] Isolated yield. [b] Cs_2CO_3 was added after formation of the sulfur salt. [c] 20 mol % of THT was used.

This reaction could also be performed under catalytic conditions. For example, substrate **1f** worked well to give the corresponding 4*H*-chromene **4f** in 75% yield in the presence of 20 mol % of THT. Thus, the product distribution could be controlled easily and both 4*H*-chromenes and 2*H*-chromenes could be prepared selectively at will, just by changing the base. Compounds **3a**−**j** and **4a**−**g** were characterized by ^{1}H and ^{13}C NMR. The structure of compound **4e** was further confirmed by X-ray crystallographic analysis (Figure 1).

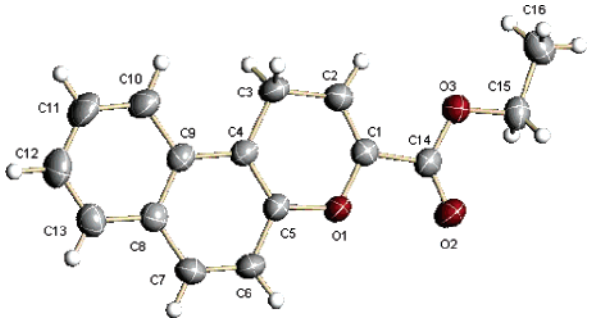
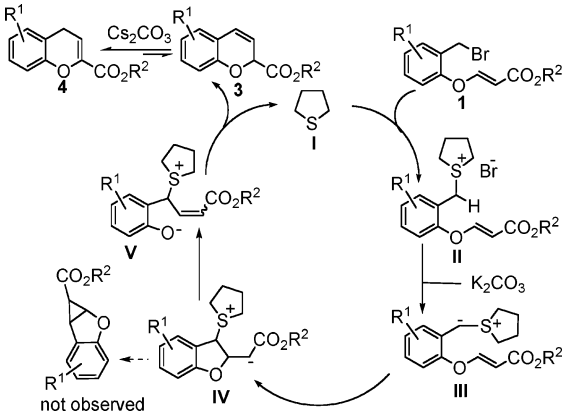


Figure 1. Molecular structure of compound **4e**.

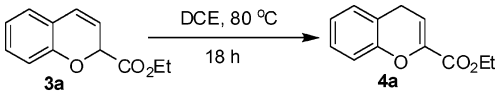
On the basis of the experimental observations, a possible mechanism is proposed to explain the aforementioned reactions. As shown in Scheme 4, tetrahydrothiophene **I** reacted with bromide **1** to form sulfonium salt **II**, which was deprotonated by K_2CO_3 to generate the corresponding sulfonium ylide **III** in situ. An intramolecular Michael addition of the ylide to acrylate, followed by a β-elimination, produced intermediate **V**. An intramolecular S_N2' reaction of intermediate **V** afforded 2*H*-chromene **3** and regenerated tetrahydrothiophene to finish a catalytic cycle.

Scheme 4. Plausible Mechanism for the Annulation Reaction



Using Cs_2CO_3 instead of K_2CO_3, 4*H*-chromene was obtained as the major product. A rationale is that 2*H*-chromene is easily isomerized into 4*H*-chromene under the reaction conditions because the basicity of Cs_2CO_3 is stronger

Scheme 5. Isomerization of 2*H*-Chromene



3a/**4a** = 34:1	Cs_2CO_3	**3a**/**4a** = 1:30
3a/**4a** = 34:1	K_2CO_3	**3a**/**4a** = 27:1

than that of K_2CO_3. This rationale is consistent with the following experimental results: 2*H*-chromene was transformed into 4*H*-chromene easily in the presence of Cs_2CO_3, but the same transformation proceeded very slowly in the

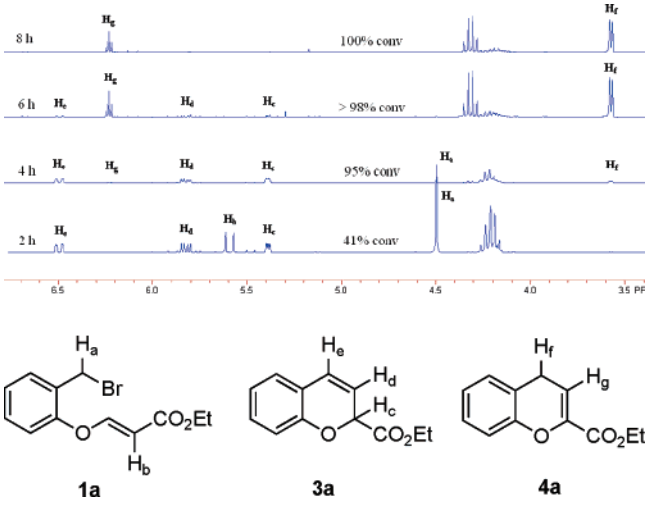


Figure 2. ^{1}H NMR monitoring on the annulation of **1a** using Cs_2CO_3.

presence of K_2CO_3 (Scheme 5). Monitoring of the annulation reaction of **1a** by ^1H NMR further demonstrated this assumption. As shown in Figure 2, using Cs_2CO_3 as the base, 41 mol % of **1a** was converted into 2*H*-chromene **3a** after 2 h and **4a** was not detected. After 4 h, the annulation was almost complete (>95% conversion) and only a trace amount of **4a** was observed. However, when the reaction was allowed to carry out for another 4 h, more than 95 mol % of 2*H*-chromene **3a** was isomerized into 4*H*-chromene **4a**.

In summary, we have developed a tandem ylide Michael addition/elimination/substitution reaction for the controllable synthesis of 2*H*-chromenes and 4*H*-chromenes just by choice of base. The mechanism for the formation of 4*H*-chromenes is well-studied. The cheap and commercially available catalyst, the simple procedure, and the mild conditions make these methods potentially useful in organic synthesis. Further investigation of the mechanism of the reaction and development of its asymmetric version are in progress in our laboratory.

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Supporting Information Available: General synthetic procedures and characterization and spectral data for key compounds and the cif file for **4e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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