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Regioselective synthesis of benzo[*c*]chromen-6-ones by one-pot cyclocondensation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde

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ABSTRACT

The cyclocondensation of 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde with 1,3-bis(silyloxy)-1,3-butadienes provides a convenient synthesis of benzo[*c*]chromen-6-ones.

The benzo[*c*]chromen-6-one core structure represents a highly privileged and biologically relevant molecular scaffold which occurs in many natural products. For example, autumnariol has been isolated from onions of *Eucomis autumnalis Greab.* (*Liliaceae*).[1] A number of related natural products, such as autumnariniol,[2] alternariol,[3] and altenuisol,[4] have been isolated (Fig. 1).[5] 6*H*-Benzo[*c*]chromen-6-ones are inhibitors of endothelic cell[6] and oestrogene receptor[7] growth. Ellagic and coruleoellagic acid are isolated from plants, they occur both as glycosides and aglycons.[8] Moreover many benzo[*d*]naphthopyran-6-ones are known as antibiotics and antitumor compounds isolated from *Streptomyces*. This includes, for example, defucogilvocarcin V, gilvocarcins, chrysomycins, and ravidomycins.[9]

The first synthetic approach to benzo[*c*]chromen-6-one was developed in 1929 by Hurtley, based on the cyclization of *o*-bromobenzoic acids with phenols. This method is limited to the activated substrates and the yields are often low.[10] Harris and Hay prepared 9-*O*-methylalternariol by condensation of dilithiated 2,4-pentanedione with a protected salicylate and subsequent domino cyclization.[11] In the last 3 decades, a number of syntheses using transition-metal-catalyzed reactions have been reported. For example, 6*H*-benzo[*c*]chromen-6-ones can be obtained by intramolecular Pd(II)-catalyzed coupling reactions of aryl benzoates.[12] An efficient and versatile synthesis of 6*H*-benzo[*c*]chromen-6-ones, developed by Snieckus and co-workers, relies on a sequence of directed

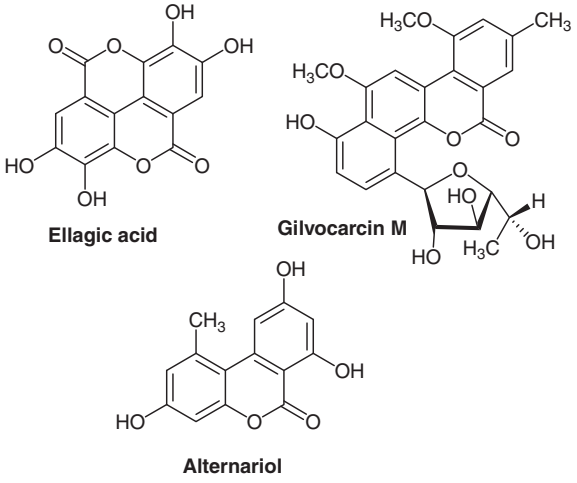

Figure 1. Natural occurring products with benzo[*c*]chromen-6-one core.

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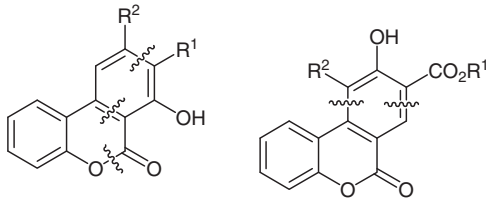


Figure 2. Retrosynthetic analysis.

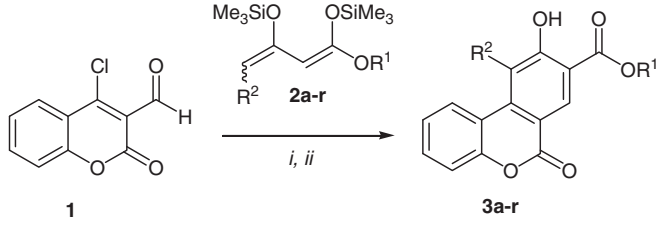
ortho-metalation (DoM) and Suzuki reactions.[13] Zhou et al. reported the palladium-catalyzed insertion of carbon oxide into boroxarenes, which are readily synthesized from *ortho*-hydroxybiaryls.[9]

During the last 5 years, we have been involved in a program dedicated to the exploration of new synthetic methods for the assembly of 6*H*-benzo[*c*]chromen-6-ones. We have reported the synthesis of 6*H*-benzo[*c*]chromen-6-ones by $TiCl_4$-mediated [3+3] cyclization of 1,3-bis(silyloxy)-1,3-butadienes with 3-(2-methoxyphenyl)-3-silyloxy-2-en-1-ones and subsequent BBr_3-mediated lactonization.[14] An alternative approach relies on the Me_3SiOTf-mediated reaction of 1,3-bis(silyloxy)-1,3-butadienes with chromones and subsequent NEt_3-mediateddomino retro-Michael-aldol-lactonization reaction.[15] Both methods provide an access to functionalized 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones which may contain a substituent located at carbon atoms C-8 or C-9. The new bonds are formed between carbon atoms C8 and C9 and between C6a and C10a (Fig. 2).

Herein, we report a new synthesis of functionalized 9-hydroxy-6*H*-benzo[*c*]chromen-6-ones based on the cyclocondensation of 1,3-bis(silyloxy)-1,3-butadienes with 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde. The new bonds of the benzo[*c*]chromen-6-one system are formed between carbon atoms C7 and C8 and between C10 and C10a (Fig. 2). Previously this type of strategy was reported only once. The cyclization of 3-acetyl-2*H*-chromen-2-one with ethyl 2-cyanoacetate has been reported to lead to the formation of a benzo[*c*]chromene system.[16]

The reaction of 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde **1** with enolate synthons has, to the best of our knowledge, not been previously reported. In contrast to previously reported syntheses of benzo[*c*]chromen-6-ones, the approach reported herein allows the assembly of the products in a single step and with a different substitution pattern.

4-Chloro-2-oxo-2*H*-chromene-3-carbaldehyde (**1**) is readily available in one step from commercially available 4-hydroxycoum-

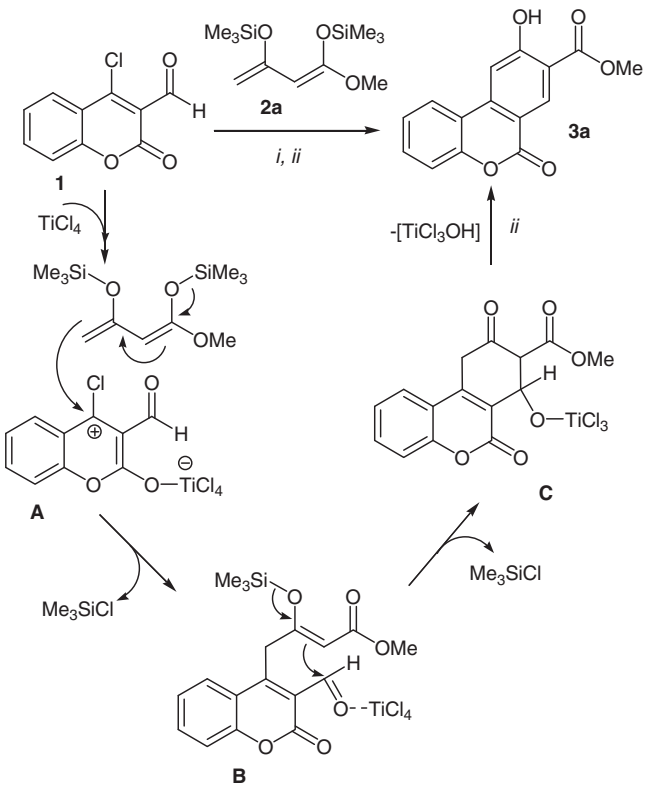


Scheme 2. Synthesis of 3a–r. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, −78→20 °C, 16 h; (ii) HCl (10%).

Table 1
Synthesis of 9-hydroxy-6*H*-benzo[*c*]chromen-6-ones **3a–l**

3	R^1	R^2	%[a] (3)
a	Me	H	40
b	Me	Me	41
c	Et	Et	52
d	Me	*n*Pr	44
e	Me	*n*Pent	47
f	Me	*n*Hex	50
g	Et	*n*Hex	45
h	Et	*n*Dec	47
i	Et	Cl	41
j	Me	MeO	44
k	$(CH_2)_2OMe$	H	53
l	*i*Pr	H	46
m	*t*Bu	H	49
n	Me	CH_2Ph	47
o	Me	CH_2CH_2Ph	44
p	Me	$CH_2CH_2CH_2Ph$	48
r	Me	$CH_2CH_2CH_2Cl$	43

[a] Yields of isolated products.



Scheme 1. Proposed mechanistic pathway for the [3+3] cyclization of **1** with **2a**. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, −78→20 °C, 16 h; (ii) HCl (10%).

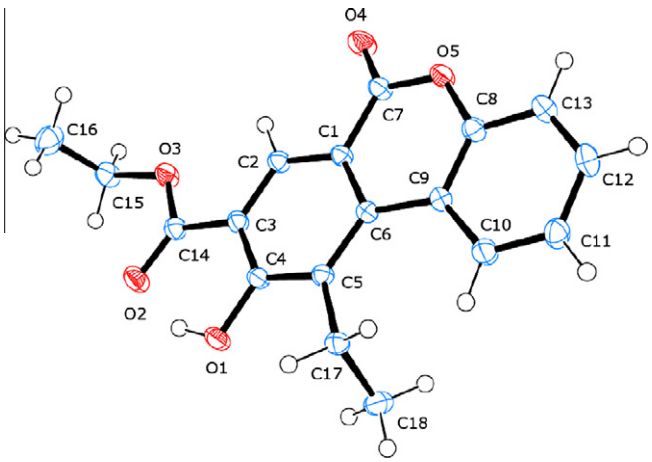


Figure 3. Crystal structure of **3c**.

arin by Vilsmeier–Haack formylation.[17] Our starting point was the reaction of **1** with the dianion of methyl acetoacetate which failed under a variety of conditions. We were pleased to find that the $TiCl_4$-mediated reaction of **1** with 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**2a**, Chan's diene), which can be regarded as a masked dianion,[18] regioselectively afforded 9-hydroxy-6*H*-benzo[*c*]chromen-6-one **3a** (Scheme 1).

During the optimization of the reaction conditions, we have found that the best yields were obtained when a stoichiometric ratio of **1**/**2a**/$TiCl_4$ = 1.0:1.1:1.1 was used and when the reaction was carried out in a fairly concentrated solution (c(**1**) = 0.5 M).[19] The relatively low yield (40%) can be explained by practical problems during the chromatographic purification and by partial hydrolysis of the starting materials.

The formation of the product **3a** can be explained by $TiCl_4$-mediated conjugate addition of **2a** to **1** (intermediates A and B), intramolecular Mukaiyama aldol reaction (intermediate C), and aromatization (before or during the aqueous work-up).

Encouraged by these findings we have studied the reaction of **1** with a set of substituted 1,3-bis(trimethylsilyloxy)-1,3-butadienes **3b–r**. These reactions result in the formation of the desired benzo[*c*]chromen-6-ones **3b–r** in 40–53% yields (Scheme 2, Table 1).[20] The structures of all the products **3a–r**, were established by spectroscopic methods. The structure of **3c** was independently confirmed by X-ray crystal structure analysis (Fig. 3).[21]

In summary, we have reported a facile and direct access to functionalized 9-hydroxy-6-oxo-6*H*-benzo[*c*]chromenes by cyclization of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde.

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19. *General procedure for synthesis of* **3a–r**: To a stirred dichloromethane solution (2 mL/1 mmol of starting materials) of 4-chloro-2-oxo-2*H*-chromene-3-carbaldehyde **1** (1.0 equiv) and 1,3-bis(silyl enol ethers) **2** (1.1 equiv) was added $TiCl_4$ (1.1 equiv) at −78 °C under an argon atmosphere. The temperature of the reaction mixture was allowed to rise to 20 °C in the period of 16 h. To the solution was added hydrochloric acid (10%, 20 mL) and the mixture was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, heptanes/EtOAc) to give **3a–r**.
20. *Ethyl 10-ethyl-9-hydroxy-6-oxo-6H-benzo[c]-chromene-8-carboxylate* (**3c**): starting with **1** (0.313 g, 1.5 mmol) and **2c** (0.499 g, 1.65 mmol), **3c** was isolated by chromatography (silica gel, heptanes/EtOAc) as a pink solid (0.244 g, 52%); mp. 197–198 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 1.37–1.42 (m, 6H, 2 × CH_3), 3.12 (q, ^3J = 7.4 Hz, 2H, CH_2CH_3), 4.40 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 7.23–7.46 (m, 3H, CH_{Ar}), 8.12–8.15 (m, 1H, CH_{Ar}), 8.83 (s, 1H, CH_{Ar}), 11.89 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.6, 13.2 (CH_3), 19.9 (CH_2), 61.3 (OCH_2), 111.5 ($CCOOC_2H_5$), 112.9 (C_{Ar}), 117.2 (CH_{Ar}), 117.6 (C_{Ar}), 123.2, 126.6 (CH_{Ar}), 127.7 (C_{Ar}), 129.9, 131.3 (CH_{Ar}), 137.5, 150.9 (C_{Ar}), 160.1 (COH), 163.8, 168.8 (CO). IR (neat, cm^{-1}): $\bar{\nu}$ = 3089 (w), 2983 (w), 2967 (w), 2937 (w), 2875 (w), 1864 (w), 1727 (m), 1663 (m), 1604 (m), 1555 (m), 1455 (m), 1403 (m), 1341 (m), 1264 (s), 1205 (s), 1155 (m), 1115 (m), 1054 (m), 990 (m), 890 (m), 804 (s), 750 (s), 652(m), 591 (m), 562 (m), 536 (m). GC–MS (EI, 70 eV): m/z (%) = 312 ([M]$^+$, 48), 265 (12), 251 (13), 238 (100), 223 (8), 152 (10), 139 (12). HRMS (EI): calcd for $C_{18}H_{16}O_5$([M]$^+$): 312.09923; found: 312.09959.
21. CCDC 778934 contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; Fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk.