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Synthesis of 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones based on a '[3+3] cyclization/domino retro-Michael–aldol–lactonization' strategy

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Abstract—The $TiCl_4$-mediated [3+3] cyclization of 2,4-bis(trimethylsilyloxy)penta-1,3-diene with 3-silyloxyalk-2-en-1-ones afforded 2-acetylphenols, which were transformed into functionalized chromones. The Me_3SiOTf-mediated condensation of the latter with 1,3-bis(silyl enol ethers) and subsequent domino 'retro-Michael–aldol–lactonization' reaction afforded 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones.

1. Introduction

Functionalized 6*H*-benzo[*c*]chromen-6-ones (dibenzo[*b*,*d*]-pyran-6-ones) are present in a number of pharmacologically relevant natural products. For example, autumnariol has been isolated from *Eucomis autumnalis* Greab. (Liliaceae).[1] The isolation of related 6*H*-benzo[*c*]chromen-6-ones, such as autumnariniol,[2] alternariol,[3] or altenuisol,[4] has been reported (Chart 1).[5] It has been demonstrated that 6*H*-benzo[*c*]-chromen-6-ones are specific inhibitors of the growth of endothelic cells[6] and represent estrogen receptors.[7] Ellagic and coruleoellagic acid, which have been isolated mainly from plant sources,[8] occur both as glycosides and aglycons. Dibenzo[*c*,*d*]chromen-6-ones occur in a number of natural antibiotics and antitumor agents, such as the gilvocarcins, chrysomycins, and ravidomycins.[9]

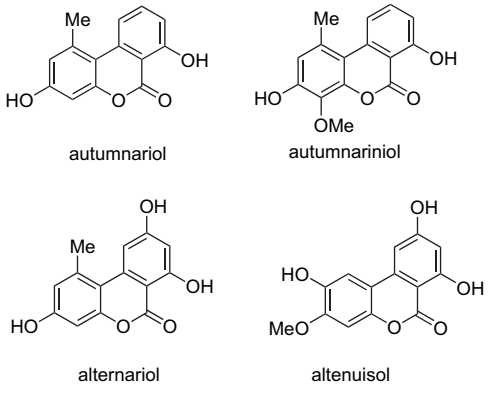

Chart 1. 7-Hydroxy-6*H*-benzo[*c*]chromen-6-ones in nature.

6*H*-Benzo[*c*]chromen-6-ones have been prepared by cyclizations of *o*-bromobenzoic acids with phenols,[10] intramolecular palladium(II) catalyzed coupling reactions of aryl benzoates,[11] and Suzuki reactions.[12–14] Harris et al. reported the synthesis of 9-*O*-methylalternariol by condensation of the dianion of acetylacetone with a protected salicylate.[15,16] We have recently reported[17] the synthesis of 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones by condensation of 1,3-bis(silyl enol ethers)[18] with 4-silyloxybenzopyrylium triflates, in situ generated from chromones,[19] and subsequent base-mediated domino 'retro-Michael–aldol–lactonization' reaction. The preparative scope of this method severely depends on the availability of the chromones as starting materials. Chan and co-workers developed an elegant approach to arenes by [3+3] cyclization of 1,3-bis(silyl enol ethers) with 3-siloxyalk-2-en-1-ones.[20] Based on this work we herein report a new approach to functionalized chromones by [3+3] cyclization of 2,4-bis(trimethylsilyloxy)penta-1,3-diene with 3-silyloxyalk-2-en-1-ones. The combination of these reactions with the domino reaction of chromones with 1,3-bis(silyl enol ethers) provides a versatile strategy for the synthesis of 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones. Notably, this strategy relies on the sequential use of 1,3-bis(silyl enol ethers)[18] at two stages of the synthesis.

Keywords: Chromones; Cyclizations; Domino reactions; Oxygen heterocycles; Silyl enol ethers.
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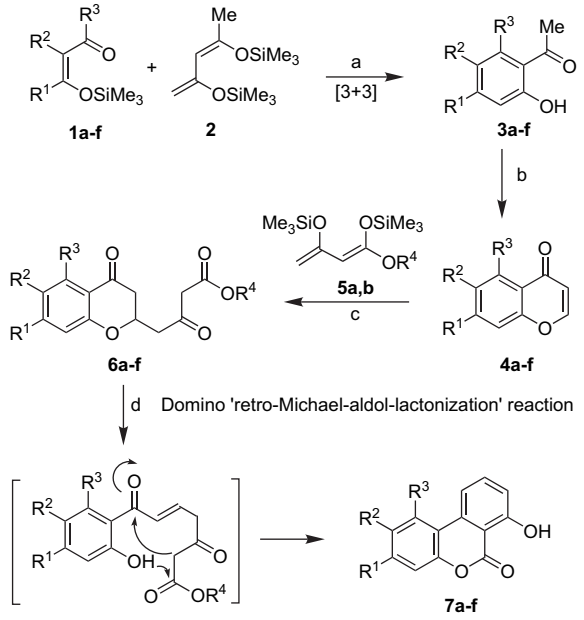
2. Results and discussion

The $TiCl_4$-mediated [3+3] cyclization of 2,4-bis(trimethylsilyloxy)penta-1,3-diene (**2**) with 3-silyloxyalk-2-en-1-ones, following the conditions reported by Chan[20] and us,[21] afforded the 2-acetylphenols **3a–f** (Scheme 1, Table 1). The synthesis of chloro-[21e] and acetoxy-substituted[21f] salicylates by [3+3] cyclizations of 1,3-bis(silyl enol ethers) with appropriate 3-silyloxyalk-2-en-1-ones has been previously reported. The cyclization of 1,3-bis(silyl enol ether) **2** with **1d** and **1e** proceeded with very good regioselectivity, which can be explained as previously reported.[20,21i] Treatment of the acetylphenols with $HC(OEt)_3$ and $HClO_4$ afforded the chromones **4a–f**. During the formation of **4f**, the acetoxy group was cleaved to give a hydroxyl group. The Me_3SiOTf-mediated condensation of **4a–f** with 1-ethoxy or 1-methoxy-1,3-bis(trimethylsilyloxy)buta-1,3-diene (**5a**,**b**) gave the 2,3-dihydrobenzopyrans **6a–f**. Treatment of the latter with NEt_3 in EtOH afforded the novel 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones **7a–f**. The formation of the latter can be explained by a domino 'retro-Michael–aldol–lactonization' reaction.[17] The synthesis of compounds **3b**,[22] **3c**,[23] and **4c**[24] has been previously reported.



Scheme 1. Synthesis of 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones **7a–f**: (a) $TiCl_4$, CH_2Cl_2, −78 °C; (b) $HC(OEt)_3$, $HClO_4$ (70%), reflux, 12 h; (c) (1) Me_3SiOTf (1.3 equiv), 20 °C, 1 h; (2) **5a**,**b** (1.3 equiv), CH_2Cl_2, 0→20 °C, 12 h; (3) HCl (10%); (d) NEt_3 (2.0 equiv), EtOH, 20 °C, 12 h.

The combination of two different cyclization reactions of 1,3-bis(silyl enol ethers) allows a facile approach to a number of novel 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones. The core structure of the products contains 13 carbon atoms out of which 9 carbons are derived from the two 1,3-bis(silyl enol ethers), 3 carbons from the 3-silyloxyalk-2-en-1-one and 1 carbon from the orthoformate.

In conclusion, we have reported the synthesis of 7-hydroxy-6*H*-benzo[*c*]chromen-6-ones based on sequential reactions of 1,3-bis(silyl enol ethers) with 3-silyloxyalk-2-en-1-ones and chromones.

3. Experimental

3.1. General comments

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For the ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Chemical shifts δ are reported in parts per million relative to $CHCl_3$ (^1H, 7.26 ppm) and $CDCl_3$ (^{13}C, 77.0 ppm) as internal standards. ^{13}C NMR spectral assignments are supported by DEPT analyses. Mass spectral data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O), or electrospray ionization (ESI). For preparative scale chromatography silica gel (60–200 mesh) was used. Melting points are uncorrected.

3.2. General procedure for the synthesis of 2-acetylphenols 3a–f

To a stirred CH_2Cl_2 solution (2 mL/mmol) of 1,3-bis(silyl enol ether) **2** (1.0 mmol) and 3-siloxyalk-2-en-1-one **1** (1.0 mmol) was added $TiCl_4$ (1.0 mmol) at −78 °C under argon atmosphere. The temperature of the reaction mixture was allowed to rise to 20 °C during 20 h and a saturated aqueous solution of $NaHCO_3$ (10 mL) was added. The organic layer was separated and extracted with diethyl ether (3×30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (silica gel, EtOAc/heptane=1:4).

3.2.1. 1-(3-Chloro-2,4-diethyl-6-hydroxyphenyl)ethanone (3a). Starting with 4-chloro-5-(trimethylsilyloxy)hept-4-en-3-one (**1a**) (1.021 g, 4.3 mmol), 2,4-bis(trimethylsilyloxy)penta-1,3-diene (**2**) (1.041 g, 4.3 mmol), and $TiCl_4$ (0.812 g, 4.3 mmol), **3a** was obtained (0.490 g, 50%) as

Table 1. Products and yields

	R^1	R^2	R^3	R^4	**3** (%)[a]	**4** (%)[a]	**6** (%)[a]	**7** (%)[a]
a	Et	Cl	Et	Me	50	80	77	28 (48)
b	Me	Me	Me	Et	51	70	65	22 (42)
c	Me	H	Me	Et	40	84	68	24 (46)
d	Me	$-(CH_2)_4-$		Et	36	78	61	50
e	Me	$-(CH_2)_3-$		Me	20	69	73	35 (60)
f	Me	OAc	Me	Me	42	—	—	—
f	Me	OH	Me	Me	—	70	68	33 (40)

[a] Yields of isolated products; the synthesis of compounds **3b**,[22] **3c**,[23] and **4c**[24] has been previously reported; values in brackets: yields based on recovered starting material.