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Synthesis of chromanes by sequential '[3+3]-cyclization/Williamson' reactions of 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-dienes

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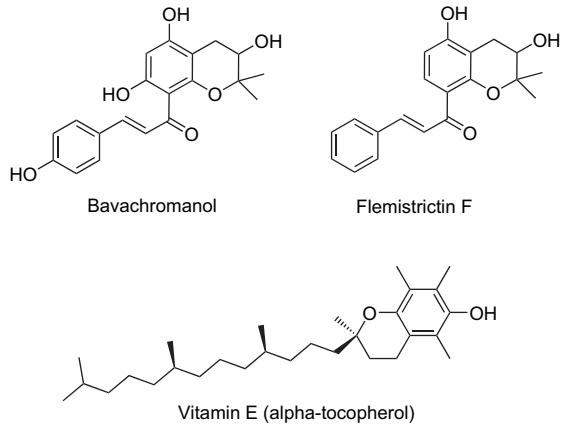
Abstract—Functionalized chromanes were prepared by sequential '[3+3]-cyclization/Williamson' reactions of 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-dienes with 1,1,3,3-tetramethoxypropane, 3-silyloxyalk-2-en-1-ones, and 1,1-diacetylcyclopropane. The first step of the sequence involves [3+3] cyclizations of the starting materials to give 2-(3-chloropropyl)phenols. The subsequent cyclization proceeds by intramolecular nucleophilic substitution. 6-(2-Hydroxybenzoyl)chromanes were prepared based on sequential '[3+3]-cyclization/Williamson' reactions of 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-dienes with 3-formylchromones.

1. Introduction

3,4-Dihydro-2*H*-chromenes (chromanes) represent pharmacologically relevant heterocycles, which occur in a variety of natural products (Scheme 1).[1,2] For example, bavachromanol has been isolated from leaves of *Maclura tinctoria* L. (Venezuela).[2a] The chromanol moiety of vitamin E (α-tocopherol) exhibits anti-androgen properties. Many synthetic approaches to 3,4-dihydro-2*H*-chromenes are based on intramolecular Friedel–Crafts alkylations.[2] Finn et al. have prepared chromanes from salicylic aldehydes and vinylboronic acids in the presence of catalytic amounts of dibenzylamine.[3] Jones et al. reported the synthesis of chromanes by Diels–Alder reactions of *o*-quinone methides, which were generated from salicylic aldehydes and alcohols.[4]



Scheme 1. Chromane natural products.

Chan and co-workers reported an efficient one-pot synthesis of salicylates based on [3+3] cyclizations of 1,3-bis-silyl enol ethers[5] with 3-silyloxyalk-2-en-1-ones or 1,1,3,3-tetramethoxypropane.[6] Recently, we have reported[7] an extension of this method by the first use of 1,3-bis-(trimethylsilyloxy)-7-chlorohepta-1,3-dienes (chloro-substituted 1,3-bis-silyl enol ethers)[8] in [3+3] cyclizations. The combination of these [3+3] cyclizations with subsequent intramolecular Williamson reactions allows for the synthesis of functionalized chromanes. Herein, we report full details of these studies. With regard to our preliminary communication in this field,[7] we herein report, for the first time, the synthesis of 6-(2-hydroxybenzoyl)-3,4-dihydro-2*H*-chromenes based on sequential '[3+3]-cyclization/Williamson' reactions of 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-dienes with 3-formylchromones. The general strategy reported herein allows for a convenient synthesis of a variety functionalized chromanes. Notably, the substitution patterns of these products are not readily available by other methods.

Keywords: Benzopyrans; Cyclizations; Ethers; Lewis acids; Silyl enol ethers.
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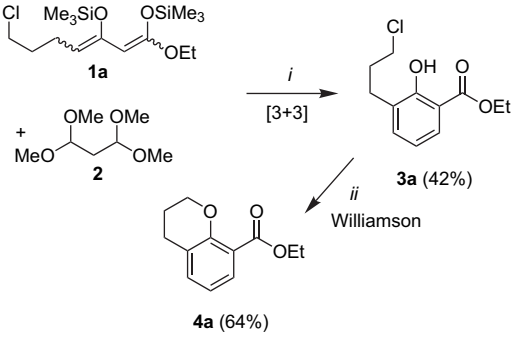
2. Results and discussion

2.1. [3+3] Cyclization of 1,1,3,3-tetramethoxypropane

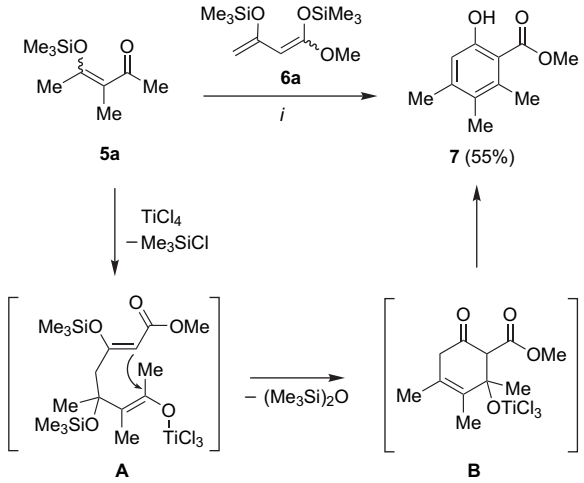
The key substrates of this study—1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-dienes **1a**,**b**—were prepared in three steps from ethyl acetoacetate as previously reported.[7,9] The $TiCl_4$-mediated [3+3] cyclization of **1a** with 1,1,3,3-tetramethoxypropane (**2**) afforded the 2-(3-chloropropyl)phenol **3a**. The formation of **3a** proceeds by attack of carbon atom C-4 of **1a** onto **2**, cyclization via carbon C-2, and finally aromatization. Notably, the chloride functionality remained unattacked during the reaction. Treatment of a THF solution of **3a** with sodium hydride (NaH), in the presence of tetrabutylammonium iodide (TBAI), afforded chromane **4a** (Scheme 2).



Scheme 2. Synthesis of chromane **4a**. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, −78→20 °C; (ii) NaH, TBAI, THF, 20 °C.

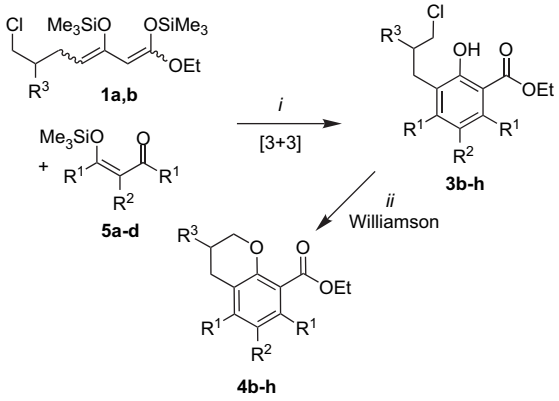
2.2. [3+3] Cyclizations of 3-silyloxyalk-2-en-1-ones

The [3+3] cyclization of 1,3-bis-silyl enol ether **6a** with 3-silyloxyalk-2-en-1-one **5a** has been reported to give salicylate **7**.[6] The cyclization proceeds by $TiCl_4$-mediated conjugate addition of the terminal carbon atom of the bis-silyl enol ether onto **5a**, cyclization, extrusion of siloxane, and aromatization (Scheme 3).



Scheme 3. Synthesis of salicylate **7** by Chan et al. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, −78→20 °C.

The [3+3] cyclization of 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-dienes **1a**,**b** with 3-silyloxyalk-2-en-1-ones **5a–d** afforded the 2-(3-chloropropyl)phenols **3b–h**. The latter were transformed (by NaH and TBAI) into chromanes **4b–h** (Scheme 4, Table 1). The formation of **3b–h** can be explained, following the mechanism proposed by Chan,[6] by initial attack of carbon atom C-4 of **1a**,**b** onto the carbon atom attached to the silyloxy group of **5a–d**, cyclization by attack of carbon C-2 onto the carbonyl group and subsequent aromatization.



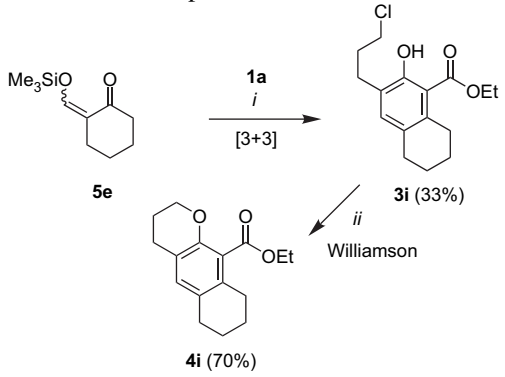
Scheme 4. Synthesis of chromanes **4b–h**. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, −78→20 °C; (ii) NaH, TBAI, THF, 20 °C.

Table 1. Synthesis of chromanes **4b–h**

5	3,4	R^1	R^2	R^3	% (3)[a]	% (4)[a]
a	**b**	Me	Me	H	52	90
b	**c**	Me	H	H	46	70
c	**d**	Me	Et	H	43	82
d	**e**	Et	H	H	42	65
a	**f**	Me	Me	Me	44	94
b	**g**	Me	H	Me	46	80
c	**h**	Et	H	Me	53	97

[a] Yields of isolated products.

The [3+3] cyclization of 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-diene **1a** with 3-silyloxyalk-2-en-1-one **5e**, prepared from 2-(hydroxymethylidene)cyclohexan-1-one, furnished tetrahydronaphthalene **3i** (Scheme 5). In contrast to **3b–h**, the formation of regioisomers is theoretically possible in case of **3i**. The regioselective formation of **3i** can be explained by the same mechanism as described for **3b–h**, i.e. by initial attack of carbon atom C-4 of **1a** onto the carbon attached to the silyloxy group of **5e**. Treatment of **3i** with NaH/TBAI afforded the tricyclic benzopyran **4i**. The structure of **4i** was established by H,H-COSY, C,H-COSY, HMBC, and NOESY experiments.



Scheme 5. Synthesis of chromane **4i**. Reagents and conditions: (i) $TiCl_4$, CH_2Cl_2, −78→20 °C; (ii) NaH, TBAI, THF, 20 °C.

The [3+3] cyclization of **1a** with 3-silyloxyalk-2-en-1-one **5f**, available by silylation of 2-acetylcyclohexanone,