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Polycyclic Chromans Via Novel Tricyclic-2-phenyl-4H-1,3,2-benzodioxaborins

Suzanne Bissada, Cheuk Kun Lau, Michael A. Bernstein, Claude Dufresne*

Merck Frosst Centre for Therapeutic Research
P.O. Box 1005, Pointe Claire-Dorval, Québec, Canada H9R 4P8

Abstract: This paper describes a straightforward synthesis of complex polycyclic chromans. They are prepared from novel tricyclic-2-phenyl-4H-1,3,2-benzodioxaborins via a bicyclic orthoquinone-methide intermediate generated in situ under thermolysis or Lewis acid condition. The dioxaborins react with various allyl trimethylsilanes or with ethyl vinyl ether to give polycyclic chromans after acid cyclization or directly.

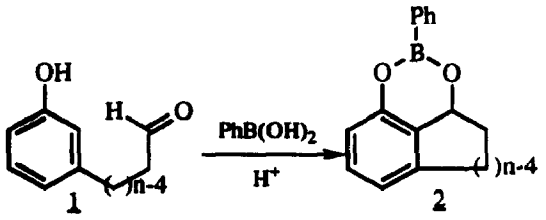
There is a widespread occurrence of polycyclic chroman ring systems in natural products.[1] They are found in plant pigments (anthocyanins and flavones),[2] in constituents of hashish (tetrahydrocannabinol),[3] in vitamin E[4], as well as in coumarin and catechin.[5] Chroman fused ring systems have been synthesized using the inter- or intramolecular cyclization of a dienophile with a reactive orthoquinone methide intermediate generated in situ.[6] A few general methods are presently available for orthoquinone methide generation.[7]

We have developed the 2-phenyl-4H-1,3,2-benzodioxaborin as a stable orthoquinone-methide precursor and studied its reaction with various nucleophiles and dienophiles.[8] As a complement to these methodologies, we now report the synthesis of novel tricyclic-2-phenyl-4H-1,3,2-benzodioxaborins and their use as starting materials for a straightforward route to polyclic chromans.

The tricyclic benzodioxaborins starting materials were prepared in an annulation reaction, heating a phenol bearing in the meta position an alkyl aldehyde of various chain lengths[9] with phenylboronic acid. The results are summarized in Table 1. In a typical experiment, 3-(3-hydroxyphenyl) butanal (1b), phenylboronic acid (1.6 eq) and propanoic acid (0.3 eq) in toluene were refluxed for 18h with azeotropic removal of water to give 72% yield of the tetralin dioxaborin 2b after chromatography. The results show that 5, 6 and 7 membered rings were obtained in fair yields while the larger ring (8-10) were difficult to form, thus showing the limitation of the annulation reaction. In the case of the nine member ring, none of the desired dioxaborin was observed.

TABLE 1

ANNULATION REACTION VIA THE FORMATION OF 2-PHENYL-4H-1,3,2-BENZODIOXABORINS



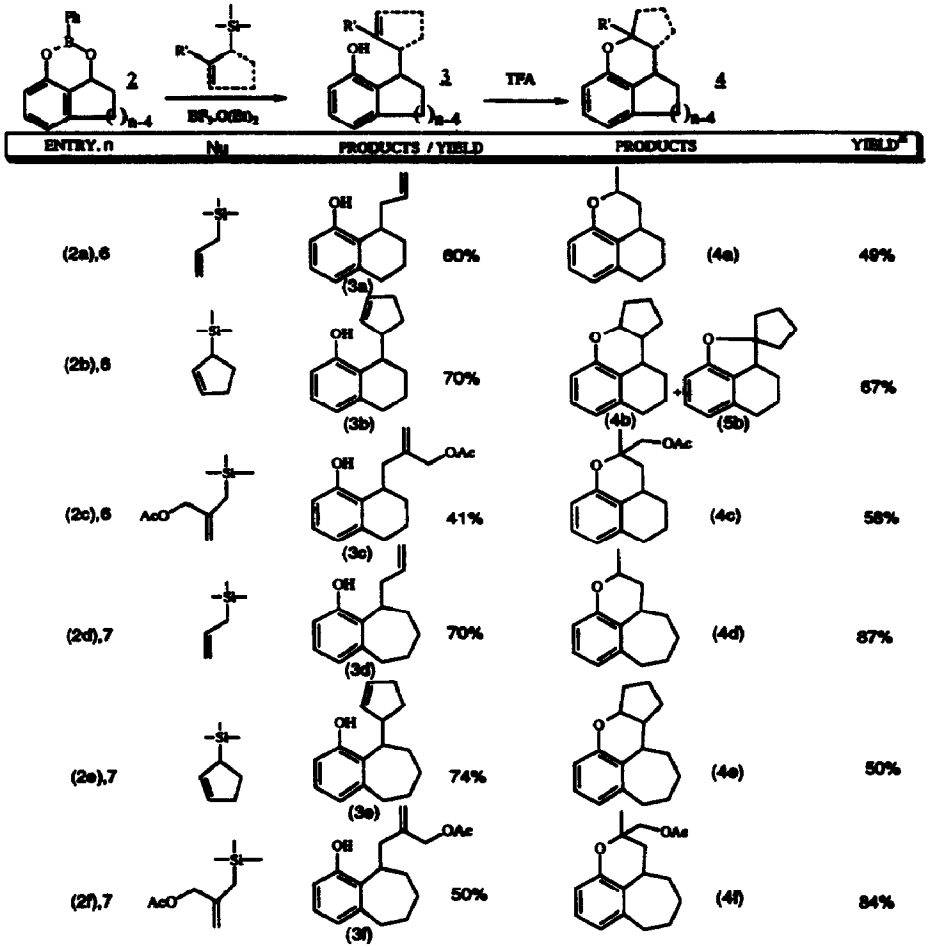
ENTRY / n		YIELD [a]
1a	5	45%
1b	6	72%
1c	7	79%
1d	8	15%
1e	9	0%
1f	10	30%

a) Yield of isolated products , characterized by ^{1}H NMR, IR and combustion analysis.

The tricyclic benzodioxaborins 2 were then treated with various allyl trimethylsilane derivatives in the presence of BF_3-etherate. The allyl trimethylsilane reacts with the bicyclic orthoquinone-methide intermediate generated in situ from the dioxaborin to give the bicyclic phenol 3. Intramolecular cyclization of the phenol on the olefin under trifluoroacetic acid condition gave the corresponding polycylic chroman ring systems 4. The results are summarized in Table 2. Typically, a mixture benzodioxaborin 2d, BF_3-etherate (4eq) and allyl trimethylsilane (4eq) in dichloroethane was heated at 100°C in a heavy wall pyrex pressure bottle for 18h, to give 3d in 70% yield after chromatography. This compound was then cyclized in trifluoroacetic acid overnight at room temperature to give polycyclic chroman 4d in 87% yield. The 2,2 substituted 4c and 4f as well as the 2,3-fused cyclopentyl 4b and 4e were prepared similarly in good yields. In the cyclization of 3b, the secondary product 5b was obtained in a 1:2 product ratio with 4b in 67% combined yield.

TABLE 2

POLYCYCLIC CHROMANS VIA 2-PHENYL-4H-1,3,2-BENZODIOXABORINS

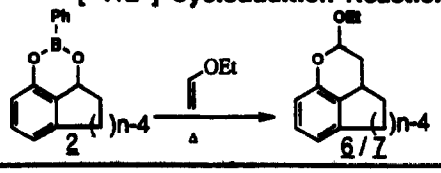


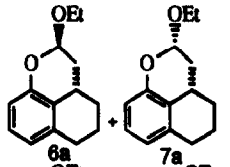
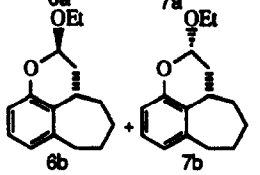
a) Yield of isolated products, characterized by ^{1}H NMR,IR and combustion analysis.

In a second key application, tricyclic dioxaborins are used as the precursor of the corresponding bicyclic orthoquinone-methide, which undergoes a thermal [4+2] cycloaddition reaction with electron rich dienophiles giving a direct access to 2-substituted polycyclic chroman ring system. This is illustrated in Table 3 by the reaction of 2a and 2b with ethyl vinyl ether at 250°C, overnight, to give the corresponding 2-ethoxy tricyclic chromans 6a, 7a and 6b, 7b in 60% and 78% yield respectively. A 4:1 ratio of trans to cis isomers was obtained in both cases. This trans/cis product ratio probably results from an equilibration of the favored endo (kinetic) adduct under the harsh reaction conditions, leading to the thermodynamic mixture of products.[10]

TABLE 3

[4+2] Cycloaddition Reactions



SUBSTRATES / n	PRODUCTS	YIELD [a]
2a / n=6		60% TRANS / CIS 4 /1
2b / n=7		78 % TRANS / CIS 4 /1

A)Yield of isolated products, characterized by ^{1}H NMR,IR and combustion analysis.

In summary, we have presented a straightforward synthesis of complex polycyclic chromans, starting from a simple phenol substituted with an aldehyde, via novel tricyclic-2-phenyl-4H-1,3,2-benzodioxaborins. The use of an enol ether in the cycloaddition reaction yields 2-alkoxy chromans thus giving access to coumarin and other ring systems.

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