Synthesis of 2*H*-Chromenes through the Reduction of Chromones with 9-BBN

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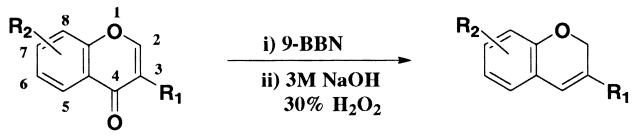
Chromones were regioselectively reduced to 2*H*-1-benzopyrans through the 1,2-addition of 9-borabicyclo-[3.3.1]nonane. Although transition-metal complexes did not have a catalytic effect on the reaction, only by using palladium(II) chloride, could both 2*H*-1-benzopyran and dihydro-1-benzopyran be obtained to a similar extent. Also, the reduction of chromone using other organoboranes led not to 2*H*-1-benzopyran, but rather to chromanone through the reduction of only an olefin moiety.

2*H*-1-Benzopyrans (**2**, 2*H*-Chromenes), which have been well-known as natural pigments, have broadly served as important intermediates to synthesize many natural products. In particular, anthocyanins (2-aryl-2*H*-1-benzopyrans) are becoming increasingly noteworthy because of their health-promoting effects found in vegetables, fruits, fruit juices, and red wines. **2** are also employed as intermediates to produce many medicinal reagents, such as antimicrobiral, antitumor, antiulcer, anti-HIV, antituberculer agent, and venom antidotes.[1] In spite of several reports concerning methods for the synthesis of chromenes,[2] general strategies for the syntheses which can efficiently afford various substituted chromene systems are still required.

Recently, on the other hand, organic syntheses using organoboranes have been dramatically developed. Among them, 9-borabicyclo[3.3.1]nonane (9-BBN) has been known to reduce rapidly and quantitatively conjugated aldehydes and ketones to the corresponding allylic alcohols in tetrahydrofuran in excellent purities.[3] In addition, even cyclic enones, such as 2-cyclopentene-1-one and 2-cyclohexene-1-one, are also cleanly reduced to the desired allylic alcohols without an incidental attack at the double bond. Unlike more conventional reagents, such as aluminum hydride and diisobutylaluminum hydride (DIBAH), a mildness in the reactivity of 9-BBN, tolerates the presence of almost any other functional groups, such as ester, amide, carboxylic acid, nitro, halogen, and nitrile. In the course of our investigations on the synthesis of **2** by the reduction of 4*H*-1-benzopyran-4-ones (chromones, **1**), we decided to examine the scope of the hydroboration route to **2**. An article concerning the reductions of 2*H*-1-benzopyran-2-ones (coumarins) and **1a** with diborane has already been reported by Still and Goldsmith.[4] In this case, **1a** was treated with diborane and reduced at both the carbonyl group and the olefin moiety to afford 2,3-dihydro-1-benzopyran-3-ol. It was also suggested that the reduction of **1a** proceeded through a step involving hydride addition to a pyrylium salt intermediate to yield **2a**. From it, it can be assumed that this reaction can be completed at the stage of the formation of **2a** by means of controlling the amount of hydride ion, H^-. Thus the authors carried out the reaction of **1** with 9-BBN, instead of diborane, being able to donate only a hydride ion, and succeeded in obtaining moderate-satisfactory results. In this article, we describe the obtained results (Scheme 1).



1 **2**

a) $R_1 = R_2 = H$
b) $R_1 = H$, $R_2 = 6\text{-OMe}$
c) $R_1 = H$, $R_2 = 6\text{-Ph}$
d) $R_1 = H$, $R_2 = 6\text{-Me}$
e) $R_1 = H$, $R_2 = 6\text{-Cl}$
f) $R_1 = H$, $R_2 = 6\text{-NO}_2$
g) $R_1 = H$, $R_2 = 7\text{-OMe}$
h) $R_1 = H$, $R_2 = 7\text{-Me}$
i) $R_1 = H$, $R_2 = 8\text{-Me}$
j) $R_1 = H$, $R_2 = 8\text{-Cl}$
k) $R_1 = H$, $R_2 = 8\text{-NO}_2$
l) $R_1 = Ph$, $R_2 = H$
m) $R_1 = Me$, $R_2 = H$

Scheme 1.

Results and Discussion

Reduction of 1a with 9-BBN. The reductions of **1a** (1 mmol) were carried out with varying amounts of 9-BBN at room temperature followed by the treatment of alkaline hydrogen peroxide, the obtained results are summarized in Table 1. As shown in the table, 3 molar amounts of 9-BBN (Run 4) showed the greatest yield upon this reaction. No reduction occurred in the absence of 9-BBN (Run 1) to give salicylic acid resulting from a chromone ring cleavage. In the case using a large excess of 9-BBN (Run 5), a remarkable decrease in the yield of **2a** was observed, which should be recognized to be due to a further reduction, such as in the case of diborane.[4] H. C. Brown and his coworkers[5] have already reported on the hydroboration of allyl-substituted 2-butenyl (crotyl) derivatives with diborane, and proposed that the reaction proceeded through double hydroborations and a subsequent elimination

Table 1. Reduction of Chromone (**1a**) with 9-BBN[a)]

Run	Amount of 9-BBN / mmol	Yield of **2a**[b)] / %
1	0	—
2	1	7
3	2	44
4	3	79
5	5	53

a) All the reactions were carried out under a nitrogen atmosphere at room temperature, using 1 mmol of **1a**.
b) GLC yields based on the substrate.

of borane moieties by heating, resulting in double-bond migration. If the present reaction occured via the same pathway, though not heated, the reaction scheme may be pictured as follows (Scheme 2(a)). An alternative aspect is a participation of pyrylium salt intermediate, as mentioned in the foregoing section. In this case, the first hydroboration occurs at the carbonyl group of substrate followed by the elimination of a borate moiety, resulting in the formation of pyrylium intermediate. Then, the second one proceeds at the C_2-C_3-position of the intermediate with the borane moiety on the C_3-position. A subsequent elimination of the borane moiety is presumably induced by the coordination of base with the boron atom, facilitanting heterolysis of the boron–carbon bond, yielding the olefin, as shown in Scheme 2(b). Actually, the reaction solution was initially colored pale yellow, and finally dark red to suggest the presence of ionic species. However we were puzzled by the discrepancy in the optimum amount of 9-BBN (three molar amounts). Only two molar amounts of borane are required in both reaction schemes. As a possibility, a part of 9-BBN may be consumed by a side reaction, such as a ring cleavage, though this is not clear at the present stage. Furthermore, since Brown et al[5] carried out eliminations in the presence of mathanol, acetic acid, and methanesulfonic acid after hydroboration, to determine whether acids would increase the rate, the authors conducted the same experiment by the addition of methanesulfonic acid after hydroboration. But, a decrease in the yield of **2a** (47%) was merely observed. Accordingly, the authors consider at present that the reaction presumably proceeded through the pyrylium intermediate, though this is still not clear in detail.

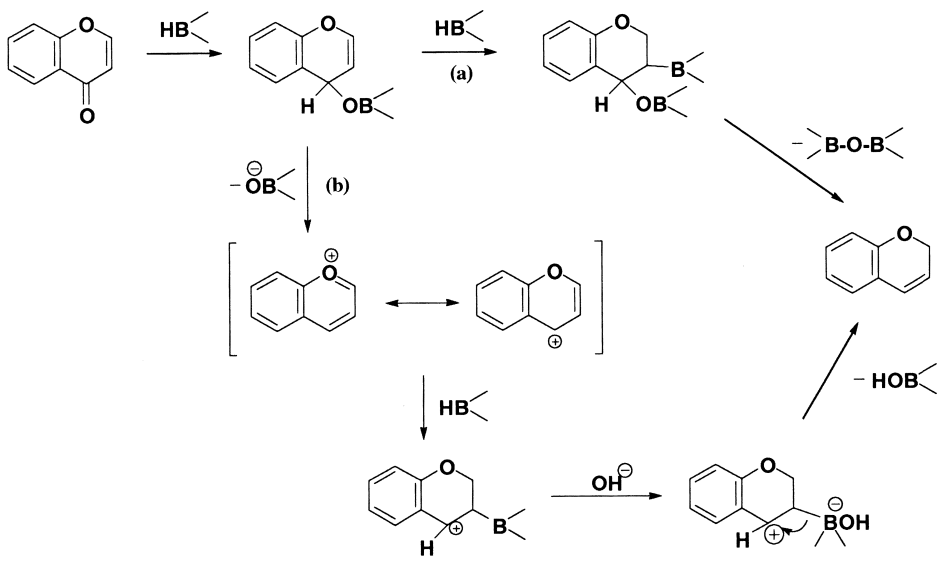
On the other hand, one is often confronted with reactions promoted by some transition-metal catalysts, particularly by palladium complexes, where organoboranes participate.[6] Thus, the hydroborations were conducted in the presence of some palladium and rhodium catalysts, those results are given in Table 2. It is apparent that these catalysts have practically a negative effect, rather than positive one, on this reduction. In the case of using palladium(II) chloride [$PdCl_2$] as a catalyst, dihydro-1-benzopyran (chroman) also reduced at olefin moiety was obtained in 31% yield, as well as **2a**. From these facts, it may be reasonable to consider that palladium catalyses accelerate the reaction so powerfully that a further reduction of **2a** once produced proceeds through the formation of a π-allyl type complex followed by some side reaction, for example, such as a ring cleavage.

Reactions Using Other Boranes. For the purpose of comparing various boron compounds, as well as 9-BBN, the

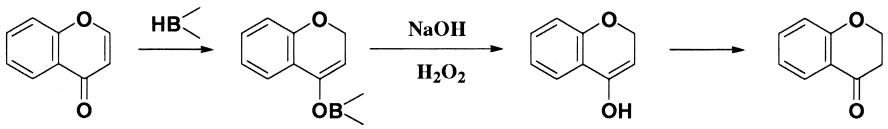
Table 2. Reduction of Chromone (**1a**) with 9-BBN in the Presence of Transition Metal Catalysts[a)]

Run	Catalyst[b)]	Yield of **2a**[c)] / %
1	$[Pd(PPh_3)_4]$ (0.03)	57
2	$PdCl_2$ (0.1)	24[d)]
3	$[PdCl_2(dppf)]$[e)] (0.03)	54
4	$RhCl_3 \cdot 3H_2O$ (0.1)	47

a) All the reactions were carried out under a nitrogen atmosphere at room temperature, using 1 mmol of **1a** and 3 mmol of 9-BBN.
b) Figure in parenthese indicate the added amount in a mmol-unit.
c) GLC yields based on the substrate.
d) Chroman was also obtained 31% yield.
e) dppf: 1,1′-bis(diphenylphosphino)ferrocene.



Scheme 2.



Scheme 3.

representative hydroborating reagents, such as bis(1,2-dimethylpropyl)borane (disiamylborane), 1,3,2-benzodioxaborole (catecholborane) and dicyclohexylborane, were attempted in reactions with **1a**. While **2a** was not obtained in every case, dihydro-1-benzopyran-4-one (chromanone) reduced only at olefin moiety of **1a** was given in 33, 12, and 31% yields, respectively. Although no definitive evidence could be detected, 9-BBN seems clearly to be specific for this reduction, compared with the other one-hydride donor boranes, such as the above-mentioned ones.

In general, catecholborane is thought to be far less reactive than dialkylboranes, and to be more favorable to the hydroboration of a carbon-carbon triple bond than to that of a double bond. Although the reactivities both of disiamylborane and dicyclohexylborane should be essentially regarded as being comparable to that of 9-BBN, these stabilities and regioselectivities seem to be slightly less than those of the latter. Additionally, while disiamyl- and dicyclohexylborane have bulky alkyl groups around the boron atom, that in 9-BBN is comparatively exposed.[7] Thus, a predominance of 9-BBN toward the ring system, such as **1**, may arise from this steric reason. In the former three cases, the formations of chromanone in low yield would be due to the 1,4-addition of boranes toward the carbonyl group followed by elimination of the borane moiety to give the enol, which would immediately isomerize to the ketone (Scheme 3).

Substituent Effect. For twelve derivatives (**1b**–**1m**), which introduced some substituents on the condensed benzene ring or C_3-position of **1a**, the reductions were carried out under the same conditions in order to examine the generality of this reaction. The obtained results are summarized in Table 3. A substituent effect was observed, more or less, depending upon its position and on the electronic property. 6-OMe-derivative (**1b**, Entry 1 in Table 3) gave a desired product (**2b**) in the highest yield among them, whereas 7-OMe-derivative (**1g**, Entry 6 in Table 3) provided **2g** in fairly low yield. These results seem to be due to a difference of the stability between the benzopyrylium salts formed as an intermediate in the present reaction. Similarly, it may be assumed that the lower yields of Cl-derivatives (**2e**, **2j**, Entries 4 and 9 in Table 3) and NO_2-derivatives (**2f**, **2k**, Entries 5 and 10 in Table 3) are due to the lability of the intermediates resulting from the presence of an electron-withdrawing group. By introducing a methyl group (Entries 3, 7, 8, and 12 in Table 3), there is a tendency to diminish the yields of **2** to a certain extent, compared to that in the case of unsubstituted chromone. The lower yield of **2m** can be recognized to arise from a decrease in the basicity of the carbonyl group of **1m**, as already reported in our earlier study concerning the basicity of chromones,[8] resulting in a difficulty concerning the addition of 9-BBN in the initial stage of the reaction. However, both basicities of **1d** and **1h** are slightly greater than that of **1a**.[8] Thus, the low yields of **2d** and **2h** should be considered to be due to another reason, such as a thermodynamic one, though this is still not clear. A steric hindrance of isoflavone (**1l**) against the carbonyl group must be greater than that of **1m**. Accordingly, it seems reasonable to assume that the higher yield of **2l** compared with that of **2m** is due to an increase in the stability of the pyrylium intermediate by means of the introduction of a phenyl group at the C_3-position, spreading the conjugated system.

Table 3. Reduction of Substituted Chromones (**1b**–**1m**) with 9-BBN[a)]

Entry	Substituent	Yield of **2**[b)] / %
1	6-OMe	93 (**2b**)
2	6-Ph	52 (**2c**)
3	6-Me	55 (**2d**)
4	6-Cl	37 (**2e**)
5	6-NO_2	10 (**2f**)
6	7-OMe	19 (**2g**)
7	7-Me	51 (**2h**)
8	8-Me	62 (**2i**)
9	8-Cl	30 (**2j**)
10	8-NO_2	12 (**2k**)
11	3-Ph	61 (**2l**)
12	3-Me	47 (**2m**)

a) All the reactions were carried out under a nitrogen atmosphere at room temperature, using 1 mmol of substrate and 3 mmol of 9-BBN. b) Isolated yields based on the substrate.

Conclusion

Although its reaction mechanism is still not clear in detail, the reduction of chromones with 9-BBN has been demonstrated to proceed regioselectively to give the corresponding 2*H*-1-benzopyrans, while reactions using reductants, such as disiamylborane, catecholborane, and dicyclohexylborane, afforded chromanone in low yield.

Experimental

All of the reactions were carried out under a nitrogen atmosphere. The melting points were determined by using a Yanaco micro-melting-point apparatus and are uncorrected. The IR spectra were recorded on a JASCO-IRA-1 spectrometer by means of a KBr pellet or neat. ^{1}H NMR spectra were obtained with a JEOL JNM-EX270 Fourier Transform NMR spectrometer (270 MHz), and are reported in δ units using tetramethylsilane as an internal standard. Mass spectra were taken on a JEOL-JMS-D300. GLC analyses were performed on a Hitachi-263-30 instrument with Silicone SE-30 (2 m) on Uniport B using hexadecane as an internal standard. THF was purified by distillation from diphenylketyl under a nitrogen atmosphere before use. Column chromatography was performed using a Wakogel C-200 (silica gel).

Boranes. 9-Borabicyclo[3.3.1]nonane in THF and 1,3,2-ben-

zodioxaborole in THF from Aldrich Chemical Co. were used directly. Other dialkylboranes were prepared via the hydroboration of appropriate alkenes with diborane, and were transferred to a main reaction flask with double-ended needles under a nitrogen atmosphere.

Transition Metal Catalysts. Tetrakis(triphenylphosphine)-palladium(0)[9] and dichloro[1,1′-bis-(diphenylphosphino)-ferrocene]palladium(II)[10] were prepared according to reported procedures. Rhodium(III) chloride trihydrate was commercially available grade, and was used without further purification.

Materials. Solvents were commercially available grade and were purified by ordinary procedures before use. Chromones (**1a**–**1m**) were prepared according to known procedures,[11] and were identified by means of IR and ^{1}H NMR spectra. 2*H*-Chromenes, isolated in the present reactions, were identified on the basis of values given in the literature,[2,12] except for the following derivatives.

6-Phenyl-2*H*-chromene (2c): Mp 64.1–65.6 °C; IR (KBr) 1230 (–O–), 1480 cm^{-1}(–C=C–); ^{1}H NMR ($CDCl_3$) δ 4.78 (dd, J = 1.7, 2.0 Hz, 2H, C_2–H), 5.82 (m, 1H, C_3–H), 6.49 (d, J = 9.6 Hz, 1H, C_4–H), and 6.83–7.55 (m, 8H, aromatic). MS Found: *m*/*z* 208.0882. Calcd for $C_{15}H_{12}O$: M, 208.0888.

6-Methyl-2*H*-chromene (2d): IR (neat) 1250 (–O–), 1510 cm^{-1} (–C=C–); ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 3H, –CH_3), 4.78 (dd, J = 2.0, 2.0 Hz, 2H, C_2–H), 5.76 (m, 1H, C_3–H), 6.38 (d, J = 9.9 Hz, 1H, C_4–H), and 6.65–6.91 (m, 3H, aromatic). MS Found: *m*/*z* 146.0733. Calcd for $C_{10}H_{10}O$: M, 146.0732.

7-Methyl-2*H*-chromene (2h): IR (neat) 1250 (–O–), 1510 cm^{-1} (–C=C–); ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3H, –CH_3), 4.79 (dd, J = 2.0, 2.0 Hz, 2H, C_2–H), 5.70 (m, 1H, C_3–H), 6.39 (d, J = 9.8 Hz, 1H, C_4–H), and 6.60–6.86 (m, 3H, aromatic). MS Found: *m*/*z* 146.0728. Calcd for $C_{10}H_{10}O$: M, 146.0732.

8-Methyl-2*H*-chromene (2i): IR (neat) 1210 (–O–), 1470 cm^{-1} (–C=C–); ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 3H, –CH_3), 4.83 (dd, J = 1.9, 1.7 Hz, 2H, C_2–H), 5.76 (m, 1H, C_3–H), 6.41 (m, 1H, C_4–H), and 6.73–6.98 (m, 3H, aromatic). MS Found: *m*/*z* 146.0720. Calcd for $C_{10}H_{10}O$: M, 146.0732.

8-Chloro-2*H*-chromene (2j): IR (neat) 1230 (–O–), 1575 cm^{-1} (–C=C–); ^{1}H NMR ($CDCl_3$) δ 4.95 (dd, J = 3.3, 2.0 Hz,, 2H, C_2–H), 5.80 (m, 1H, C_3–H), 6.40 (m, 1H, C_4–H), and 6.75–7.17 (m, 3H, aromatic). MS Found: *m*/*z* 166.0183. Calcd for C_9H_7ClO: M, 166.0185.

8-Nitro-2*H*-chromene (2k): Mp 53.0–53.5 °C; IR (KBr) 1230 (–O–), 1520 cm^{-1} (–C=C–); ^{1}H NMR ($CDCl_3$) δ 5.01 (dd, J = 3.3, 2.0 Hz,, 2H, C_2–H), 5.91 (m, 1H, C_3–H), 6.46 (m, 1H, C_4–H), and 6.88–7.70 (m, 3H, aromatic). MS Found: *m*/*z* 177.0433. Calcd for $C_9H_7NO_3$: M, 177.0426.

3-Phenyl-2*H*-chromene (2l): Mp 89.5–90.0 °C; IR (KBr) 1220 (–O–), 1590 cm^{-1} (–C=C–); ^{1}H NMR ($CDCl_3$) δ 5.17 (s, 2H, C_2–H), 6.81 (s, 1H, C_4–H), and 6.81–7.46 (m, 9H, aromatic). MS Found: *m*/*z* 208.0890. Calcd for $C_{15}H_{12}O$: M, 208.0888.

General Procedure. To a solution of chromone (**1a**, 146 mg, 1 mmol) in THF was added dropwise 6 mL (3.0 mmol) of a 0.5 M (1 M = 1 mol dm^{-3}) 9-BBN solution in THF for 1 h. The resulting mixture was stirred overnight at room temperature. Then, 2 mL of 3M aqueous sodium hydroxide and 2 mL of 30% hydrogen peroxide were added with cooling, if necessary, and the mixture was stirred for 6 h at room temperature, following by acidification with dilute hydrochloric acid and extracted three times with ether. The combined extracts were washed with 2 M aqueous sodium hydroxide, water, and brine, and the ethereal layer was dried with anhydrous magnesium sulfate. After removal of the solvent, the residue was chromatographed on a silica-gel column (benzene/hexanes = 1:9) to give the reduced product, 2*H*-chromene (**2a**), as a colorless liquid.

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