

SELECTIVE REDUCTION OF THE CARBONYL GROUP OF CHROMONE AND THIOCHROMONE TO THE METHYLENE GROUP

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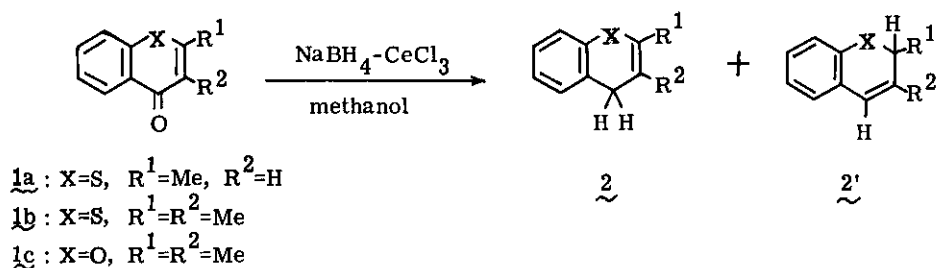
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Abstract 2-Methyl and 2,3-dimethylthiochromones were reduced selectively to the corresponding thiochromenes with NaBH_4 in the presence of $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ in methanol in good yields. 2,3-Dimethylchromone was reduced to the corresponding chromene with sodium bis(2-methoxyethoxy)aluminum hydride in benzene in a moderate yield.

In our previous reports it has been demonstrated that the Wittig-Horner reaction of the phosphonates attached to heterocycles is a versatile method for the direct introduction of the exomethylene moiety to a variety of heterocycles.¹ In order to apply this synthetic procedure to 4H-1-benzopyranyl system or its sulfur analogue, it is necessary to establish some convenient synthetic route to prepare the corresponding 4-unsubstituted benzo(thia)pyrylium salts which are precursors for the phosphonates.¹ Although 4H-1-benzopyran-4-one (chromone) derivatives and their sulfur analogues (thiochromones) (1) can be easily available,² there has been little and no satisfactory work on their reduction to give the corresponding 4H(or 2H)-1-benzo(thia)pyran [(thio)chromene] (2),³ which can be easily converted to benzo(thia)pyrylium salts. We wish to describe herein two simple and efficient reductions of 1 to 2 by either sodium borohydride in the presence of cerium trichloride heptahydrate or sodium bis(2-methoxyethoxy)aluminum hydride (SMEAH or Red-Al).⁴

When 2-methylthiochromone (1a) was treated with sodium borohydride in methanol at room temperature for a couple of days, 1a was recovered quantitatively. A complicated mixture resulted when the solution was refluxed for 50 h. Then, cerium trichloride was found satisfactory

to activate the carbonyl group for reduction with NaBH_4 and reaction conditions are summarized in the Table. The utility of lanthanides as catalysts for selective reduction of enones to the corresponding allyl alcohols has been recently reported,^{5,6} but the present results are somewhat different in that the carbonyl group was directly reduced to the methylene group.



Thus, thiochromenes (2a and 2b) were obtained from 1a and 1b in yields of 80 and 69%, respectively, after purification by alumina column chromatography, when molar ratio of reagents was as follows, i.e., $\underline{1} : \text{NaBH}_4 : \text{CeCl}_3 \cdot 7\text{H}_2\text{O} = 1.0 : 2.5 : 1.5$. A small amount of 2' accompanied in both cases.

The standard procedure of the $\text{NaBH}_4\text{-CeCl}_3 \cdot 7\text{H}_2\text{O}$ reduction: thiochromone (1) (5.5 mM) and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (3.10 g, 8.3 mM) are dissolved in methanol (15 mL). To the mixture is added NaBH_4 (523 mg, 13.8 mM) in several portions with stirring for 5 h at room temperature. Solvent is evaporated under reduced pressure and the residue is extracted with ether after addition of aqueous NaCl .⁷ Ether layer is dried and concentrated to obtain a crude mixture which is analyzed by means of ^1H NMR and/or purified by deactivated alumina chromatography (activity III),

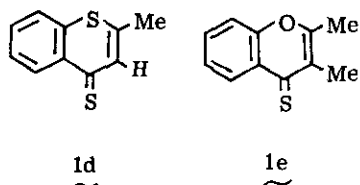
Table Reduction of Thiochromone (1a) with $\text{NaBH}_4/\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ ^{a)}

Entry	Substrate	Molar ratio		Reaction conditions	Yield(%) ^{b)}		Recovery(%) ^{b)}
		NaBH ₄	CeCl ₃ ·7H ₂ O		(<u>2a</u> + <u>2'a</u>)	of <u>1a</u>	
1	1	1	none	reflux 50h	complicated	mixture	
2	1	1	1	r. t. 5h	35	40	
3	1	1	2	r. t. 5h	40	40	
4	1	3	1	r. t. 5h	70	20	
5	1	2.5	1.5	r. t. 5h	80	10	
6 ^{c)}	1	1	1	r. t. 5h	0	80	

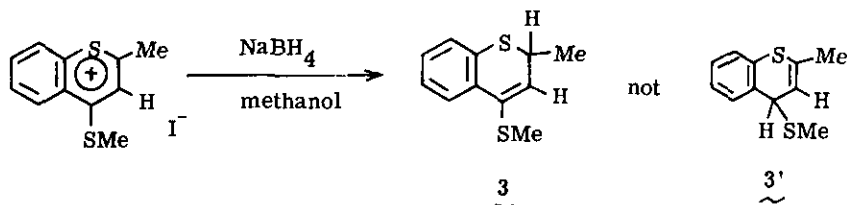
a) Methanol is used as the solvent unless otherwise stated. b) Isolated yields.
c) 2-Propanol is used as the solvent.

eluted with light petroleum. 2a: bp 117-120°C/0.2 mmHg (Kugelrohr), m/e 162(M^+), no OH absorption in IR, 1H NMR (δ in CCl_4) 1.98(3H, br. s), 3.27(2H, br. d, $J=6$ Hz), 5.58(1H, br. t, $J=6$ Hz), 6.8-7.3(4H, m); 2b: bp 124-127°C/0.3 mmHg (Kugelrohr), m/e 176(M^+), δ (CCl_4) 1.90(3H, s), 1.97(3H, s), 3.20(2H, br. s), 6.8-7.3(4H, m).⁸

It should be noted here that present method is applicable only to thiochromones (1a, b) and not to chromone (1c) and their thiones (1d and 1e). They are recovered intact under the same or even more drastic conditions.

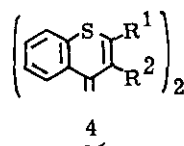


Methiodide of 1d afforded with $NaBH_4$ solely 3 (69% isolated yield),⁹ which is not necessary for the present purpose. 3: colorless oil, m/e 208(M^+), δ ($CDCl_3$) 1.37(3H, d, $J=7$ Hz), 2.27(3H, s), 3.4-4.0(1H, dq, $J=6$ and 7Hz), 5.87(1H, d, $J=6$ Hz), 6.9-7.5(3H, m), 7.5-7.9(1H, m).⁸



When we tried SMEAH reduction of chromone (1c) in benzene according to recent reports,¹⁰ 2H-chromene (2'c) was obtained predominantly (38% purified yield) accompanied by 4H-chromen-4-ol (8%) which was the expected product, and 4H-chromene (2c) could not be detected at all even under scrutiny. In the case of thiochromone (1b), the major product was not 4H-thiochromene (2b, 12%) but a reductive dimer 4 (mp 193-200°C, 49%)⁸.

A typical procedure of SMEAH reduction: To a solution of chromone (1c, 5.75 mM) in dry benzene (10 mL) was added a 70% solution of SMEAH in toluene (2.00 mL, 6.90 mM) carefully via



a syringe with stirring under nitrogen cooling with an ice-water bath. The solution at first turned red then yellowish orange, and was stirred 1 h at room temperature; then a dilute aqueous NaOH solution was carefully added until granular precipitates formed. Products were isolated by ether extraction followed by drying and concentration. The crude mixture was chromatographed by deactivated alumina with light petroleum-ether (100:0 to 50:50). 2'c: m/e 160, δ (CCl_4) 1.32(3H, d, $J=6$ Hz), 1.76(3H, br. s), 4.71(1H, q, $J=6$ Hz), 6.03(1H, br. s), 6.6-7.3(4H, m).

Some other approaches to selective reduction of (thio)chromone skeleton, e.g., $LiAlH_4$ or Li-liq. NH_3 , were not successful because of either their poor reactivity or production of a compli-

cated mixture, therefore we recommend $\text{NaBH}_4\text{-CeCl}_3$ and SMEAH reduction for selective thiochromene and chromene syntheses, respectively. It is still unknown why there is such a difference in reactivity among 1a-e, in spite of their close skeletal resemblance.

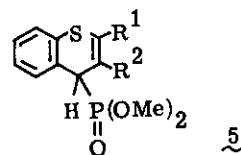
Since chromones and thiochromones are easily accessible materials from (thio)phenol and β -ketoesters,² the present method should be useful to prepare (thio)chromenes and thus the corresponding phosphonates via benzo(thia)pyrylium salts.¹¹

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References and Notes

1. K. Akiba, K. Ishikawa, and N. Inamoto, Bull. Chem. Soc. Jpn., 51, 2674 (1978); Idem., 2684 (1978). One of the features of this synthetic procedure is that the introduced exo-methylene moiety can possess a variety of alkyl or aryl substituents.
2. B. P. Ellis ed. "Chromenes, Chromanones, and Chromones," John Wiley & Sons, N.Y. (1977); for thiochromone synthesis, F. Bossert, Liebigs Ann. Chem., 680, 40 (1964).
3. Either LiAlH_4 or Clemmensen reduction of substituted (iso)flavone to (iso)flavenes is reported; A. C. Waiss, Jr. and L. Jurd, Chem. and Ind., 1968, 743; K. H. Dudley, H. W. Miller, R. C. Corley, and M. E. Wall, J. Org. Chem., 32, 2317 (1967).
4. Both reagents are commercially available and are inexpensive.
5. J. -L. Luche, J. Am. Chem. Soc., 100, 2226 (1978).
6. J. -L. Luche and A. L. Gemal, J. Am. Chem. Soc., 101, 5848 (1979).
7. In the case of a large scale operation, a turbid reaction mixture is often obtained. In this case, the extraction may be carried out by means of a proper continuous extraction apparatus.
8. Structural assignments of all new compounds are based upon their spectral data (^1H NMR, IR, MS) and satisfactory microanalyses data.
9. Synthesis of 1,3-dithiolylum tetrafluoroborate has been reported; F. Wudl and M. L. Kaplan, J. Org. Chem., 39, 3608 (1974).

$$\left[\begin{array}{c} \text{S} \\ \oplus \\ \text{S} \end{array} \right] \text{-SMe} \xrightarrow{\text{NaBH}_4} \left[\begin{array}{c} \text{S} \\ \text{H} \\ \text{S} \end{array} \right] \text{-SMe} \xrightarrow{\text{HBF}_4} \left[\begin{array}{c} \text{S} \\ \oplus \\ \text{S} \end{array} \right] \text{-H} \text{BF}_4^-$$
10. W. S. Johnson, B. E. McCarry, R. L. Marquezich, and S. G. Boots, J. Am. Chem. Soc., 102, 352 (1980); M. E. Semmelhack, R. D. Stanffer, and A. Yamashita, J. Org. Chem., 42, 3180 (1977).
11. Phosphonates (5a : mp $99\text{-}100^\circ\text{C}$ ¹ and 5b : mp $124\text{-}127^\circ\text{C}$)⁸ were prepared in high yields by the reported manner¹ via the corresponding benzothiapyrylium hexachloroantimonates.



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