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SYNTHESIS OF 2,2-DIMETHYL-2*H*-CHROMENES*

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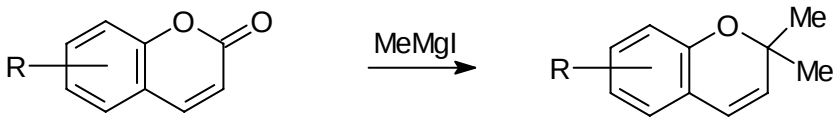
Abstract – In the present review article, the most important procedures developed and utilized for the synthesis of 2,2-dimethyl-2*H*-chromenes are compiled and discussed. Special emphasis is layed on the most convenient and most important methods, *viz.* the dehydration of 2,2-dimethyl-4-hydroxychromans or the thermal rearrangement of phenyl propargyl ethers. However, less general and/or special procedures are critically discussed. Examples for the synthesis of nitrogen and sulfur analogues of 2,2-dimethyl-2*H*-chromenes have also been included.

1. INTRODUCTION

First representatives of the 2,2-dimethyl-2*H*-chromenes have already been described in the literature about six decades ago.[1,2] Various 2,2-dialkyl-2*H*-chromenes were obtained by the reaction of coumarins with Grignard reagents.[1,2] However, less attention was directed to such chromenes until the middle of the seventies. It was in 1976 that Bowers *et al.*[3] isolated the precocene 1 (2,2-dimethyl-7-methoxy-2*H*-chromene) and precocene 2 (6,7-dimethoxy-2,2-dimethyl-2*H*-chromene) from *Ageratum houstonianum*[3] and other sources.[4] These two compounds proved to induce precocious metamorphosis in *Oncopeltus fasciatus, Lygaens kalmii* and *Dysdercus cingulatus*[3,5] owing to their antijuvenile hormone activity. For this reason, these precocenes were considred as useful lead compounds for the development of a new generation of convenient insecticides for a highly selective insect control. Since that invention, an intense research has been carried out to find more effective insect regulators of this type. A major aim of these studies was to produce synthetic analogues of the natural precocene 1 and 2 with more pronounced anti-juvenile hormone activity. Another aim was to get information on the role of the substituents of the aromatic ring in the bioactivity of the 2,2-dimethyl-2*H*-chromenes through qualitative and quantitative studies of their structure-activity relationships. As a result, various procedures have been developed and numerous 2,2-dimethyl-2*H*-chromenes substituted in their aromatic ring have been prepared. In our present review article, the most important synthetic procedures are discussed.

2. GRIGNARD REACTION OF COUMARINS

2,2-Dimethyl-2*H*-chromenes (**2**) were prepared by Shriner and Sharp by the reaction of coumarin (**1**) with Grignard reagent in 1939[1] (Scheme 1). One year later, Smith and Ruoff obtained 2,2-dialkyl-2*H*-chromenes by the same chemical transformation.[2] Later, precocene 1,[6] precocene 2[7] and 2,2,6-trimethyl-2*H*-chromene[8] have been prepared by the reaction of the apropriate coumarins with methylmagnesium iodide. However, the transformation of coumarins into 2,2-dialkyl-2*H*-chromenes by using Grignard reagent has not been developed into a general protocol for the preparation of such chromenes. This can be concluded from the fact that only few papers have hitherto been published on the utilization of this methodology.



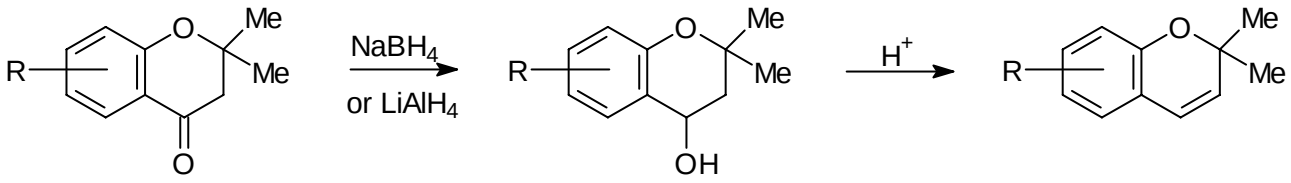
1 **2**

R = H, Me, MeO

Scheme 1

3. DEHYDRATION OF 2,2-DIMETHYL-4-HYDROXYCHROMANS

For the preparation of 2,2-dimethyl-2*H*-chromenes undoubtedly the most convenient and most popular method is the dehydration of the appropriate 2,2-dimethyl-4-hydroxychromans beneficially applied by numerous research groups.[9-26] 2,2-Dimethyl-4-hydroxychromans (**4**) are obtained by the reduction of the easily available 2,2-dimethyl-4-chromanones (**3**) with sodium borohydride or lithium aluminum hydride. Compounds (**4**) can then be dehydrated on treatment with acid to afford the desired 2,2-dimethyl-2*H*-chromenes (**2**) in high yields (Scheme 2). The utilization of this protocol made available the synthesis of different series of variously substituted 2,2-dimethyl-2*H*-chromenes required for the study of their structure-activity relationships.



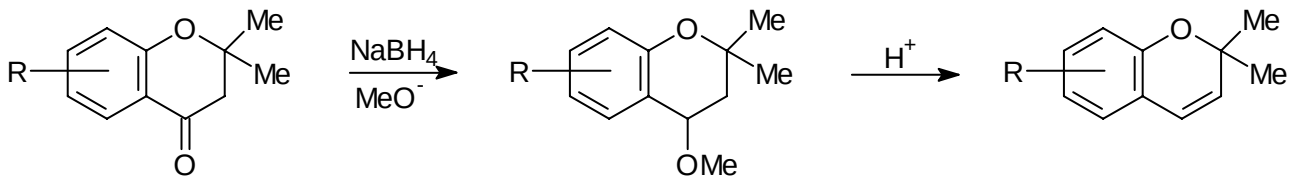
3 **4** **2**

R = H, acyloxy, alkoxy, alkyl, halogen. NO_2

Scheme 2

4. CONVERSION OF 2,2-DIMETHYL-4-METHOXYCHROMANS INTO 2,2-DIMETHYL-2*H*-CHROMENES

The first representative of the 2,2-dimethyl-4-methoxychromans was prepared by Messeguer *et al.*[19] as a by-product of the reduction of 6,7-dimethoxy-2,2-dimethyl-4-chromanone with sodium borohydride in methanol. Synthesis of 2,2-dimethyl-4-methoxychromans (**5**) was investigated in details by Lévai and Tímár.[27] 2,2-Dimethyl-4-chromanones (**3**) were allowed to react with sodium borohydride in methanol and then this solution was acidified with hydrochloric acid. Depending on the substituents of the aromatic ring, 2,2-dimethyl-4-methoxychromans (**5**) were obtained instead of the expected 2,2-dimethyl-2*H*-chromenes (**2**). This observation was developed into a convenient and general procedure for the synthesis of 2,2-dimethyl-4-methoxychromans. These 2,2-dimethyl-4-methoxychromans (**5**) were then allowed to react either with hydrochloric acid in hot acetone or with *p*-toluenesulfonic acid in hot benzene to afford 2,2-dimethyl-2*H*-chromenes (**2**) (Scheme 3).[28] This is the first example for the preparation of such chromenes in this way.



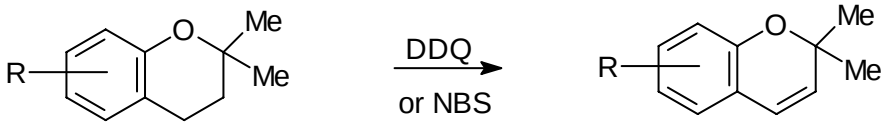
3 **5** **2**

R = acyloxy, alkoxy, alkyl

Scheme 3

5. OXIDATION OF 2,2-DIMETHYLCHROMANS

2,2-Dimethylchromans (**6**) can be easily synthesized either by the reaction of phenols with 2-methylbuta-1,3-diene (isoprene) in the presence of orthophosphoric acid or by a similar reaction using 1,3-dichloro-3-methylbutane instead of isoprene.[29] For the preparation of 2,2-dimethylchromans (**6**) we have developed new convenient procedures by the catalytic hydrogenation of either 2,2-dimethyl-4-methoxychromans (**5**) or 2,2-dimethyl-2*H*-chromenes (**2**).[30] Compounds (**6**) can then be utilized as convenient intermediates for the preparation of 2,2-dimethyl-2*H*-chromenes (**2**). Ahluwalia *et al.*[29] allowed to react the 2,2-dimethylchromans (**6**) with DDQ or with NBS to afford 2,2-dimethyl-2*H*-chromenes (**2**) (Scheme 4). This procedure was used by Solladié *et al.*[31] for the preparation of 6,7-dimethoxy-2,2-dimethyl-2*H*-chromene (precocene 2).



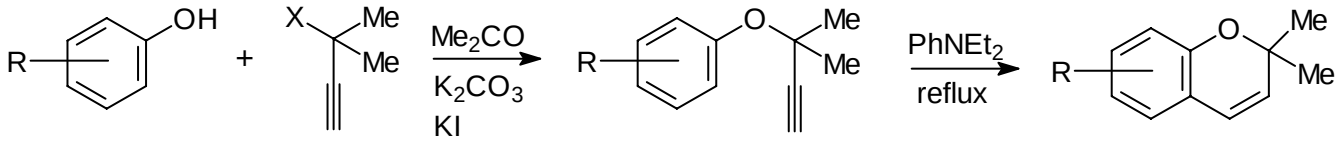
6 **2**

R = H, Me, MeO

Scheme 4

6. THERMAL REARRANGEMENT OF PHENYL PROPARGYL ETHERS

It has been mentioned in Chapter 3 of this review that the dehydration of the 2,2-dimethyl-4-hydroxychromans (**4**) is the most popular procedure for the preparation of 2,2-dimethyl-2*H*-chromenes (**2**). It can be added to this statement that for the synthesis of 2,2-dimethyl-2*H*-chromenes (**2**) the thermal rearrangement of the phenyl propargyl ethers (**9**) is another general and convenient method utilized in numerous laboratories.[32-51] Phenyl propargyl ethers (**9**) can be synthesized easily by the alkylation of phenols (**7**) with 3-substituted 3-methylbut-1-ynes (**8**). Compounds (**9**) are then refluxed in a solvent of high boiling point for several hours to afford 2,2-dimethyl-2*H*-chromenes (**2**) (Scheme 5).



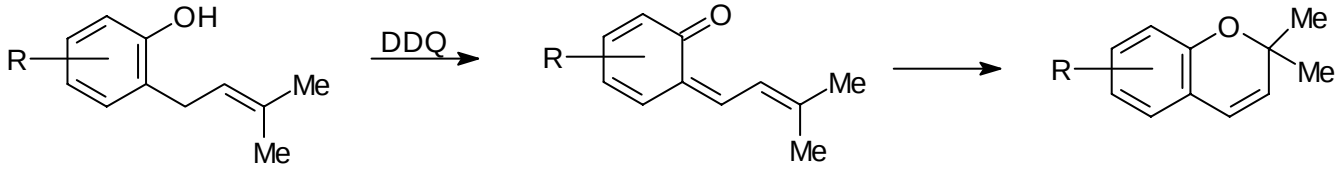
7 **8** **9** **2**

X = Cl, Br or OAc; R = H, Me, MeO, Cl, CN, NO_2

Scheme 5

7. OXIDATIVE CYCLIZATION OF *o*-(3,3-DIMETHYLALLYL)PHENOLS

Synthesis of 2,2-dimethyl-2*H*-chromenes (**2**) by the oxidative cyclization of *o*-(3,3-dimethylallyl)phenols (**10**) has been studied in several laboratories.[52-61] An early example of this chemical transformation was described by Cardillo *et al.*[52] Hydride ion abstraction from the *o*-(3,3-dimethylallyl)phenol (**10**) was performed by DDQ affording an unstable intermediate quinonemethide (**11**) which immediately rearranged into 2,2-dimethyl-2*H*-chromene (**2**) (Scheme 6). As an oxidizing agent, DDQ was used successfully for this oxidative cyclization by other research groups.[53,54,57] Oxidative transformation of *o*-prenylphenols has been performed under Pd-catalyzed reaction conditions as well.[60,61]

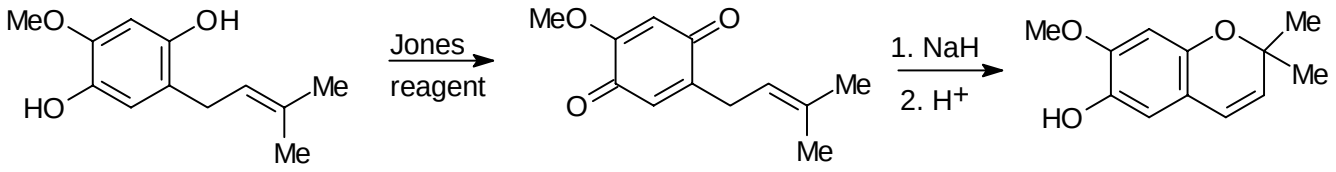


10 **11** **2**

R = OH, alkoxy, alkyl

Scheme 6

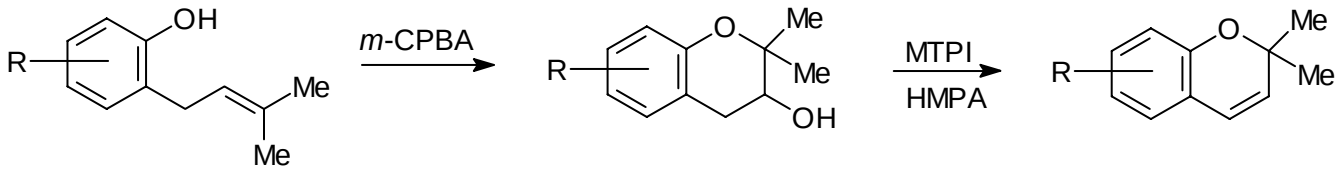
2,2-Dimethyl-6-hydroxy-7-methoxy-2*H*-chromene (**14**) was synthesized *via* a prenylated *p*-benzoquinone (**13**) obtained by the oxidation of an *o*-prenylphenol (**12**) with Jones reagent in acetone (Scheme 7).[56]



12 **13** **14**

Scheme 7

Oxidation of the *o*-prenylphenol (**10**) with *m*-CPBA leads to the formation of 2,2-dimethyl-3-hydroxychroman (**15**) which gives then the target 2,2-dimethyl-2*H*-chromene (**2**) on dehydration with methyltriphenoxyphosphonium iodide (MTPI) in anhydrous HMPA (Scheme 8).[58]



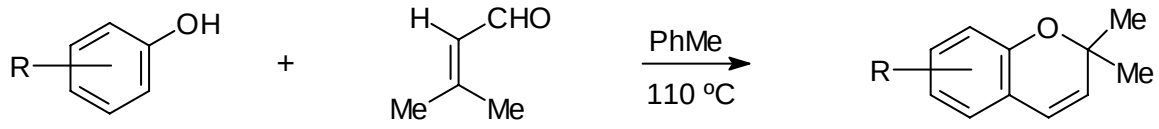
10 **15** **2**

R = H, OH, MeO

Scheme 8

8. REACTION OF PHENOLS WITH α,β-UNSATURATED ALDEHYDES

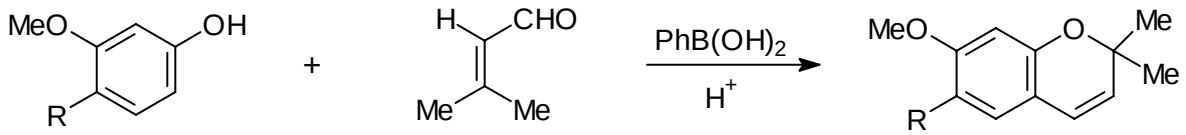
One of the special procedures utilized for the synthesis of 2,2-dimethyl-2*H*-chromenes (**2**) is based on the reaction of phenols with *α,β*-unsaturated aldehydes.[62-69] In some cases titanium salts of phenols (**7**) were allowed to react with 3-methyl-2-butenal (**16**) in hot anhydrous toluene to yield 2,2-dimethyl-2*H*-chromenes (**2**) (Scheme 9).[62,64] The reaction of aryllithium derivatives with *α,β*-unsaturated aldehydes also provided 2,2-dialkyl-2*H*-chromenes.[65,67,68] Precocene 1 and 2 have also been synthesized by the reaction of the appropriate phenol (**17**) with 3-methyl-2-butenal (**16**) in hot benzene in the presence of phenylboric acid (Scheme 10).[66,69]



7 **16** **2**

R = H, OH, MeO, Cl, Ac

Scheme 9

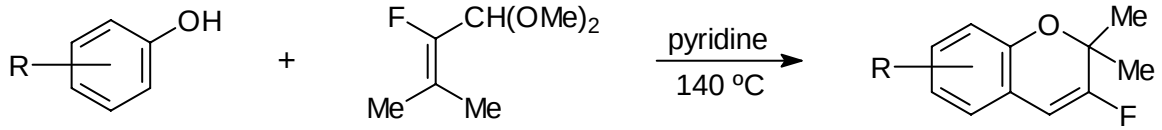


17 **16**

R = H: precocene 1; R = OMe: precocene 2

Scheme 10

Camps *et al.*[63] synthesized 2,2-dimethyl-3-fluoro-2*H*-chromenes (**19**) by the reaction of phenols (**7**) with 2-fluoro-1,1-dimethoxy-3-methylbut-2-ene (**18**) in hot anhydrous pyridine (Scheme 11). These chromene derivatives served as 3-fluoro analogues of the natural insect antijuvenile hormones precocene 1 and 2.



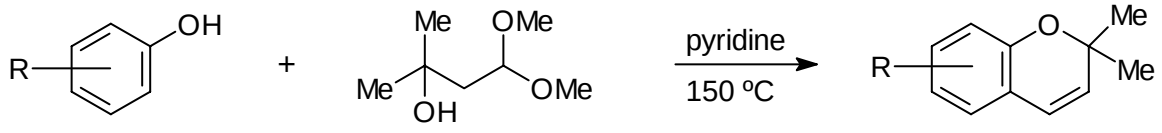
7 **18** **19**

R = H, Ac, OH, Me, MeO

Scheme 11

9. REACTION OF PHENOLS AND ALDEHYDE DIMETHYL ACETALS

Pyridine-catalyzed condensation of phenols (**7**) with 3-hydroxy-3-methylbutyraldehyde dimethyl acetal (**20**) has also been utilized for the preparation of 2,2-dimethyl-2*H*-chromenes (**2**) (Scheme 12).[70-72] This protocol has, however, been restricted to several examples and cannot be considered as a convenient and general procedure for the synthesis of such chromenes.



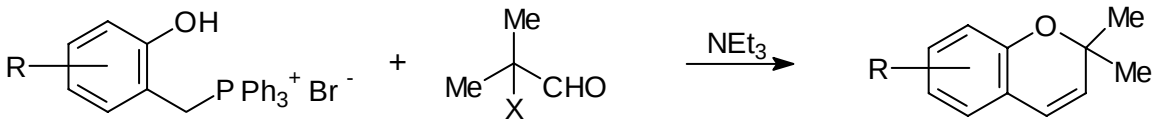
7 **20** **2**

R = H, Me, MeO

Scheme 12

10. SYNTHESIS OF 2,2-DIMETHYL-2*H*-CHROMENES BY YLIDE REACTIONS

For the preparation of 2,2-dimethyl-2*H*-chromenes (**2**) another special procedure is the reaction of *o*-hydroxybenzyltriphenylphosphonium salts (**21**) with α-halogenated carbonyl compounds (**22**) to afford 2,2-dimethyl-2*H*-chromenes (**2**) as described by Begasse and Le Corre (Scheme 13).[73]



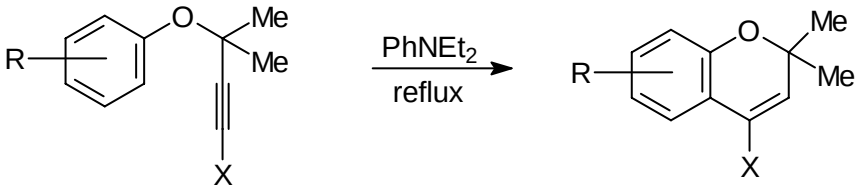
21 **22** **2**

X = halogen; R = H, Ac

Scheme 13

11. SYNTHESIS OF 4-HALO- AND 3,4-DIHALO-2,2-DIMETHYL-2*H*-CHROMENES

Arimalia and Balasubramanian[74-76] synthesized 2,2-dimethyl-4-halo-2*H*-chromenes (**25**) (X: Br or Cl) by a thermal ring closure of γ-halopropargyl aryl ethers (**23**) in hot *N*,*N*-diethylaniline (Scheme 14).

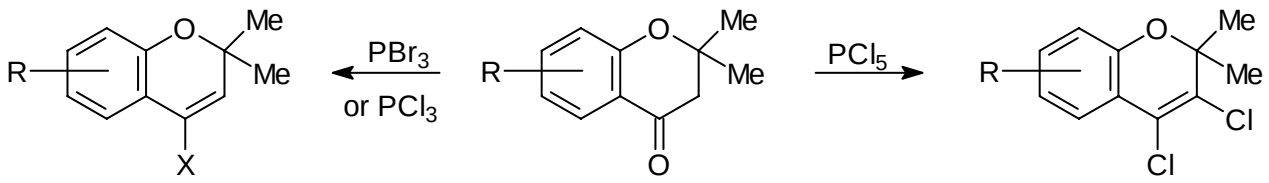


23 **24**

X = Cl or Br; R = H, Me, MeO, Cl

Scheme 14

However, this procedure has hitherto remained an exception for the synthesis of 2,2-dimethyl-4-halo-2*H*-chromenes (**24**). 4-Halo and 3,4-dihalo derivatives of the 2,2-dimethyl-2*H*-chromenes are generally prepared by the reaction of the appropriate 2,2-dimethyl-4-chromanone (**3**) with a halogenating agent. 4-Chloro-2,2-dimethyl-2*H*-chromenes (**24**) have been prepared by the reaction of 2,2-dimethyl-4-chromanones (**3**) with thionyl chloride in dry dichloromethane in the presence of anhydrous pyridine[77] or with phosphorus oxychloride in anhydrous dimethylformamide[78] (Scheme 15). Phosphorus trihalides (PBr_3 or PCl_3) or phosphorus pentachloride have been generally used for the conversion of the 2,2-dimethyl-4-chromanones (**3**) into 2,2-dimethyl-4-halo-2*H*-chromenes (**24**).[79-83] 3,4-Dichloro-2,2-dimethyl-2*H*-chromenes (**25**) have also been prepared by the reaction of 2,2-dimethyl-4-chromanones (**3**) with phosphorus pentachloride in carbon tetrachloride (Scheme 15).[83]



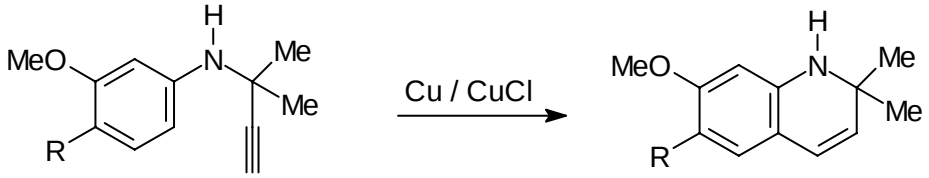
24 **3** **25**

X = Cl or Br; R = H, alkoxy, Me

Scheme 15

12. NITROGEN AND SULFUR ANALOGUES OF 2,2-DIMETHYL-2*H*-CHROMENES

The nitrogen analogues of the natural precocene 1 and 2 have been synthesized by the thermal cyclization of the *N*-alkylaniline derivative (**26**) into the appropriate 2,2-dimethyl-1,2-dihydroquinoline (**27**) (Scheme 16).[84]

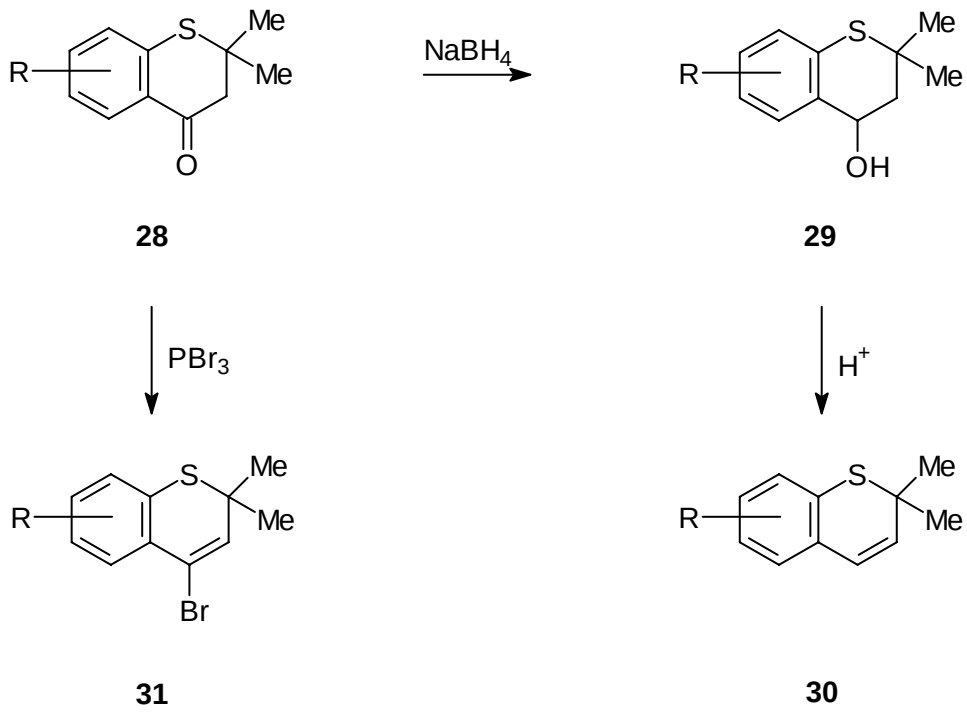


26 **27**

R = H, MeO

Scheme 16

2,2-Dimethyl-2*H*-1-thiochromenes (**30**) have been prepared by the reduction of 2,2-dimethyl-1-thio-4-chromanones (**28**) into 2,2-dimethyl-4-hydroxy-1-thiochromans (**29**) which gave then 1-thiochromenes (**30**) on dehydration (Scheme 17).[85] 4-Bromo-2,2-dimethyl-2*H*-1-thiochromenes (**31**) have also been synthesized from compounds (**28**) by PBr_3 as described for the related chromenes (Scheme 17).[81,82]



Scheme 17

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*Dedicated to Prof. Dr. Sándor Makleit on the occasion of his 70th birthday.

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