

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

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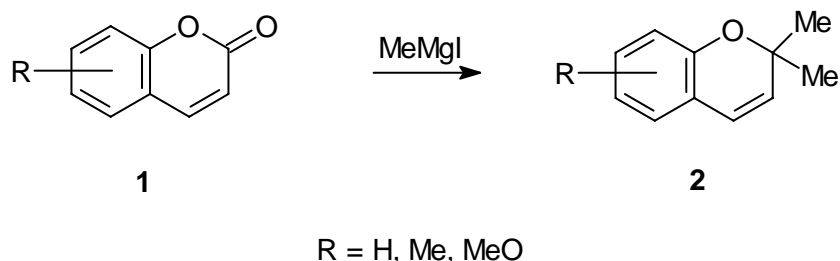
**Abstract** – In the present review article, the most important procedures developed and utilized for the synthesis of 2,2-dimethyl-2H-chromenes are compiled and discussed. Special emphasis is laid on the most convenient and most important methods, *viz.* the dehydration of 2,2-dimethyl-4-hydroxychromans 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-2H-chromenes have also been included.

## 1. INTRODUCTION

First representatives of the 2,2-dimethyl-2H-chromenes have already been described in the literature about six decades ago.<sup>1,2</sup> Various 2,2-dialkyl-2H-chromenes were obtained by the reaction of coumarins with Grignard reagents.<sup>1,2</sup> However, less attention was directed to such chromenes until the middle of the seventies. It was in 1976 that Bowers *et al.*<sup>3</sup> isolated the precocene 1 (2,2-dimethyl-7-methoxy-2H-chromene) and precocene 2 (6,7-dimethoxy-2,2-dimethyl-2H-chromene) from *Ageratum houstonianum*<sup>3</sup> and other sources.<sup>4</sup> These two compounds proved to induce precocious metamorphosis in *Oncopeltus fasciatus*, *Lygaens kalmii* and *Dysdercus cingulatus*<sup>3,5</sup> owing to their antijuvenile hormone activity. For this reason, these precocenes were considered 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-2H-chromenes through qualitative and quantitative studies of their structure-activity relationships. As a result, various procedures have been developed and numerous 2,2-dimethyl-2H-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

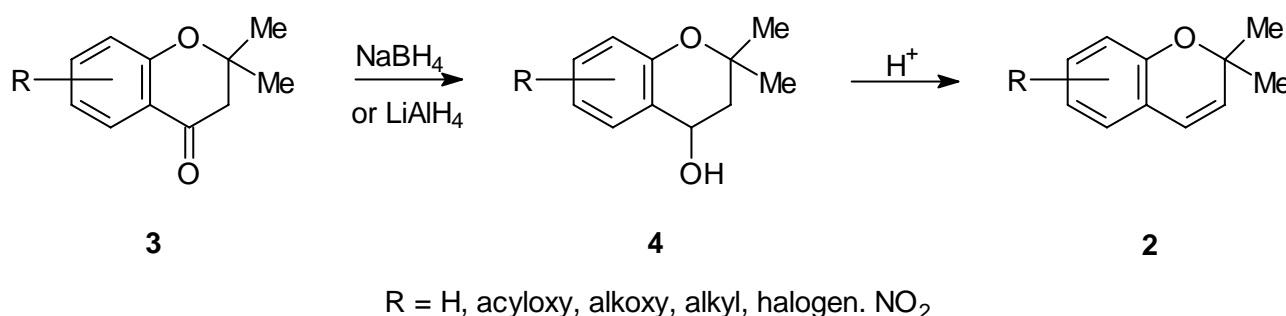
2,2-Dimethyl-2H-chromenes (**2**) were prepared by Shriner and Sharp by the reaction of coumarin (**1**) with Grignard reagent in 1939<sup>1</sup> (Scheme 1). One year later, Smith and Ruoff obtained 2,2-dialkyl-2H-chromenes by the same chemical transformation.<sup>2</sup> Later, precocene 1,<sup>6</sup> precocene 2<sup>7</sup> and 2,2,6-trimethyl-2H-chromene<sup>8</sup> have been prepared by the reaction of the appropriate coumarins with methylmagnesium iodide. However, the transformation of coumarins into 2,2-dialkyl-2H-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.



Scheme 1

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

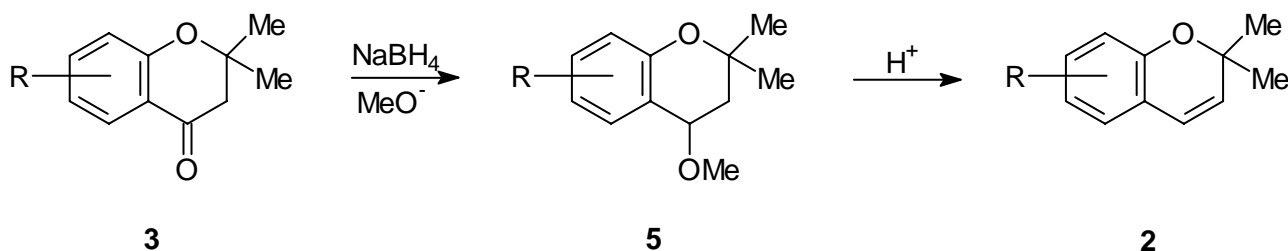
For the preparation of 2,2-dimethyl-2*H*-chromenes undoubtedly the most convenient and most popular method is the dehydration of the appropriate 2,2-dimethyl-4-hydroxychromans beneficially applied by numerous research groups.<sup>9-26</sup> 2,2-Dimethyl-4-hydroxychromans (**4**) are obtained by the reduction 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.



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.*<sup>19</sup> 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.<sup>27</sup> 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).<sup>28</sup> This is the first example for the preparation of such chromenes in this way.

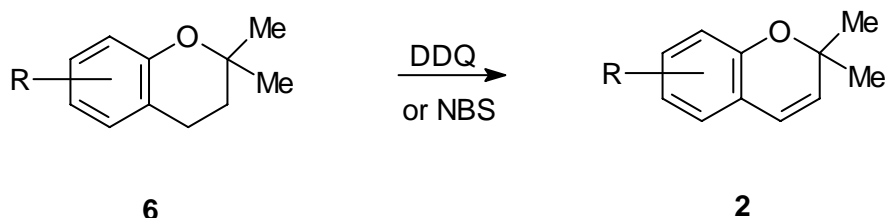


R = acyloxy, alkoxy, alkyl

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.<sup>29</sup> 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).<sup>30</sup> Compounds (6) can then be utilized as convenient intermediates for the preparation of 2,2-dimethyl-2*H*-chromenes (2). Ahluwalia *et al.*<sup>29</sup> 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.*<sup>31</sup> for the preparation of 6,7-dimethoxy-2,2-dimethyl-2*H*-chromene (precocene 2).

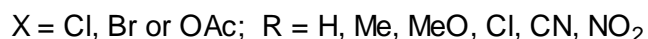
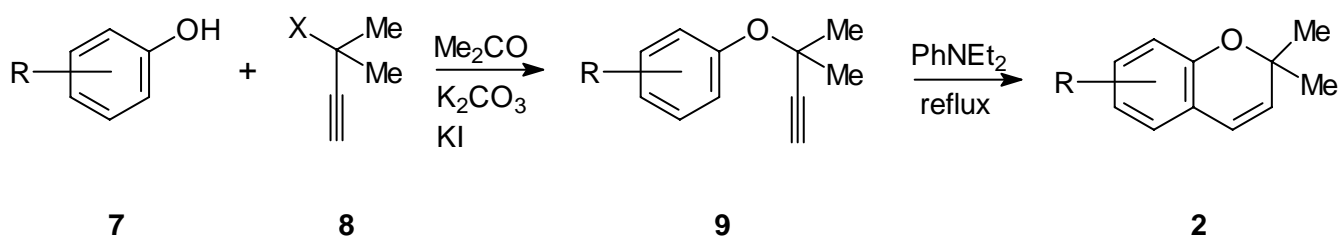


R = H, Me, MeO

Scheme 4

## 6. THERMAL REARRANGEMENT OF PHENYL PROPARGYL ETHERS

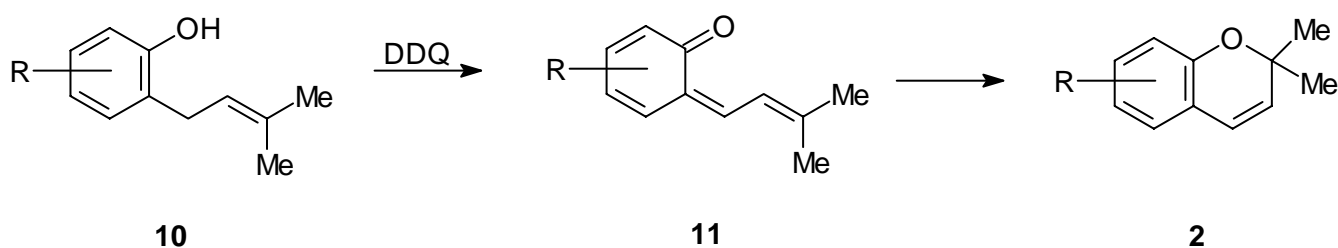
It has been mentioned in Chapter 3 of this review that the dehydration of the 2,2-dimethyl-4-hydroxychromans (4) is the most popular procedure for the preparation of 2,2-dimethyl-2*H*-chromenes (2). It can be added to this statement that for the synthesis of 2,2-dimethyl-2*H*-chromenes (2) the thermal rearrangement of the phenyl propargyl ethers (9) is another general and convenient method utilized in numerous laboratories.<sup>32-51</sup> Phenyl propargyl ethers (9) can be synthesized easily by the alkylation of phenols (7) with 3-substituted 3-methylbut-1-yne (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).



Scheme 5

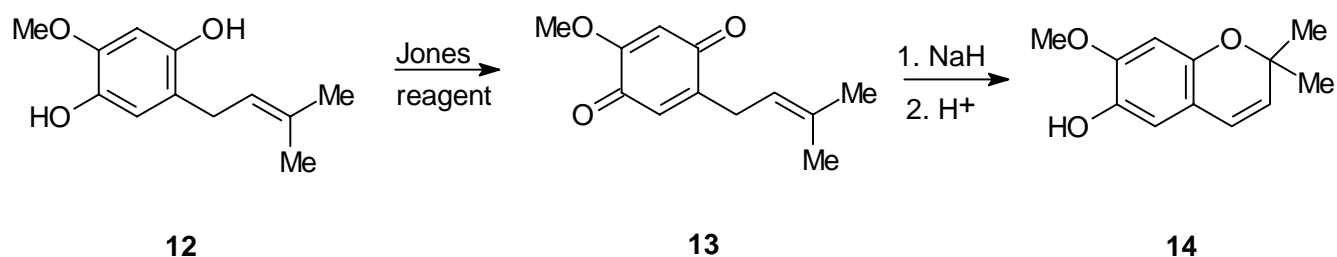
## 7. OXIDATIVE CYCLIZATION OF *o*-(3,3-DIMETHYLALLYL)PHENOLS

Synthesis of 2,2-dimethyl-2H-chromenes (**2**) by the oxidative cyclization of *o*-(3,3-dimethylallyl)phenols (**10**) has been studied in several laboratories.<sup>52-61</sup> An early example of this chemical transformation was described by Cardillo *et al.*<sup>52</sup> 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-2H-chromene (**2**) (Scheme 6). As an oxidizing agent, DDQ was used successfully for this oxidative cyclization by other research groups.<sup>53,54,57</sup> Oxidative transformation of *o*-prenylphenols has been performed under Pd-catalyzed reaction conditions as well.<sup>60,61</sup>



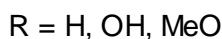
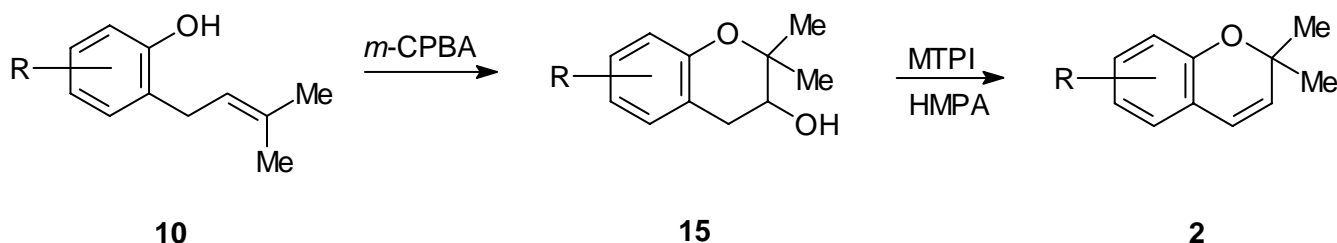
Scheme 6

2,2-Dimethyl-6-hydroxy-7-methoxy-2H-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).<sup>56</sup>



Scheme 7

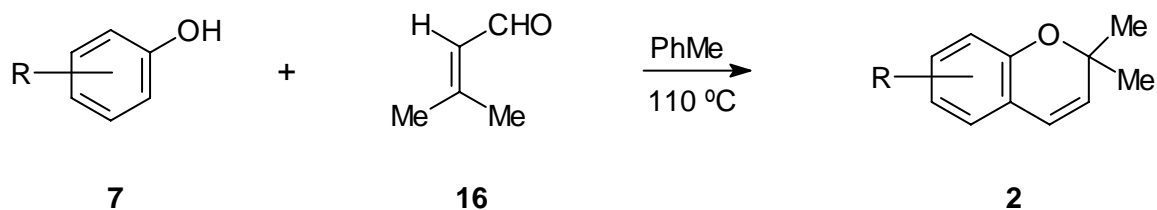
Oxidation of the *o*-prenylphenol (**10**) with *m*-CPBA leads to the formation of 2,2-dimethyl-3-hydroxychroman (**15**) which gives then the target 2,2-dimethyl-2*H*-chromene (**2**) on dehydration with methyltriphenoxyphosphonium iodide (MTPI) in anhydrous HMPA (Scheme 8).<sup>58</sup>



Scheme 8

## 8. REACTION OF PHENOLS WITH $\alpha,\beta$ -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  $\alpha,\beta$ -unsaturated aldehydes.<sup>62-69</sup> 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).<sup>62,64</sup> The reaction of aryllithium derivatives with  $\alpha,\beta$ -unsaturated aldehydes also provided 2,2-dialkyl-2*H*-chromenes.<sup>65,67,68</sup> 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).<sup>66,69</sup>

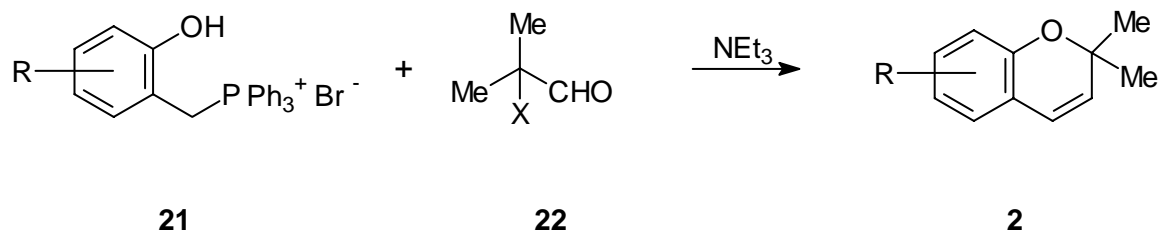


Scheme 9



## 10. SYNTHESIS OF 2,2-DIMETHYL-2H-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  $\alpha$ -halogenated carbonyl compounds (**22**) to afford 2,2-dimethyl-2*H*-chromenes (**2**) as described by Begasse and Le Corre (Scheme 13).<sup>73</sup>

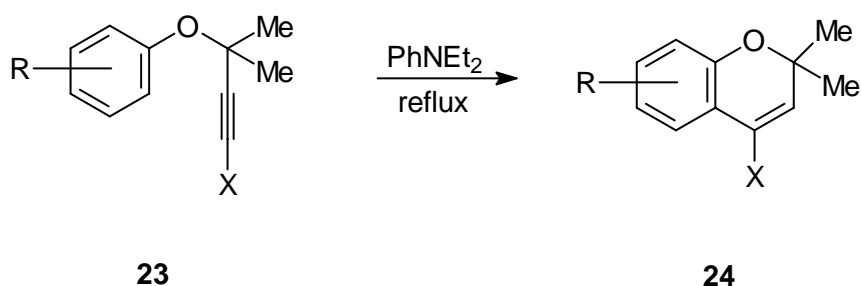


X = halogen; R = H, Ac

Scheme 13

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

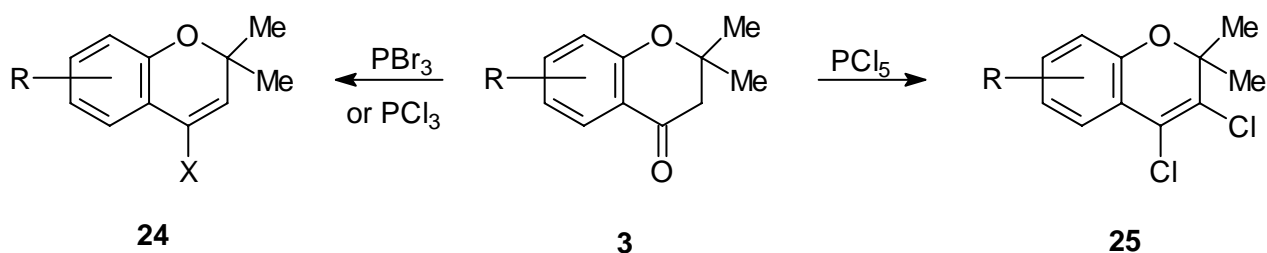
Arimalia and Balasubramanian<sup>74-76</sup> synthesized 2,2-dimethyl-4-halo-2*H*-chromenes (**25**) (X: Br or Cl) by a thermal ring closure of  $\gamma$ -halopropargyl aryl ethers (**23**) in hot *N,N*-diethylaniline (Scheme 14).



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<sup>77</sup> or with phosphorus oxychloride in anhydrous dimethylformamide<sup>78</sup> (Scheme 15). Phosphorus trihalides (PBr<sub>3</sub> or PCl<sub>3</sub>) 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**).<sup>79-83</sup> 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).<sup>83</sup>

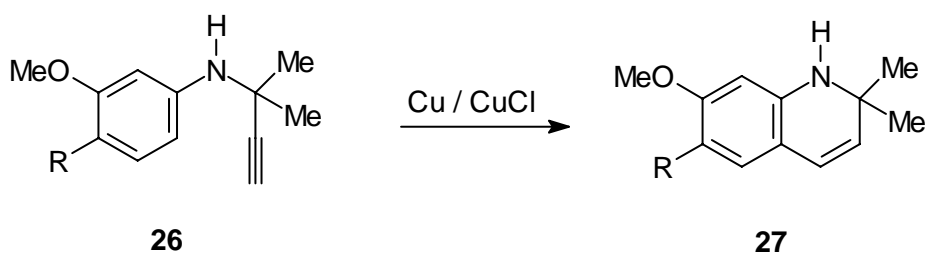


X = Cl or Br; R = H, alkoxy, Me

Scheme 15

## 12. NITROGEN AND SULFUR ANALOGUES OF 2,2-DIMETHYL-2H-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).<sup>84</sup>

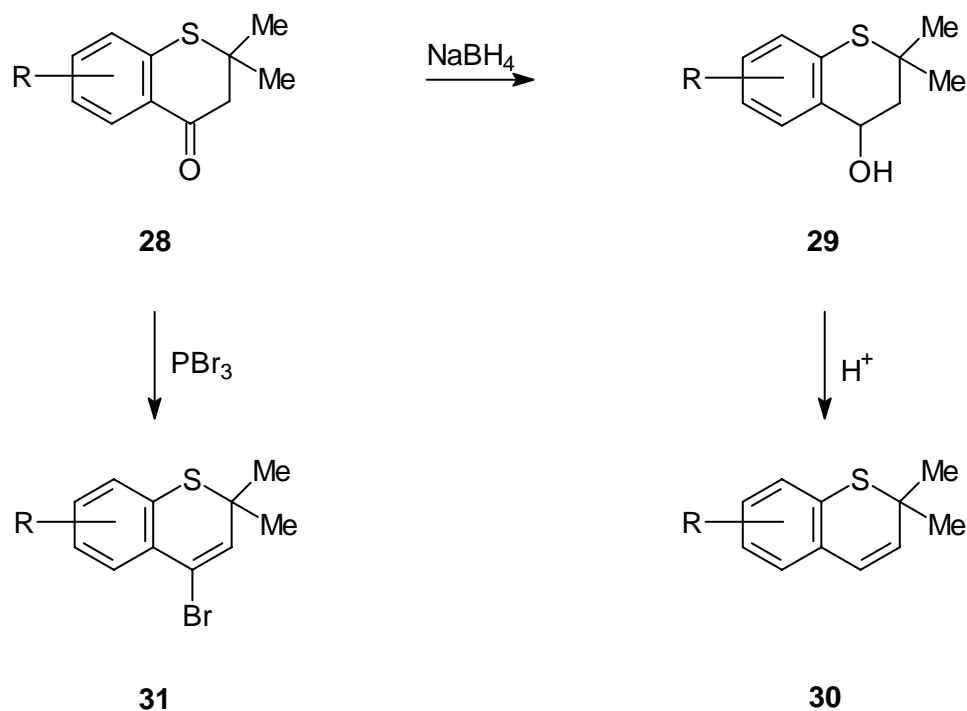


R = H, MeO

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).<sup>85</sup> 4-Bromo-2,2-dimethyl-2*H*-1-thiochromenes (**31**) have also been synthesized from compounds (**28**) by PBr<sub>3</sub> as described for the related chromenes (Scheme 17).<sup>81,82</sup>





R = H, MeO, EtO

Scheme 17

## ACKNOWLEDGEMENT

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\*Dedicated to Prof. Dr. Sándor Makleit on the occasion of his 70<sup>th</sup> birthday.

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