Tibor Tímár*[a], Albert Lévai*[b], Tibor Eszenyi [a] and Péter Sebők [a]

[a] ICN Hungary Co. Ltd., H-4440 Tiszavasvári, Hungary
[b] Department of Organic Chemistry, University of Debrecen, H-4010 Debrecen, Hungary
Received May 18, 1999
Revised August 9, 1999

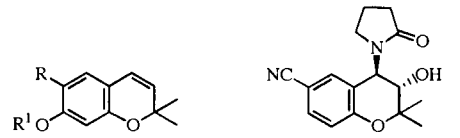
Dedicated to Professor Dr. György Bazsa on the occasion of his 60th birthday.

J. Heterocyclic Chem., **37**, 1389 (2000).

1. Introduction.

The first synthesis of 2,2-dimethyl-4-chromanones was published about eight decades ago [1]. An appropriately substituted phenol was allowed to react with 3,3-dimethylacryloyl chloride in the presence of aluminum chloride to afford the target compound. The Friedel-Crafts reaction of phenols and unsaturated acid chlorides was investigated by several research groups [2-7] to provide a large variety of 4-chromanones with the 2,2-dialkyl derivatives among them. Utilization of the Fries rearrangement contributed considerably to the preparation of variously substituted 2,2-dimethyl-4-chromanones [8-10] as well. However, the yields seem to be inadequate in many cases which is a major drawback common to both procedures. For this reason, modification of the reaction conditions to find optimum parameters, rendering high or at least acceptable yields, is a continuous challenge as far as the synthesis of 2,2-dimethyl-4-chromanones is concerned.

Since the 2,2-dimethyl-4-chromanones can be easily converted into 2,2-dimethyl-2*H*-chromenes, considerable impetus was given to the development of their synthesis by the isolation of the 2,2-dimethyl-7-methoxy-2*H*-chromene (precocene 1) and the 6,7-dimethoxy-2,2-dimethyl-2*H*-chromene (precocene 2) from the *Ageratum houstonianum* in 1976 [11]. These substances were considered as fourth generation insecticides and this assumption generated intense research activity in the field of 2,2-dimethylbenzopyrans. The aims of most studies were the syntheses of more effective 2,2-dimethyl-2*H*-chromenes (*e.g.* the 2,2-dimethyl-7-ethoxy-6-methoxy-2*H*-chromene has been found to be the most powerful synthetic derivative and is called precocene 3) and to gather information on their structure-activity relationships.



R	R^1	Precocenes	
H	Me	P 1	(±) Cromakalim
MeO	Me	P 2	(-) Levcromakalim
MeO	Et	P 3	

Chart 1

The research into modulation of potassium (K^+) channels by drugs is one of the most rapidly growing areas of pharmacology and as a result of these intensive studies a new class of the K^+ channel activators, a prototype of which was *Cromakalim,* was reported in 1986 [12]. As the archetype of the benzopyran family of K^+ channel activators, *Cromakalim* has stimulated a widespread synthetic effort for better and more selective agents. The (-) *Levcromakalim* is approximately 100-200 times more

potent than the (+)-enantiomer of *Cromakalim* [13]. These compounds are currently in Phase III clinical trials as potential long term antihypertensive agents [14]. The 2,2-dimethyl-4-chromanones are also key intermediates in the field of chemistry of benzopyran-type K^+ activators. Consequently this area again required the optimization of the known procedures and elaboration of new ones, to obtain access to some specially substituted rare derivatives. All of these requirements were beneficial for the development of synthetic procedures to obtain appropriately substituted 2,2-dimethyl-4-chromanones as convenient intermediates for the preparation of 2,2-dimethyl-2*H*-chromenes.

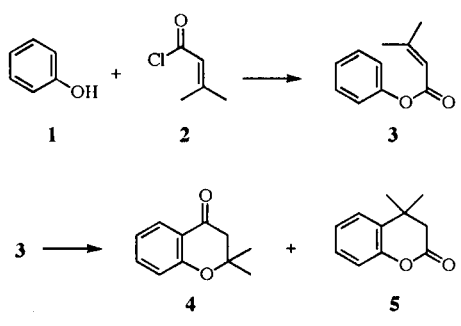
A survey of the synthesis of 4-chromanones was published more than twenty years ago [15]. Since during the last two decades so much development has been performed, it appeared appropriate to provide a newer account on the synthesis of 2,2-dimethyl-4-chromanones. Our present review article is organized according to the substitution pattern of the chromanone skeleton. Their 3-subtituted derivatives and complex natural products with this structural unit are not included.

2. Unsubstituted 2,2-Dimethyl-4-chromanone

The synthesis of 2,2-dimethyl-4-chromanone (**4**) has long been the subject of controversy. Skraup and Beng [16,17] claimed to have prepared the chromanone by thermal rearrangement of phenyl 3,3-dimethylacrylate (**3**) alone or in the presence of zinc chloride. However, Auwers and Mauss [18] were unable to repeat the Fries rearrangement even in the presence of aluminum chloride. Some three decades later Baker *et al.* [19] found that the ester **3**, conveniently prepared by heating phenol **1** with 3,3-dimethylacryloyl chloride (**2**) in 79% yield, when heated with aluminum chloride gave a 45% yield of 2,2-dimethyl-4-chromanone (**4**). The same ester **3**, when treated with aluminum chloride in carbon disulfide is reported [20] to give 3,4-dihydro-4,4-dimethylcoumarin (**5**) in 67% yield and a trace of 2,2-dimethyl-4-chromanone (**4**) (Scheme 1).

All of these previously mentioned procedures have the following disadvantages: harsh reaction conditions, relatively low to moderate yields, poor selectivity because of the possible *ortho* and *para* Fries rearrangement of the ester as well as the alternative ring closure leading to the formation of coumarin derivative (**5**).

Scheme 1



1 2 3 4 5

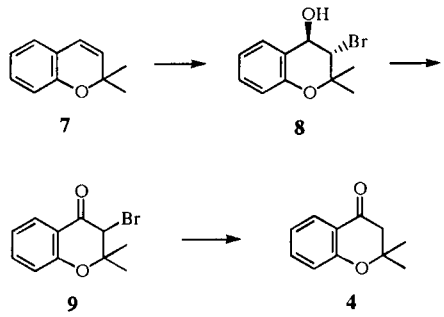
The reaction of excess methylmagnesium iodide with 4-ethoxycoumarin (**6**) resulted in a 57% yield of crude material [21]. After a lengthy and complicated purification the 2,2-dimethyl-4-chromanone (**4**) was obtained in very low yield (Scheme 2).

Scheme 2

6 4

Livingstone [22] reported an alternative approach. The reaction of 2,2-dimethyl-2*H*-chromene (**7**) with hypobromous acid furnished the corresponding 3-bromo-4-hydroxy-2,2-dimethylchroman (**8**) in 71% yield. The latter, on oxidation with chromium trioxide in acetic acid gave 3-bromo-2,2-dimethyl-4-chromanone (**9**, 72%). Treatment with zinc dust in acetic acid converted the bromoketone into 2,2-dimethyl-4-chromanone (**4**). No yield was reported for this final step (Scheme 3).

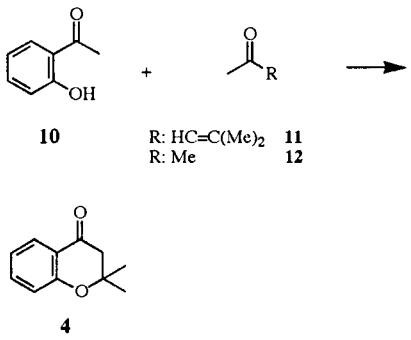
Scheme 3



Kabbe and Widdig [23] gave an account in 1982 of their elegant work for the one step synthesis of a large number of substituted 4-chromanone derivatives including 2,2-dimethyl-4-chromanones. The reaction of 2-hydroxyacetophenone (**10**) with mesityl oxide (**11**) or acetone (**12**) in pyrrolidine leads to the formation of 2,2-dimethyl-4-chromanone (**4**) in 75% and 65% yields, respectively (Scheme 4).

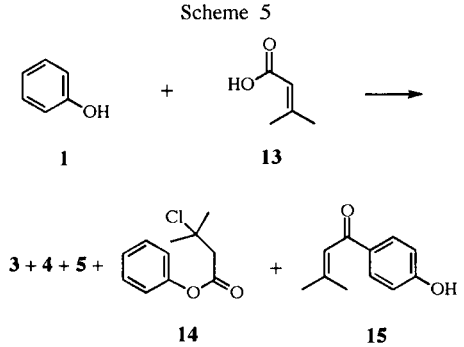
Sebők *et al.* [24, 25] have performed the first systematic and comparative study of the reaction of a series of substituted phenols and 3-methylbut-2-enoic acid in zinc chloride/phosphorus oxychloride and aluminum chloride/phosphorus oxychloride. It was established that the formation of phenolic esters and 2,2-dimethyl-4-chromanones is strongly influenced by the substituents, their position on the aromatic ring of the starting phenols. Based on this study [25], a

Scheme 4



mixed Friedel-Crafts and Fries rearrangement mechanism is considered in these reactions. The reaction of phenol **1** and 3-methylbut-2-enoic acid **13** in zinc chloride/phosphorus oxychloride afforded a multicomponent reaction mixture. The main product (76%) was the ester **14** arising from addition of hydrochloric acid to the alkene portion of the α,β-unsaturated ester (**3**). Using shorter reaction time (2 hours) the **3** → **14** sequence can be proved, since in this particular case the main product was the α,β-unsaturated ester **3**. A mechanism for the formation of 1-(4-hydroxyphenyl)-3-methyl-2-buten-1-one (**15**, 9%) could not be easily decided. This latter compound could be formed by *para*-acylation of the starting phenol (**1**) or *para*-Fries rearrangement reaction of the corresponding ester **3**. The formation (3%) of 3,4-dihydro-4,4-dimethylcoumarin (**5**) could be rationalized by the intramolecular Friedel-Crafts alkylation reaction of **14** or acid catalyzed cyclization of **3**. The 2,2-dimethyl-4-chromanone (**4**) was formed only in 4% yield. The reaction of phenol (**1**) and 3-methylbut-2-enoic acid (**13**) in aluminum chloride/phosphorus oxychloride afforded the corresponding ester (**3**) in 99% yield (Scheme 5).

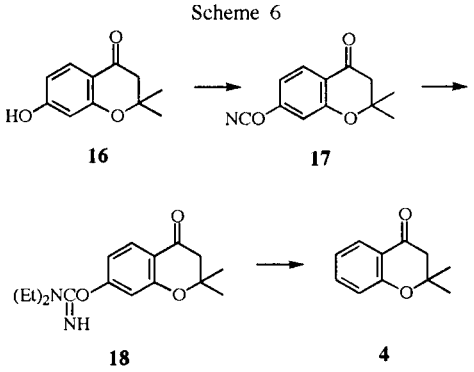
Scheme 5



On the bases of these findings it can be concluded that, although the direct synthesis of the 2,2-dimethyl-4-chromanone (**4**) has been thoroughly studied by several research groups, they failed to develop a convenient procedure for this purpose. For this reason, the dehydroxylation of the 2,2-dimethyl-7-hydroxy-4-chromanone (**16**) seemed to be an opportunity to overcome this difficulty.

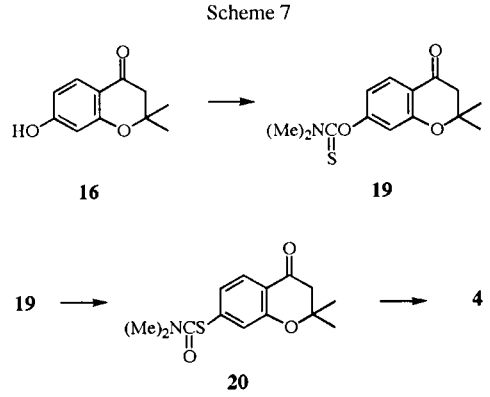
In 1994 Sebők *et al.* [26] reported on the facile deoxygenation of 2,2-dimethyl-7-hydroxy-4-chromanone (**16**). The reaction of **16** with cyanogen bromide in the presence of triethylamine furnished the corresponding cyanate **17** in excellent yield. The latter compound was then treated with diethylamine whereupon the *O*-aryl *N,N*-diethylisourea **18** was formed an almost quantitative yield. Catalytic hydrogenation of this derivative over palladium on activated carbon resulted in 2,2-dimethyl-4-chromanone (**4**) in 65% overall yield (Scheme 6).

Scheme 6



Alternatively, 2,2-dimethyl-7-hydroxy-4-chromanone (**16**) was allowed to react with dimethylthiocarbamoyl chloride in the presence of DABCO in DMF to yield 2,2-dimethyl-7-(*N,N*-dimethylthiocarbamoyloxy)-4-chromanone (**19**) which was then thermally rearranged into 2,2-dimethyl-7-(*N,N*-dimethylcarbamoylthio)-4-chromanone (**20**) in *N,N*-diethylaniline. Compound **20** was readily desulfurized by Raney nickel in ethanol to furnish the corresponding 2,2-dimethyl-4-chromanone (**4**) in good (80%) overall yield [26] (Scheme 7).

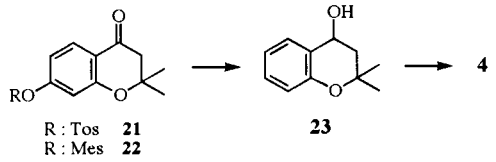
Scheme 7



Similarly, sulfonates **21** and **22** of 2,2-dimethyl-7-hydroxy-4-chromanone (**16**) were treated with Raney nickel in ethanol under hydrogen atmosphere to furnish the deoxygenated product **4** in 76-82% yield but up to 15% of

2,2-dimethyl-7-hydroxy-4-chromanone (**16**) was also formed. The reduction of sulfonates **21** and **22** with $NaBH_4$-$NiCl_2$ in methanol gave 2,2-dimethyl-4-hydroxychroman (**23**) in practically useful yield (94%). This latter compound can be oxidized back to 2,2-dimethyl-4-chromanone (**4**) using CrO_3 in AcOH [27] in good yield (91%) [26] (Scheme 8).

Scheme 8

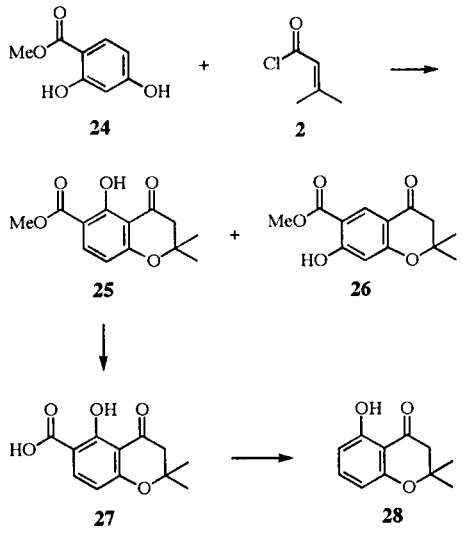


Our own results [26] unequivocally prove that for the preparation of the unsubstituted 2,2-dimethyl-4-chromanone (**4**) the most convenient procedures are based on the dehydroxylation of its 7-hydroxy derivative (**16**).

3. 5-Substituted 2,2-Dimethyl-4-chromanones

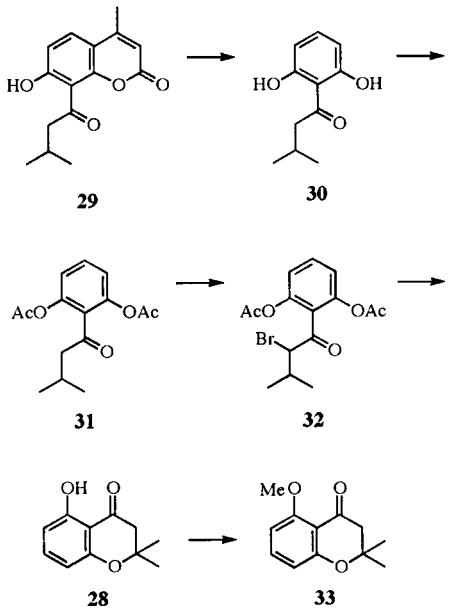
According to our careful and extensive literature search there is no direct, high yielding synthetic method for the preparation of 5-substituted 2,2-dimethyl-4-chromanones. In 1959 Nickl [28] prepared 2,2-dimethyl-5-hydroxy-4-chromanone (**28**) by the Friedel-Crafts reaction of β-resorcilate (**24**) and 3,3-dimethylacryloyl chloride (**2**). Two 2,2-dimethyl-4-chromanone derivatives (**25** and **26**) were formed in 15% and 33% yields, respectively. Compound **25** was hydrolyzed to the corresponding acid derivative (**27**) and the subsequent decarboxylation gave the target compound **28** in 10% overall yield (Scheme 9).

Scheme 9



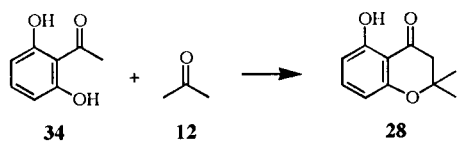
Fukami and Nakajima [29] reported an alternative but clumsy method. 7-Hydroxy-8-isovaleryl-4-methylcoumarin (**29**) was converted by 20% sodium hydroxide to 2,6-dihydroxy-isovalerophenone (**30**) which was acetylated without further purification to give the acetate (**31**) in excellent yield. The bromination of this acetate with *N*-bromosuccinimide yielded bromocompound **32**, which was easily cyclized by dilute alkali to 2,2-dimethyl-5-hydroxy-4-chromanone (**28**). The overall yield was 15%. Methylation of compound **28** afforded the corresponding 2,2-dimethyl-5-methoxy-4-chromanone (**33**) (Scheme 10).

Scheme 10



Starratt and Stoessl [30] prepared 2,2-dimethyl-5-hydroxy-4-chromanone (**28**) by the reaction of 2,6-dihydroxyacetophenone (**34**) and acetone (**12**) in anhydrous ether using sodium dispersion. After lengthy work up and column chromatography the product was isolated in rather low yield (17%) (Scheme 11).

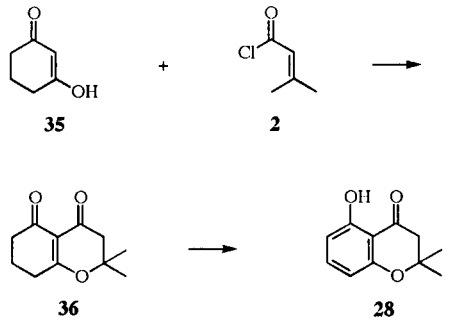
Scheme 11



Arnoldi [31] elaborated an elegant and regioselective method for the synthesis of 5-hydroxy-4-chromanones starting from 1,3-cyclohexanediones. Whereas the alkylation of these highly enolized and acidic compounds in basic medium may afford *C*- or *O*-alkyl derivatives, their *acylation* proceeds only at the enolic hydroxyl group. The enol ester obtained from dienone **35** and 3,3-dimethylacryloyl chloride (**2**) in acidic medium undergoes Fries rearrangement with

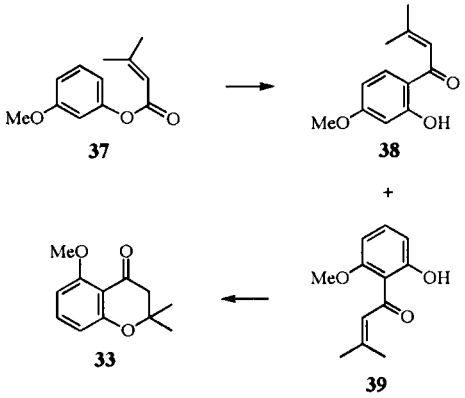
ring closure in the presence of certain Lewis acids (titanium(IV) chloride was found to be the best) to give 4,5-dioxo-5,6,7,8-tetrahydrochroman (**36**) which can be dehydrogenated (10% palladium on carbon or DDQ) to 2,2-dimethyl-5-hydroxy-4-chromanone (**28**). The overall yield of this two-step methodology is up to 30% for the target compound (Scheme 12).

Scheme 12



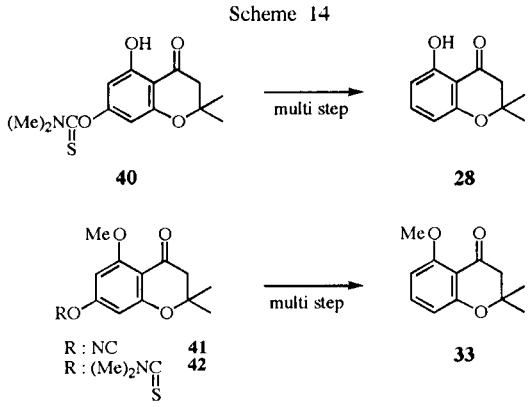
Camps *et al.* [32] reported on Fries rearrangement of methoxyphenyl 3-methylbut-2-enoates and found that *O*-acylation was the major reaction course in the photochemical rearrangement. 2,2-Dimethyl-5-methoxy-4-chromanone (**33**) was obtained in 7% yield by means of their procedure. Later, Miranda *et. al.* [33] studied the photo-Fries rearrangement of a series of aryl esters of α,β-unsaturated carboxylic acids in order to explore the possibilities of this reaction as a key step in the synthesis of precocenes and related compounds. Thus, the irradiation of 3-methoxyphenyl 3,3-dimethylacrylate (**37**) through quartz in hexane with a medium pressure mercury lamp did not produce any observable transformation, even after 20 hours. On the contrary, when potassium carbonate was added, a mixture of the two possible rearrangement products (**38** and **39**) (ratio 3.5:1) was obtained. After chromatographic separation (HPLC) the *o*-hydroxyketone (**39**, 8%) was cyclized to 2,2-dimethyl-5-methoxy-4-chromanone (**33**) by means of a two phase system (hexane/10% aqueous sodium hydroxide) with nearly quantitative yield (Scheme 13).

Scheme 13



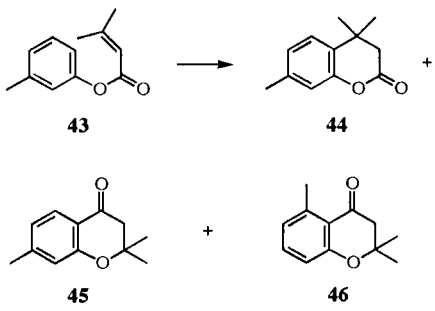
According to Sebők *et al.* [26] the dimethylthiocarbamate derivative **40** as well as the cyanate and dimethylthiocarbamate derivatives **41** and **42** were again readily transformed and deoxygenated to the corresponding 2,2-dimethyl-5-hydroxy-4-chromanone (**28**) and 2,2-dimethyl-5-methoxy-4-chromanone (**33**) in good overall yield (70-81%) (Scheme 14).

Scheme 14



The rearrangement of 3-methylphenyl 3-methylbut-2-enoate (**43**) when treated with aluminum chloride in carbon disulfide was reported [20] to give (after complicated work up and purification procedure) 3,4-dihydro-4,4,7-trimethylcoumarin (**44**, 10%), 2,2,7-trimethyl-4-chromanone (**45**, 18%), and 2,2,5-trimethyl-4-chromanone (**46**). Unfortunately, no yield was reported for compound **46** (Scheme 15).

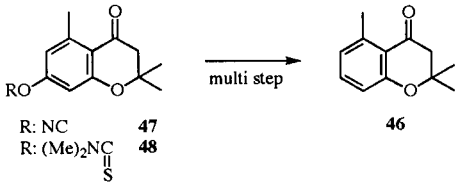
Scheme 15



The most powerful method for the synthesis of 2,2,5-trimethyl-4-chromanone (**46**) was reported by Sebők *et al.* [26]. The cyanate and dimethylthiocarbamate derivatives **47** and **48** were smoothly converted and deoxygenated to the target chromanone **46** in very good (80-82%) overall yield (Scheme 16).

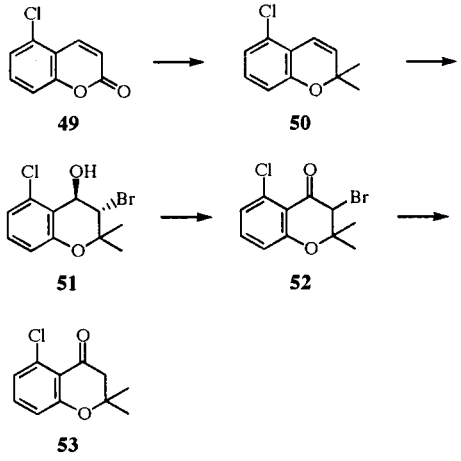
In 1981 Hepworth *et al.* [27] described the synthesis of a series of chloro-2,2-dimethyl-4-chromanones. Thus, the

Scheme 16



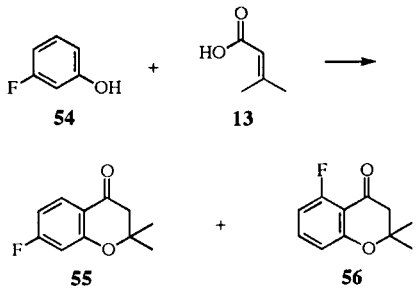
reaction of 5-chlorocoumarin (**49**) with methyl magnesium iodide and cyclization of the resulting diol in boiling acetic acid yielded 5-chloro-2,2-dimethyl-2*H*-chromene (**50**). Addition of bromine in chloroform and the subsequent hydrolysis in boiling acetone afforded the corresponding 3-bromo-5-chloro-4-hydroxychroman (**51**). The latter, on oxidation with chromium trioxide in acetic acid, led to the formation of 3-bromo-5-chloro-4-chromanone (**52**) which was then debrominated with benzoin to 5-chloro-2,2-dimethyl-4-chromanone (**53**) (Scheme 17). The overall yield of this multistep procedure is rather low.

Scheme 17



Recently, Shawcross and Sard [34] communicated on the reaction of 3-fluorophenol (**54**) and 3-methylbut-2-enoic acid (**13**) in methanesulfonic acid at 90°. The ^{1}H nmr analysis of the crude product (obtained in 47% yield) revealed *ca.* 1:10 mixture of 2,2-dimethyl-7-fluoro-4-chromanone (**55**) and 2,2-dimethyl-5-fluoro-4-chromanone (**56**). The use of repeated column and flash chromatography provided pure **56** in 21% yield (Scheme 18).

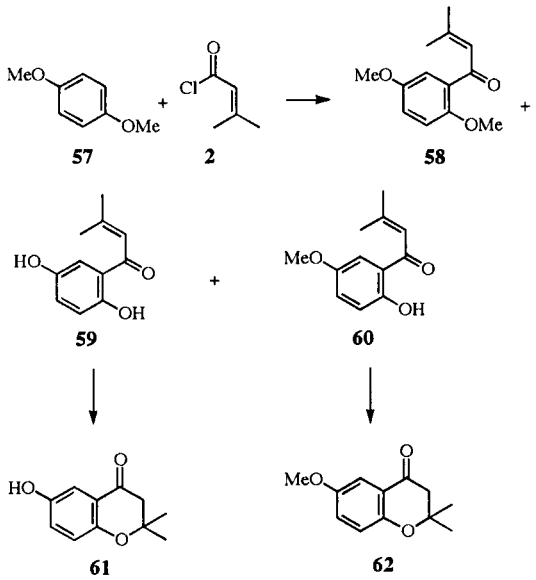
Scheme 18



4. 6-Substituted 2,2-Dimethyl-4-chromanones

There are several methods for the direct preparation of 6-substituted 2,2-dimethyl-4-chromanones. The first synthesis of 2,2-dimethyl-6-hydroxy-4-chromanone (**61**) and 2,2-dimethyl-6-methoxy-4-chromanone (**62**) was reported in 1950 [2,35]. Anhydrous aluminum chloride was added slowly to 3,3-dimethylacryloyl chloride (**2**) and hydroquinone dimethyl ether (**57**) in carbon disulfide and refluxed; the acrylophenone **58** was isolated, while further reaction in the presence of aluminum chloride afforded the partially demethylated compound **60**. Distillation of the latter, or treatment with aqueous alkali afforded 2,2-dimethyl-6-methoxy-4-chromanone (**62**). The demethylated product **59** was also isolated and converted into 2,2-dimethyl-6-hydroxy-4-chromanone (**61**) on treatment with alkali (Scheme 19). No yields were given for this synthetic sequence.

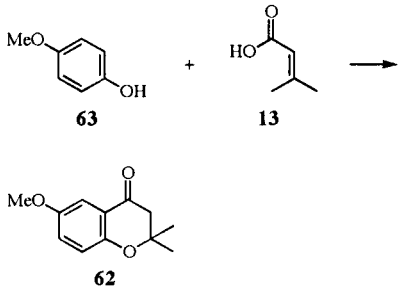
Scheme 19



Ohta and Bowers [36] elaborated a one step synthesis of 2,2-dimethyl-4-chromanones. Their synthetic approach is based on a combination of Michael type condensation and cyclodehydration with polyphosphoric acid. Thus, the reaction of 4-methoxyphenol (**63**) and 3-methylbut-2-enoic acid (**13**) at 100° resulted in the formation of 2,2-dimethyl-6-methoxy-4-chromanone (**62**) in 18% yield (Scheme 20).

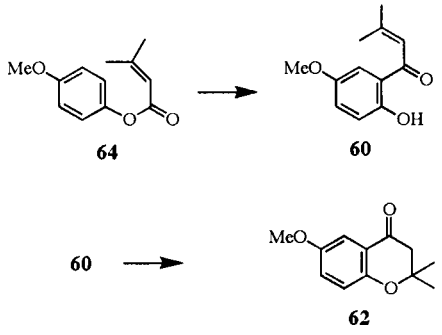
Primo and Tormos [37] studied the photo-Fries rearrangement of 4-methoxyphenyl 3,3-dimethylacrylate (**64**) (irradiation in benzene with medium pressure mercury

Scheme 20



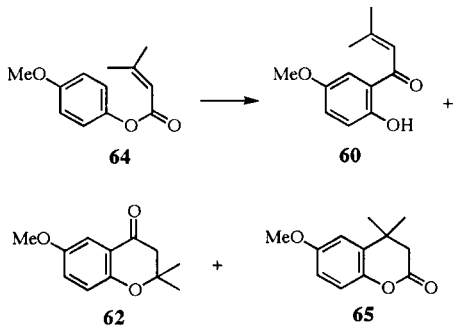
lamp in a quartz immersion well) and found that after 10 hours an equilibrium was reached in which 50% starting material **64** was present. The main rearranged product **60** was then isolated (46%) and its cyclization to 2,2-dimethyl-6-methoxy-4-chromanone (**62**) took place quantitatively by treatment with 10% aqueous sodium hydroxide in a separate step. The fact that photochemical rearrangement of 4-methoxyphenyl 3,3-dimethylacrylate (**64**) proceeded to a limited extent could be attributed to the filtering action of *o*-hydroxyketone (**60**). This would be in accord with the intense UV-absorption of this product. In order to circumvent this limitation, the authors modified the conditions, carrying out the irradiation in a two-phase system: benzene/10% aqueous sodium hydroxide. Operating this way the target compound **62** was directly obtained in good yield (82%) (Scheme 21).

Scheme 21



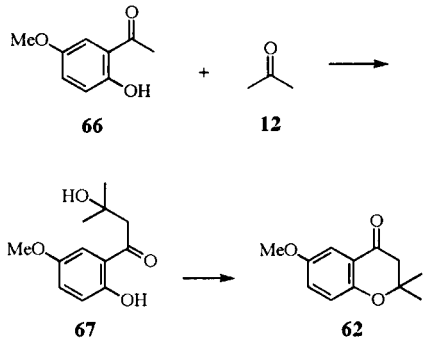
Camps *et al.* [32] reported on Fries rearrangement of 4-methoxyphenyl 3,3-dimethylacrylate (**64**) in methanesulfonic acid, polyphosphoric acid, aluminum chloride and under photochemical conditions. In each case, a rather complex mixture of products was formed. The predominant formation (20-52%) of 3,4-dihydro-4,4-dimethyl-6-methoxycoumarin (**65**), minor amounts (5-13%) of 2,2-dimethyl-6-methoxy-4-chromanone (**62**) along with *o*-hydroxyketone (**60**, 6%) was observed. However, 55% of 2,2-dimethyl-6-methoxy-4-chromanone (**62**) was formed when photochemical conditions were applied (Scheme 22).

Scheme 22



Banerji and Kalena [38] described a new method of cyclodehydration of 3,3-dimethyl-1-oxo-1-(2-hydroxyaryl)propan-3-ols to 2,2-dimethyl-4-chromanones. Thus, 2-hydroxy-5-methoxyacetophenone (**66**) was allowed to react with acetone (**12**) in the presence of lithium diisopropylamide in tetrahydrofuran to get the diol (**67**, 80%) and the latter was cyclized in hexamethylphosphorous triamide to 2,2-dimethyl-6-methoxy-4-chromanone (**62**) in 93% yield (Scheme 23).

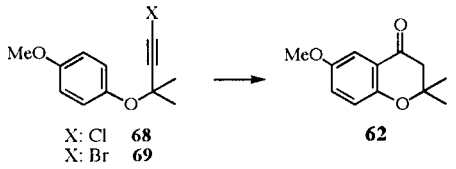
Scheme 23



Ariamala and Balasubramanian [39-41] studied the thermal behavior of aryl γ-halopropargyl ethers and found a simple route for the synthesis of 2,2-dimethyl-4-chromanones. To their observation [39,40], when γ-chloro-α,α-dimethylpropargyl-4-metoxyphenyl ether (**68**) was refluxed in ethylene glycol at 180° for 4 hours, a clean transformation to 2,2-dimethyl-6-methoxy-4-chromanone (**62**) took place and the target compound was isolated in 75% yield. They also reported [41] an alternative method where refluxing γ-bromo-α,α-dimethylpropargyl-4-metoxyphenyl ether (**69**) with mercury(II)-trifluoroacetate in trifluoroacetic acid affords 2,2-dimethyl-6-methoxy-4-chromanone (**62**) in moderate (50%) yield. During the reaction considerable cleavage of the ether **69** was observed (Scheme 24).

An elegant method for the synthesis of 2,2-dimethyl-6-methoxy-4-chromanone (**62**) was reported by Sebők *et al.* [26]. The cyanate and dimethylthiocarbamate derivatives

Scheme 24



X: Cl **68**
X: Br **69**

62

70 and **71** were easily converted and deoxygenated to the target chromanone (**62**) in very good overall yield (80-82%) (Scheme 25).

Scheme 25

72

R: CN **70**
R: $(Me)_2NC(=S)$ **71**

62

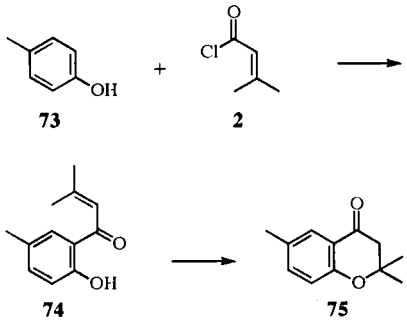
Hepworth and Livingstone [42] communicated the addition of halogens to several methoxy-2,2-dimethyl-2*H*-chromenes. In the course of this work they prepared the 3-bromo-4-hydroxy-6-methoxychroman (**72**). This derivative, on oxidation with chromium trioxide in acetic acid, was converted into 3-bromo-6-methoxy-4-chromanone which was then debrominated with zinc dust in acetic acid to 2,2-dimethyl-6-methoxy-4-chromanone (**62**) (Scheme 26).

Scheme 26

72 **62**

Cardani [43] reported on the reaction of 4-methylanisole (**73**) and 3,3-dimethylacryloyl chloride (**2**) in the presence of aluminum chloride in carbon disulfide. The uncyclized *o*-hydroxyketone **74** was isolated and then cyclized in 2% aqueous sodium hydroxide to 2,2,6-trimethyl-4-chromanone (**75**), however no yield was disclosed (Scheme 27).

Scheme 27



73 **2**

74 **75**

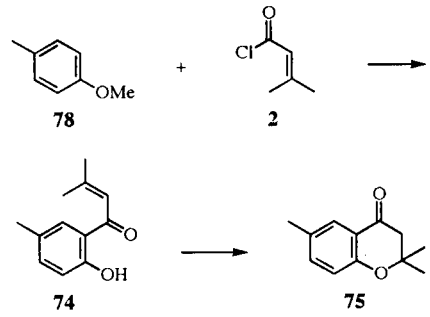
Fries rearrangement of 4-methylphenyl-3-methylbut-2-enoate (**76**) when treated with aluminum chloride in carbon disulfide was reported [20] to give (after complicated work up and purification procedure) 3,4-dihydro-4,4,6-trimethylcoumarin (**77**, 78%), but no formation of 2,2,6-trimethyl-4-chromanone (**75**) was observed (Scheme 28).

Scheme 28

76 **77**

Baldwin *et al.* [44] while investigating the rules for ring closure (ring formation by conjugate addition of oxygen nucleophiles) studied the reaction of *p*-methyl anisole (**78**) and 3,3-dimethylacryloyl chloride (**2**) in the presence of aluminum chloride in carbon disulfide. The uncyclized *o*-hydroxyketone (**74**) was isolated in 44% yield and this was then cyclized in 5% aqueous sodium hydroxide to 2,2,6-trimethyl-4-chromanone (**75**) in acceptable yield (65%) (Scheme 29).

Scheme 29

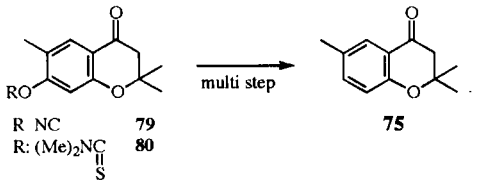


78 **2**

74 **75**

An alternative method for the synthesis of 2,2,6-trimethyl-4-chromanone (**75**) was reported by Sebők *et al.* [26] The cyanate and dimethylthiocarbamate derivatives (**79** and **80**) were easily converted and deoxygenated to the target chromanone (**75**) in good (71-82%) overall yield (Scheme 30).

Scheme 30



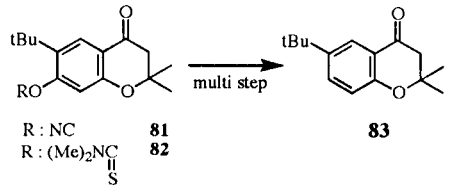
R NC **79**
R: $(Me)_2NC(=S)$ **80**

75

The same procedure [26] was applied to get 6-*tert*-butyl-2,2-dimethyl-4-chromanone (**83**). Starting from the corresponding cyanate and dimethylthiocarbamate derivatives

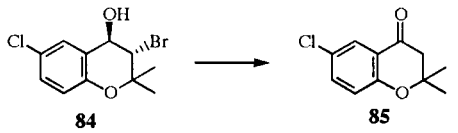
81 and **82** the final product **83** was obtained in 83-84% yield (Scheme 31).

Scheme 31



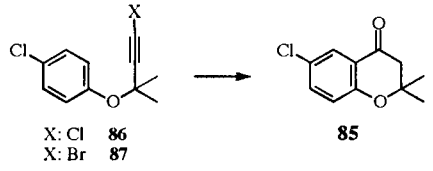
Hepworth *et al.* [27] reported on the synthesis of a series of chloro-2,2-dimethyl-4-chromanones, including 6-chloro-2,2-dimethyl-4-chromanone (**85**). Details of this synthetic strategy were discussed earlier (see Scheme 17). The 3-bromo-6-chloro-4-hydroxychroman (**84**) was obtained in 91% yield. Oxidation with chromium trioxide in acetic acid led to the formation of 3-bromo-5-chloro-4-chromanone which was then debrominated with benzoin to the target compound **85** (Scheme 32).

Scheme 32



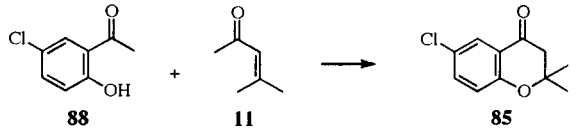
Ariamala and Balasubramanian [39-41] elaborated a simple route for the synthesis of 2,2-dimethyl-4-chromanones. To their observation [39,40], when γ-chloro-α,α-dimethylpropargyl-4-chlorophenyl ether **86** was refluxed in ethylene glycol at 180° for 5 minutes, a clean transformation to 6-chloro-2,2-dimethyl-4-chromanone (**85**) took place and the target compound was isolated in 70% yield. They also reported [41] an alternative method. Refluxing γ-bromo-α,α-dimethylpropargyl-4-chlorophenyl ether (**87**) with mercury(II)-trifluoroacetate in trifluoroacetic acid affords 6-chloro-2,2-dimethyl-4-chromanone (**85**) in moderate (40%) yield. At the same time considerable cleavage of the ether (**87**) was also observed (Scheme 33).

Scheme 33



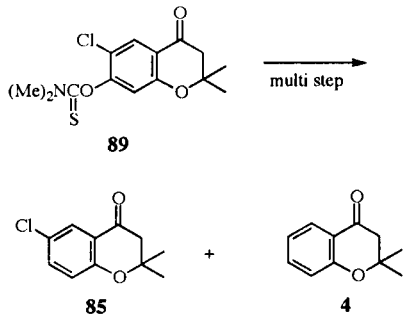
The one step synthesis elaborated by Kabbe and Widdig [23] was also applicable for the preparation of chloro-2,2-dimethyl-4-chromanones. The reaction of 2-hydroxy-5-chloroacetophenone (**88**) with mesityl oxide (**11**) in pyrrolidine leads to the formation of 6-chloro-2,2-dimethyl-4-chromanone (**85**) in good yield (79%) (Scheme 34).

Scheme 34



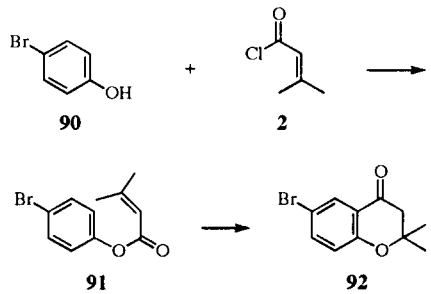
An alternative approach was elaborated by Sebők *et al.* [26] for the preparation of 6-chloro-2,2-dimethyl-4-chromanone (**85**). Some limitation of this method was revealed when dimethylthiocarbamate derivative **89** was converted and deoxygenated to the target chromanone **85**. Only 41% overall yield for compound **85** was reached since dechlorination also took place forming 2,2-dimethyl-4-chromanone (**4**, 48%) (Scheme 35).

Scheme 35



Livingstone *et al.* [8] worked out a method to obtain 6-bromo-2,2-dimethyl-4-chromanone (**92**). *p*-Bromophenol (**90**) and 3,3-dimethylacryloyl chloride (**2**) and magnesium were refluxed in benzene for 2 hours yielding the ester (**91**, 77%). Fries rearrangement of the latter in the presence of aluminum chloride afforded the target chromanone **92** in 46% yield (Scheme 36).

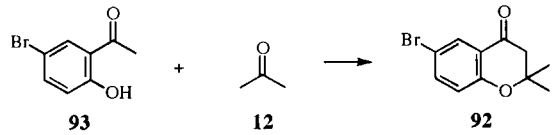
Scheme 36



Buckle *et al.* [45], in the course of structure-activity relationship studies in the field of benzopyran-type potassium

channel openers, adopted the method reported by Kabbe and Widdig [23] for the preparation of 6-bromo-2,2-dimethyl-4-chromanone (**92**). 5-Bromo-2-hydroxyacetophenone (**93**) and acetone (**12**) were refluxed in the presence of pyrrolidine in benzene for 16 hours. The target compound **92** was obtained in 60% yield (Scheme 37).

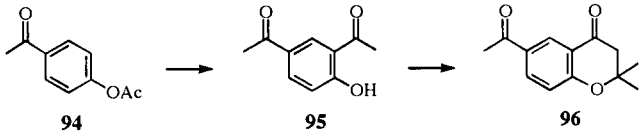
Scheme 37



93 **12** **92**

Bohlmann and Vorwerk [46] prepared the 6-acetyl-2,2-dimethyl-4-chromanone (**96**) employing the method of Kabbe and Widdig [23]. Fries rearrangement of *p*-acetoxyacetophenone (**94**) in the presence of aluminum chloride afforded the diketone **95** in good (78%) yield. The latter was then reacted with acetone (**12**) in pyrrolidine to yield 6-acetyl-2,2-dimethyl-4-chromanone (**96**) in moderate yield (44%) (Scheme 38).

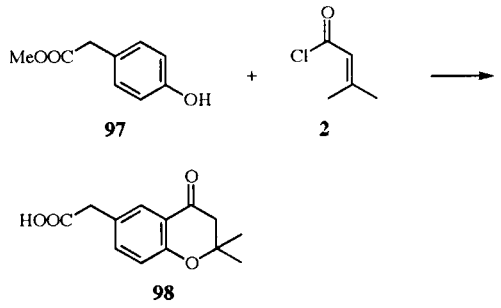
Scheme 38



94 **95** **96**

Birch *et al.* [47] communicated on the reaction of *p*-hydroxyphenylacetate (**97**) and 3,3-dimethylacryloyl chloride (**2**) with aluminum chloride in carbon disulfide and nitrobenzene. No intermediate product was isolated and 2,2-dimethyl-4-chromanone-6-ylacetic acid (**98**) was isolated in moderate yield (47%) (Scheme 39).

Scheme 39

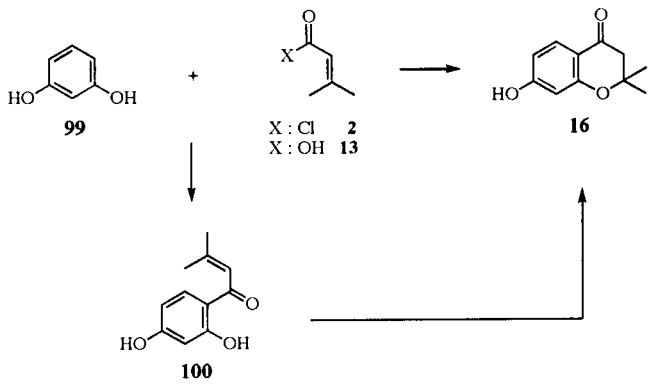


97 **2** **98**

5. 7-Substituted 2,2-Dimethyl-4-chromanones

According to Ellis [15], the most important members within the family of monosubstituted 4-chromanones are the 7-substituted 2,2-dimethyl-4-chromanones. These compounds have a central synthetic role in 2,2-dimethyl-1-benzopyran chemistry, especially in the field of potentially useful modern pesticides [11] and drug candidates of benzopyran-type potassium channel openers [13]. There are numerous procedures for their preparation and chemical transformations. Extensive use has been made of the reaction of resorcinol (**99**) with 3,3-dimethylacryloyl chloride (**2**) or 3-methylbut-2-enoic acid (**13**) in the presence of several Lewis acids and different solvents under the conditions of the Friedel-Crafts reactions. In some cases, the intermediate *o*-hydroxy unsaturated ketone **100** was isolated and its cyclization was effected quantitatively with alkali. In this section more details are given on the use of this type of reaction for the synthesis of 2,2-dimethyl-7-hydroxy-4-chromanone (**16**) (Table 1, Scheme 40.)

Scheme 40



99 X : Cl **2** X : OH **13** **16** **100**

Table 1

Reported reactions for the synthesis of 2,2-dimethyl-7-hydroxy-4-chromanone (**16**)

X[a]	Reagent	Conditions	Yield (%)	Reference
Cl	$AlCl_3/C_6H_5\text{-}NO_2$	25°, 4 days	50	[48]
HO	$SbCl_3$	140°, 15 minutes	85	[49]
HO	$BF_3/C_6H_5\text{-}NO_2$	120°, 4 hours	90	[50]
Cl	$ZnCl_2$(fused)/$POCl_3$	25°, 24 hours	73	[51]
HO	CH_3SO_3H/P_2O_5	70°, 30 minutes	94	[52]
HO	$AlCl_3/POCl_3$	25°, 5 hours	92[b]	[53]
HO	Polyphosphoric acid	85°, 40 minutes	57	[54]
HO	$ZnCl_2$(fused)/$POCl_3$	25°, 2 hours	95[b]	[55]
HO	$ZnCl_2$(unfused)/$POCl_3$	50°, 2 hours	80	[55]

[a] For X, see Scheme 40. [b] Yield of compound **100** which can be cyclized in alkali into **16** almost quantitatively.

Closely related to the Friedel-Crafts reaction in this context is the Fries rearrangement and photo Fries rearrangement [32,33]. In their application to the synthesis of 2,2-dimethyl-7-methoxy-4-chromanone (**102**) 3-methoxyphenyl 3-methylbut-2-enoate (**37**) is converted into a mixture of the isomeric *o*- and *p*-hydroxyketones **38** and **101**; the former is readily converted to the corresponding 4-chromanone **102** (Scheme 41). Details of these studies are summarized in Table 2.

Scheme 41

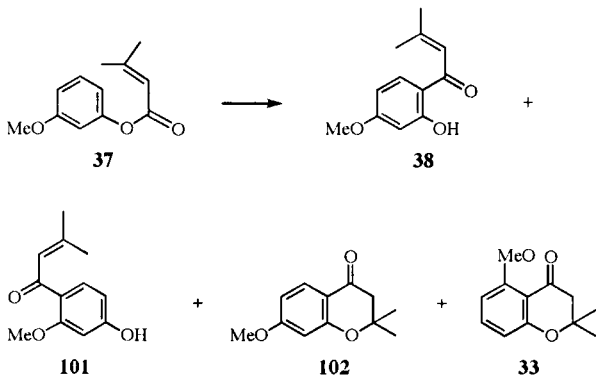


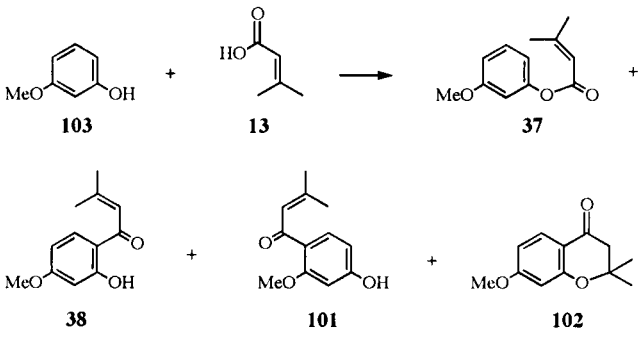
Table 2
Fries rearrangement of 3-methoxyphenyl 3-methylbut-2-enoate (**37**)

Reagent	Conditions	Products and yields (%)	Reference
CH_3SO_3H/P_2O_5	70°, 1.5 hours	**101**(13), **102**(79)	[32]
$AlCl_3/CH_3$-NO_2	70°, 3 hours	**38**(42) **101**(16), **102**(37)	[32]
Polyphosphoric acid	100°, 30 minutes	**102**(80)	[32]
$CH_3OH/h\nu$(254 nm)	25°, 24 hours	**38**(25) **101**(7), **33**(7)	[32]
hexane/$h\nu$(254 nm)	25°, 20 hours	**38**(28)[a]	[33]

[a] **38** is cyclized in alkali into **102** almost quantitatively.

The synthesis of 2,2-dimethyl-7-methoxy-4-chromanone (**102**) was also performed directly starting from 3-methoxyphenol (**103**) and 3-methylbut-2-enoic acid (**13**) in the presence of several catalysts and in different solvents (Scheme 42). Table 3 contains detailed information on these reactions.

Scheme 42



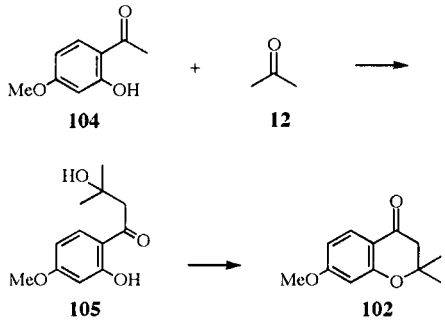
Banerji and Goomer [56,57] found that the lithium enolate of 2-hydroxy-4-methoxy-acetophenone (**104**) can be generated under mild conditions using lithium diisopropylamide in THF at -25°. This was reacted with acetone (**12**) at -40° and the cross aldol condensation product (**105**, 80%) underwent facile cyclodehydration while refluxing in methanolic HCl (10%) to give 2,2-dimethyl-7-methoxy-4-chromanone (**102**) in 80% yield (Scheme 43).

Table 3
Reported reactions of 3-methoxy-phenol (**102**) and 3-methylbut-2-enoic acid (**13**)

Reagent	Conditions	Products and yields (%)	Reference
Polyphosphoric acid	100°, 1 hour	**102**(near quant.)	[36]
CH_3SO_3H/P_2O_5	70°, 1 hour	**101**(9), **102**(80)	[52]
$ZnCl_2/POCl_3$	25°, 4 hours	**37**(7), **38**(37), **102**(52)	[24] [25]
$AlCl_3/POCl_3$	25°, 30 minutes	**38**(99)[a]	[24] [25]

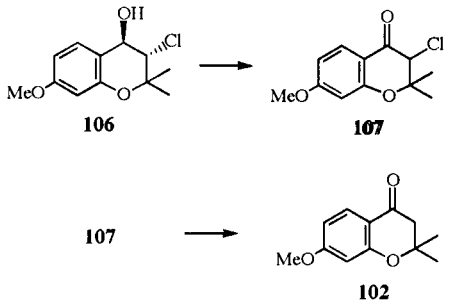
[a] **38** can be cyclized in alkali into **102** almost quantitatively.

Scheme 43



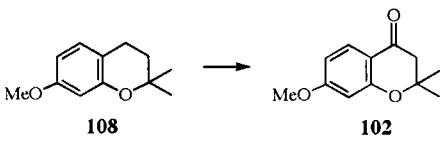
Hepworth and Livingstone [42] prepared the 3-chloro-4-hydroxy-7-methoxychroman **106**. This derivative, on oxidation with chromium trioxide in acetic acid was transformed to 3-chloro-7-methoxy-4-chromanone (**107**, 91%) which was then dechlorinated with zinc dust in acetic acid to afford 2,2-dimethyl-7-methoxy-4-chromanone (**102**) in 50% yield (Scheme 44).

Scheme 44



Kanvinde et al. [58] elaborated a mild and efficient conversion of 2,2-dimethylchromans into chromanones using ceric ammonium nitrate (CAN). Thus, the solution of 2,2-dimethyl-7-methoxychroman (**108**) in ether was added to acetic acid-water (1:1). To this two phase system CAN was added and after a simple work up 2,2-dimethyl-7-methoxy-4-chromanone (**102**) was prepared in 90% yield indicating that no nitration had occurred in the course of this oxidation (Scheme 45).

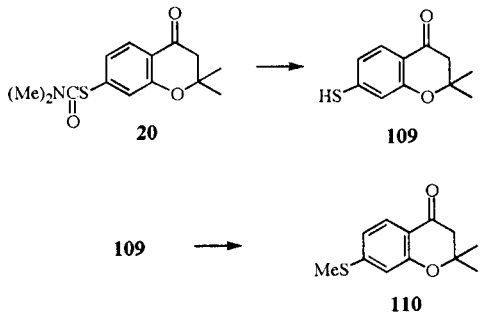
Scheme 45



108 **102**

Sebők *et al.* [59] described the first synthesis of 7-alkylthio-2,2-dimethyl-2*H*-chromenes, the thio analogs of natural and synthetic precocenes. In the course of this work 7-(*N*,*N*-dimethylcarbamoylthio)-2,2-dimethyl-4-chromanone (**20**) was prepared (see also Scheme 7) and alkaline hydrolysis of this compound furnished 2,2-dimethyl-7-mercapto-4-chromanone (**109**) which was then methylated to the corresponding 2,2-dimethyl-7-methylthio-4-chromanone (**110**) (Scheme 46).

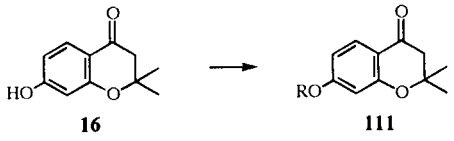
Scheme 46



20 **109** **110**

The 2,2-dimethyl-7-hydroxy-4-chromanone (**16**) was proven to be very useful intermediate in the field of 2,2-dimethyl-1-benzopyran chemistry, since a wide variety of systematic series of its derivatives (**111**) were prepared by *O*-alkylation and *O*-acylation for structure-activity relationship studies of precocenes and potassium channel activators [26,55, 59-62] (Scheme 47).

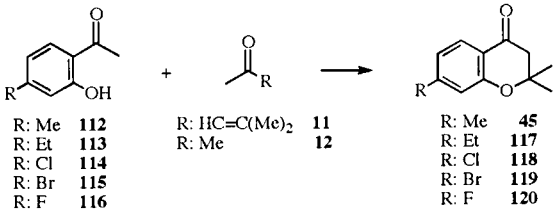
Scheme 47



16 **111**

The first preparation of 2,2,7-trimethyl-4-chromanone (**45**) was reported [20] by the rearrangement of 3-methylphenyl 3-methylbut-2-enoate (**43**). The reaction of ester **43** on treatment with aluminum chloride in carbon disulfide afforded 3,4-dihydro-4,4,7-trimethylcoumarin (**44**, 10%) and 2,2,7-trimethyl-4-chromanone (**45**) in low (18%) yield (Scheme 15). For direct synthesis of chromanone **45** the best method was elaborated by Kabbe and Widdig [23]. The 2,2-dimethyl-7-halogeno-4-chromanones (**117-120**) which were obtained by this synthetic procedure are summarized in Table 4 (Scheme 48).

Scheme 48



R: Me **112**, R: Et **113**, R: Cl **114**, R: Br **115**, R: F **116**

R: H$_2$C=C(Me)$_2$ **11**, R: Me **12**

R: Me **45**, R: Et **117**, R: Cl **118**, R: Br **119**, R: F **120**

Table 4

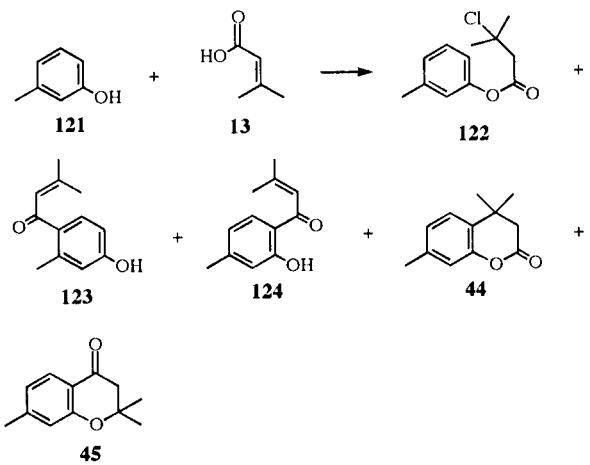
Preparation of 7-alkyl-2,2-dimethyl- and 2,2-dimethyl-7-halogeno-4-chromanones

Substrate and R[a]	Reactant	Product and yield (%)	Reference
112 Me	**11**	**45**(69)	[23]
113 Et	**11**	**117**(50)	[23]
114 Cl	**12**	**118**(79)	[23]
115 Br	**12**	**119**(70)	[45]
116 F	**12**	**120**(57)	[34]

[a] For substituent R, see Scheme 48.

According to Sebők *et al.* [24, 25] 2,2,7-trimethyl-4-chromanone (**45**) could also be obtained in 50% yield by the reaction of 3-methylphenol (**121**) and 3-methylbut-2-enoic acid (**13**) in a mixture of zinc chloride and phosphorus oxychloride. However, besides the target 4-chromanone **45** other products, such as 3'-methylphenyl 3-chloro-3-methylbutanoate (**122**, 37%), *p*-hydroxy-ketone **123**, (9%), *o*-hydroxy-ketone **124**, (5%) and 3,4-dihydro-4,4,6-trimethylcoumarin (**44**, 4%) were also formed. The same reaction in a mixture of aluminum chloride and phosphorus oxychloride afforded mainly 3-methylphenyl 3-methylbut-2-enoate (**43**) in 82% yield (Scheme 49).

Scheme 49



121 **13** **122**

123 **124** **44**

45

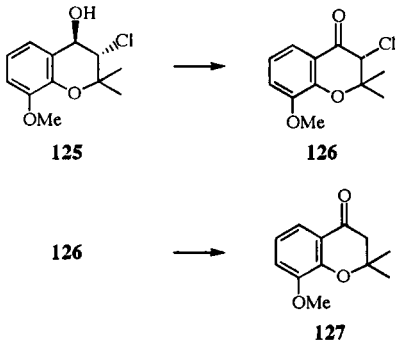
The 7-chloro-2,2-dimethyl-4-chromanone (**118**) was also obtained by the method reported by Hepworth *et al.* [27] as it was detailed earlier (see also Scheme 17).

6. 8-Substituted 2,2-Dimethyl-4-chromanones

In contrast with the previous chapters no synthetic procedure can be found in the literature for the preparation of 2,2-dimethyl-8-hydroxy-4-chromanone.

First publication on the synthesis of 2,2-dimethyl-8-methoxy-4-chromanone (**127**) appeared in 1966 when Hepworth and Livingstone [42] prepared the 3-chloro-2,2-dimethyl-4-hydroxy-8-methoxychroman (**125**). Its oxidation with chromium trioxide in acetic acid afforded 3-chloro-8-methoxy-4-chromanone (**126**, 86%) which was then dechlorinated with zinc dust in acetic acid to 2,2-dimethyl-8-methoxy-4-chromanone (**127**) in 89% yield (Scheme 50).

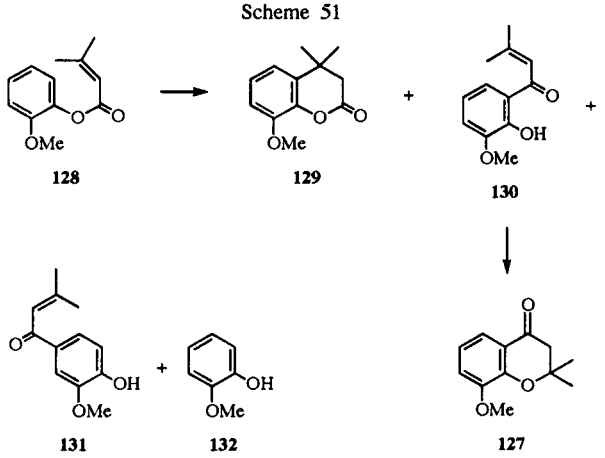
Scheme 50



Twenty years later Camps *et al.* [32] reported on the Fries rearrangement of 2-methoxyphenyl 3,3-dimethylacrylate (**128**) in methanesulfonic acid, polyphosphoric acid, aluminum chloride and under photochemical conditions. In each case a rather complex mixture of products was formed. Depending on the reaction conditions the formation of 3,4-dihydro-4,4-dimethyl-8-methoxycoumarin (**129**, 4-6%), along with *o*- and *p*-hydroxyphenylketones **130**, (6-22%) and **131**, (3-48%) as well as 2-methoxyphenol (**132**, 12-54%) was observed. No direct formation of 2,2-dimethyl-8-methoxy-4-chromanone (**127**) was detected. However, the latter was readily obtained by alkali treatment of **130** (Scheme 51).

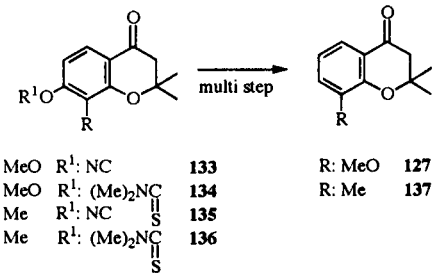
Similar observations were reported by Sebők *et al.* [24,25]. No 2,2-dimethyl-8-methoxy-4-chromanone (**126**) was obtained by the reaction of 2-methoxyphenol (**132**) and 3-methylbut-2-enoic acid (**13**) in a zinc chloride and phosphorus oxychloride mixture. At the same time, the formation of the *o*-hydroxy-ketone **130**, (30%) showed a limited value of this method for the synthesis (*via* alkaline treatment) of this 4-chromanone (**127**). The same reaction in a mixture of aluminum chloride and phosphorus oxychloride afforded mainly 2-methoxyphenyl 3,3-dimethylacrylate (**128**) in 98% yield (see also Scheme 51).

Scheme 51



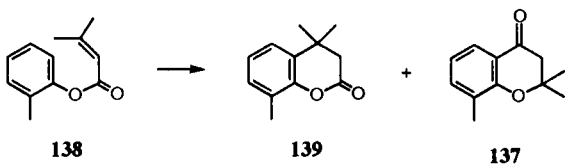
The most advantageous method for the preparation of 2,2-dimethyl-8-methoxy-4-chromanone (**127**) and 2,2,8-trimethyl-4-chromanone (**137**) was reported by Sebők *et al.* [26]. The cyanate and dimethylthiocarbamate derivatives **133**, **134** and **135**, **136** were transformed and deoxygenated in good yields to the corresponding 2,2-dimethyl-8-methoxy-4-chromanone (**127**, 78%) and 2,2,8-trimethyl-4-chromanone (**137**, 80%) (Scheme 52).

Scheme 52



The preparation of 2,2,8-trimethyl-4-chromanone (**137**) was also reported [20] by the rearrangement of 2-methylphenyl 3-methylbut-2-enoate (**138**). The reaction of ester **138** on treatment with aluminum chloride in carbon disulfide afforded 3,4-dihydro-4,4,8-trimethylcoumarin (**139**, 50%) and 2,2,8-trimethyl-4-chromanone (**137**) in low (7%) yield (Scheme 53).

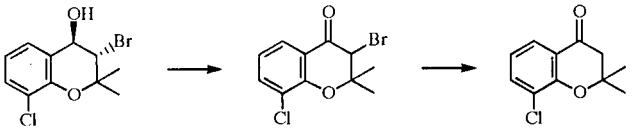
Scheme 53



The 8-chloro-2,2-dimethyl-4-chromanone (**142**) was obtained by the method reported by Hepworth *et al.* [27]. They have prepared the 3-bromo-8-chloro-4-hydroxychroman (**140**)

in high yield (98%). This derivative, on oxidation with chromium trioxide in acetic acid was transformed to 3-bromo-8-chloro-2,2-dimethyl-4-chromanone (**141**, 98%) which was then debrominated with benzoin to 8-chloro-2,2-dimethyl-4-chromanone (**142**, 51%) (Scheme 54).

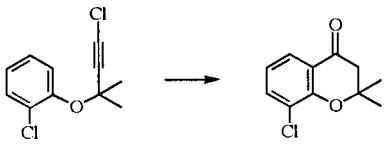
Scheme 54



140 **141** **142**

According to Ariamala and Balasubramanian [39,40] when γ-chloro-α,α-dimethylpropargyl-2-chlorophenyl ether (**143**) was refluxed in ethylene glycol at 180° for 4 hours, a clean transformation to 8-chloro-2,2-dimethyl-4-chromanone (**142**) took place and the target compound was isolated in 60% yield (Scheme 55).

Scheme 55



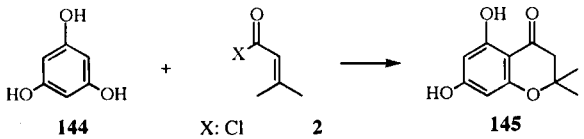
143 **142**

]7. 5,7-Disubstituted 2,2-Dimethyl-4-chromanones

Within the family of disubstituted 2,2-dimethyl-4-chromanones the 5,7-disubstituted 2,2-dimethyl-4-chromanones are well-known members. There are several well-established procedures for direct preparation and chemical transformation of 5,7-disubstituted 2,2-dimethyl-4-chromanones. The most frequently used method is the reaction of phloroglucinol (**144**) with 3,3-dimethylacryloyl chloride (**2**) or 3-methylbut-2-enoic acid (**13**) in the presence of Lewis acids and different solvents by Friedel-Crafts reaction. In Table 5 details are given on the use of this type of reaction for the synthesis of 5,7-dihydroxy-2,2-dimethyl-4-chromanone (**145**) (Table 5, Scheme 56.)

In 1963, Bhat and Venkataraman [66] elaborated a new synthesis. They found that the condensation of phloroglucinol (**144**) with β-hydroxyisovaleric acid (**146**) in the presence of boron trifluoride etherate under mild conditions (100°, 2 minutes) resulted in a 65% yield of 5,7-dihydroxy-2,2-dimethyl-4-chromanone (**145**) (Scheme 57).

Scheme 56



144 X: Cl **2** X: OH **13** **145**

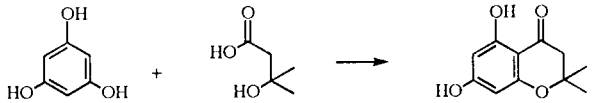
Table 5

Reported reactions for the synthesis of 5,7-dihydroxy-2,2-dimethyl-4-chromanone (**145**)

X[a]	Reagent	Conditions	Yield (%)	Reference
Cl	$AlCl_3/C_6H_5$-NO_2	25°, 4 days	72, 62	[63,64]
HO	$SbCl_3$	145°, 15 minutes	39	[49]
HO	BF_3/C_6H_5-NO_2	80°, 20 minutes	82	[50]
Cl	$ZnCl_2$(fused)/$POCl_3$	25°, 24 hours	67	[51]
HO	$AlCl_3/POCl_3$	25°, 5 hours	90	[53]
HO	$ZnCl_2$(unfused)/$POCl_3$	50°, 5 hours	80	[65]

[a] For X, see Scheme 56.

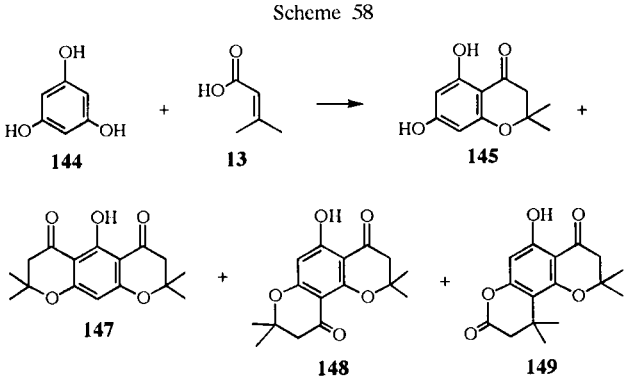
Scheme 57



144 **146** **145**

Some twenty years later Matsui [54] reported a comprehensive study of the synthesis of chromanones, coumarins and related compounds using polyphosphoric acid as a condensating agent. The condensation of phloroglucinol (**144**) with 3-methylbut-2-enoic acid (**13**) in the presence of low-polymeric polyphosphoric acid at 75-80° for 1.5 hours has yielded four chromanones (**145**, **147**, **148** and **149**). However, the similar reaction conditions in the presence of high-polymeric polyphosphoric acid afforded chromanones **145**, **147** and **148** but no **149**. Although no yields for these chromanones were reported, this method is not really suitable for the preparation of 5,7-dihydroxy-2,2-dimethyl-4-chromanone (**145**) (Scheme 58). Earlier Jefferson *et al.* [67] published the reaction of phloroglucinol (**144**) with 3-methylbut-2-enoic acid (**13**) in polyphosphoric acid at 100° for 3 hours. Under these conditions both linear and angular benzodipyrandiones **147** and **148** were formed and the angular isomer **148** can be rearranged to the linear product **147**. No formation of 5,7-dihydroxy-2,2-dimethyl-4-chromanone (**145**) was observed.

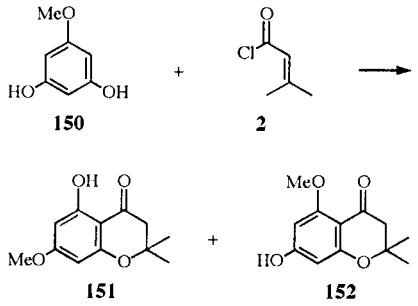
Scheme 58



144 **13** **145** **147** **148** **149**

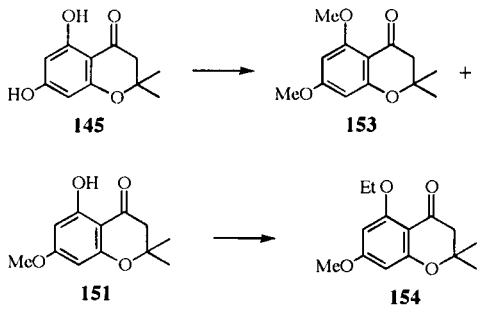
George and Robertson [68] reacted phloroglucinol monomethyl ether (**150**) and 3,3-dimethylacryloyl chloride (**2**) in nitrobenzene containing aluminum chloride at room temperature for 7 days. After a long and complicated work-up two products, the 2,2-dimethyl-5-hydroxy-7-methoxy-4-chromanone (**151**) and the regioisomer 2,2-dimethyl-7-hydroxy-5-methoxy-4-chromanone (**151**) were isolated in 4% and 1% yields, respectively (Scheme 59).

Scheme 59



Tímár and Jászberényi [65] reported on a regioselective *O*-alkylation of dihydroxy-2,2-dimethyl-4-chromanones. Thus, 5,7-dihydroxy-2,2-dimethyl-4-chromanone (**145**) was reacted with methyl iodide in the presence of potassium carbonate in *N,N*-dimethylformamide at 80° for 5 hours. After a simple work-up two products, the 2,2-dimethyl-5-hydroxy-7-methoxy-4-chromanone (**151**) and 5,7-dimethoxy-2,2-dimethyl-4-chromanone (**153**) were isolated in 90% and 6% yields, respectively. Ethylation of compound **151** under the same conditions afforded the corresponding 2,2-dimethyl-5-ethoxy-7-methoxy-4-chromanone (**154**) in 87% yield. It was very easy to recognize the flexibility and utility of this approach for the synthesis of a large number of analogs of compound **154** by the use of different alkylating agents [65,69] (Scheme 60).

Scheme 60



The synthesis of 7-hydroxy-2,2,5-trimethyl-4-chromanone (**156**) was performed directly starting from orcinol (**155**) and 3,3-dimethylacryloyl chloride (**2**) or 3-methylbut-2-enoic acid (**13**) in the presence of zinc chloride or aluminum chloride in phosphorus oxychloride (Scheme 61). Table 6 contains detailed information on these reactions.

Scheme 61

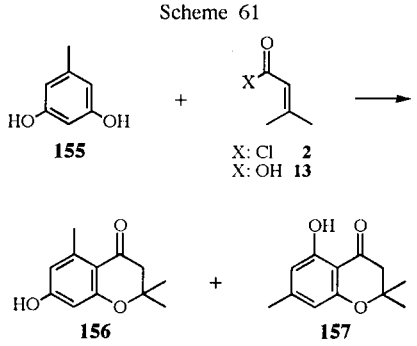


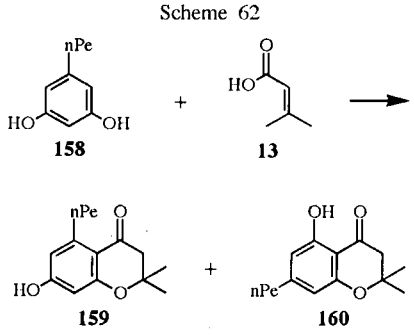
Table 6

Reported reactions for the synthesis of 7-hydroxy-2,2,5-trimethyl-4-chromanone (**156**)

Reagent	Conditions	Products and yields (%)	Reference
$ZnCl_2$(fused)/$POCl_3$	25°, 24 hours	**156** (75)	[51]
$AlCl_3$/$POCl_3$	25°, 3 hours	**156** (90)	[53]
$ZnCl_2$(unfused)/$POCl_3$	50°, 2 hours	**156** (87), **157** (7)	[70]

Fahrenholtz *et al.* [71] in the course of the total synthesis of *dl*-Δ^9-tetrahydrocannabinol needed to synthesize 2,2-dimethyl-5-hydroxy-7-pentyl-4-chromanone (**160**). They found that the reaction of olivetol (**158**) and 3-methylbut-2-enoic acid (**13**) in the presence of boron trifluoride etherate (under reflux, overnight) furnished two products, the 2,2-dimethyl-7-hydroxy-5-pentyl-4-chromanone (**159**) and the regioisomer 2,2-dimethyl-5-hydroxy-7-pentyl-4-chromanone (**160**) in 22% and 50% yields, respectively (Scheme 62).

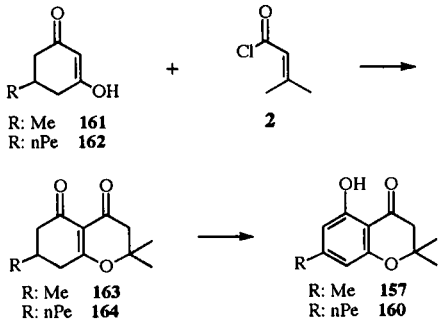
Scheme 62



Later Arnoldi [31] elaborated a regioselective method for the synthesis of 5-hydroxy-4-chromanones starting from 1,3-cyclohexanediones. The enol esters obtained from dienones **161** and **162** and 3,3-dimethylacryloyl chloride (**2**) in acidic medium undergo Fries rearrangement

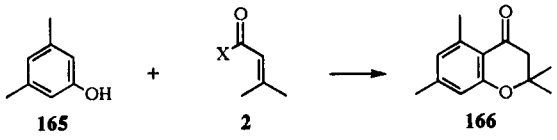
with ring closure in the presence of titanium(IV) chloride to give 4,5-dioxo-5,6,7,8-tetrahydrochroman derivatives **163** and **164** which can then be dehydrogenated (10% palladium on carbon or DDQ) to afford 5-hydroxy-2,2,7-trimethyl-4-chromanone (**157**) and 2,2-dimethyl-5-hydroxy-7-pentyl-4-chromanone (**160**). The overall yields of this two-steps procedure are 30% and 64% for the target compounds (Scheme 63).

Scheme 63



Auwers and Döll [72] obtained 2,2,5,7-tetramethyl-4-chromanone (**166**) by the reaction of 3,5-dimethylphenol (**165**) and 3,3-dimethylacryloyl chloride (**2**) in the presence of aluminum chloride in carbon disulfide. The authors omitted to report the yield in this reaction (Scheme 64).

Scheme 64

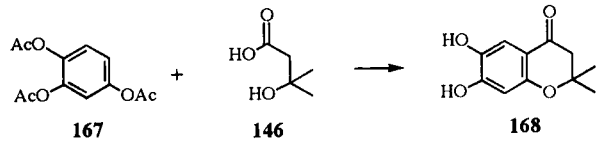


8. 6,7-Disubstituted 2,2-Dimethyl-4-chromanones

Since the discovery of precocenes [11] the synthesis of 6,7-disubstituted 2,2-dimethyl-4-chromanones have attracted increasing attention as these compounds are versatile intermediates for the preparation of natural precocene 2 as well as its synthetic analogs. Numerous procedures for direct preparation and chemical transformation of 6,7-disubstituted 2,2-dimethyl-4-chromanones have been reported.

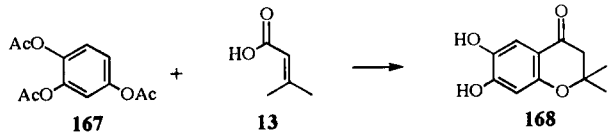
Bhat and Venkataraman [66] published the first method for the synthesis of 6,7-dihydroxy-2,2-dimethyl-4-chromanone (**168**). They found that the condensation of 1,2,4-triacetoxybenzene (**167**) with β-hydroxyisovaleric acid (**146**) in the presence of boron trifluoride etherate under mild conditions (100°, 2 minutes) resulted in a 30% yield of 6,7-dihydroxy-2,2-dimethyl-4-chromanone (**168**) (Scheme 65).

Scheme 65



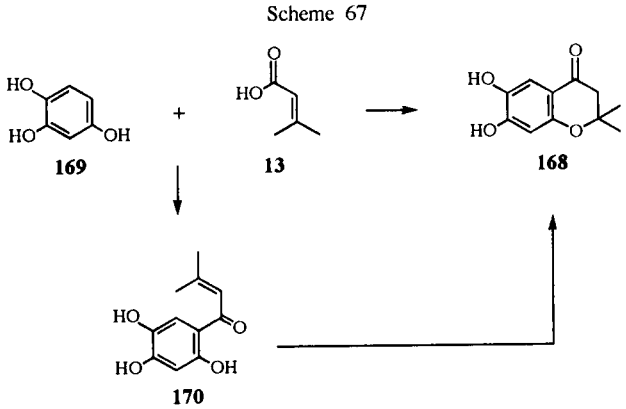
Two decades later Camps *et al.* [52] achieved some improvement. 1,2,4-Triacetoxybenzene (**167**) was reacted with 3-methylbut-2-enoic acid (**13**) in the presence of methanesulfonic acid containing polyphosphoric acid at 70° for 30 minutes. The target compound (**168**) was isolated in 42% yield (Scheme 66).

Scheme 66



Tímár and Jászberényi [65] elaborated a more efficient synthesis of dihydroxy-2,2-dimethyl-4-chromanones including two alternative methods for the preparation of 6,7-dihydroxy-2,2-dimethyl-4-chromanone (**168**). Thus, hydroxyhydroquinone (**169**) was allowed to react with 3-methylbut-2-enoic acid (**13**) in the presence of fused zinc chloride in phosphorous oxychloride at 25° for 2 hours. The intermediate *o*-hydroxyketone (**170**) was isolated in 88% yield and was subsequently cyclized in 5% aqueous sodium hydroxide (at 25° for 1 hour) to 6,7-dihydroxy-2,2-dimethyl-4-chromanone (**168**) in 92% yield. Alternatively, hydroxyhydroquinone **169** can be reacted with 3-methylbut-2-enoic acid (**13**) in the presence of unfused zinc chloride in phosphorous oxychloride at 50° for 3 hours to provide compound **168** in 79% yield (Scheme 67).

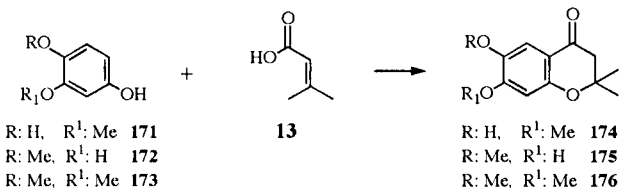
Scheme 67



The reactions of methoxyhydroquinones **171** and **172** and 3,4-dimethoxyphenol (**173**) with 3-methylbut-2-enoic

acid (**13**) were extensively investigated in different laboratories (Scheme 68). Details of these studies are summarized in Table 7.

Scheme 68



Scheme 69

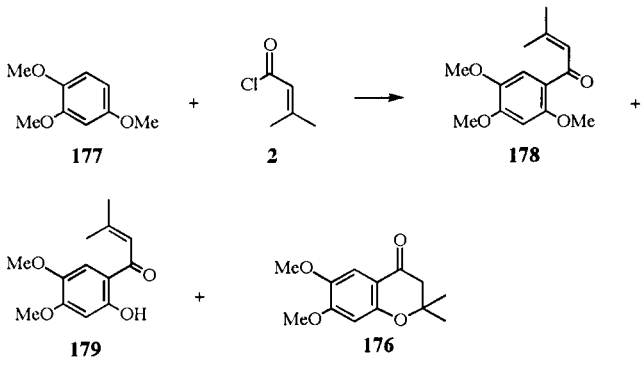


Table 7

Reported reactions of phenols (**171-173**) and 3-methylbut-2-enoic acid (**13**)

R[a]	R[1] [a]	Reagent	Conditions	Product and yield (%)	Reference
Me	H	Polyphosphoric acid	30°, 4 hours	**174** (48)	[73]
Me	H	CH_3SO_3H/P_2O_5	70°, 30 minutes	**174** (91)	[52]
H	Me	CH_3SO_3H/P_2O_5	70°, 30 minutes	**175** (89)	[52]
Me	Me	CH_3SO_3H/P_2O_5	30°, 45 minutes	**176** (85)	[52]
Me	Me	Polyphosphoric acid	100°, 1 hour	**176** (98)	[36]

[a] For R and R[1], see Scheme 68.

The first synthesis of 6,7-dimethoxy-2,2-dimethyl-4-chromanone (**176**) in connection with the work directed to the synthesis of ageratochromene (precocene 2) was reported more than forty years ago [3,4]. 1,2,4-Trimethoxybenzene (**177**) and 3,3-dimethylacryloyl chloride (**2**) were condensed under the conditions of the Friedel-Crafts reaction (aluminum chloride and ether-tetrachloroethane), to give a mixture of the unsaturated ketones **178** and **179** and 6,7-dimethoxy-2,2-dimethyl-4-chromanone (**176**). Depending on the amount of the aluminum chloride and the reaction time the ratio of these products varied considerably: the use of 1.5 molar equivalents of aluminum chloride and 24 hours reaction time resulted in the formation 78% of compound **178** and 11% of target chromanone **176**; at the same time when 3 molar equivalents of aluminum chloride and 48 hours reaction time were applied 38% of compound **179** and 51% of 6,7-dimethoxy-2,2-dimethyl-4-chromanone (**176**) were isolated (Scheme 69). This chromanone **176** has also been prepared by the reaction of 3,4-dimethoxyphenol (**173**) with 3,3-dimethylacryloyl chloride (**2**) in the presence of aluminum chloride in nitrobenzene [7], but no yield was reported.

The reactions of 3,4-alkylenedioxyphenols **180** and **181** with 3-methylbut-2-enoic acid (**13**) in polyphosphoric acid were also studied by several groups (Scheme 70). The results of these findings are summarized in Table 8.

Tímár *et al.* [76] recently worked out an alternative procedure for the preparation of compounds **182** and **183**. The reaction of 6,7-dihydroxy-2,2-dimethyl-4-chromanone (**168**) with dibromomethane or 1,2-dibromoethane in the presence of potassium carbonate in *N,N*-dimethyl-

Scheme 70

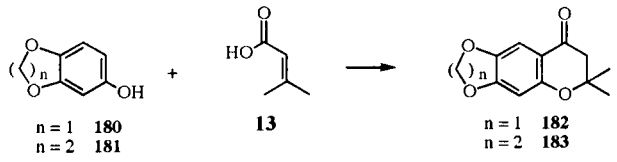


Table 8

Reported reactions of 3,4-alkylenedioxyphenols (**180,181**) and 3-methylbut-2-enoic acid (**13**)

n[a]	Reagent	Conditions	Product and yield (%)	Reference
1	Polyphosphoric acid	80°, 30 minutes	**182** (47)	[74]
2	Polyphosphoric acid	75°, 1.5 hours	**183** (60)	[75]
2	Polyphosphoric acid	100°, 1 hour	**183** (99)	[36]
1	CH_3SO_3H/P_2O_5	25°, 15 hours	**182** (75)	[52]

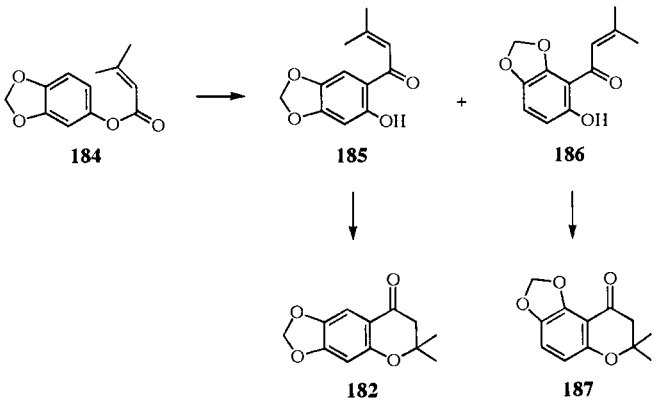
[a] For n, see Scheme 70.

formamide at 80° resulted in the formation of 2,2-dimethyl-6,7-methylenedioxy-4-chromanone (**182**) or of 2,2-dimethyl-6,7-ethylenedioxy-4-chromanone (**183**) in 68% and 72% yields, respectively.

Canela and Bowers [77] reported on the Fries rearrangement of 3,4-methylene-dioxyphenyl 3-methylbut-2-enoate (**184**) and found that the use of titanium tetrachloride, as a catalytic agent in nitromethane, eliminated the problems which occurred when more acidic catalysts were used. The dioxole ring remained unaltered, the ketone **185** was isolated in 90% yield and the formation of polymeric compounds was not observed. The ketone **185** was added to

sodium hydroxide solution and 2,2-dimethyl-6,7-methylenedioxy-4-chromanone (**182**) was obtained in 82% yield (Scheme71).

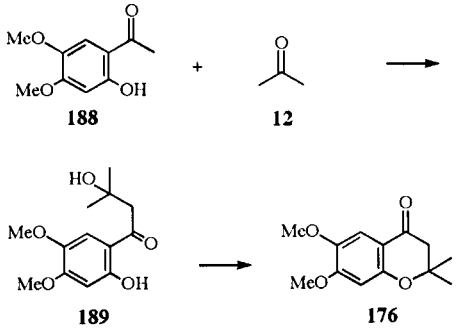
Scheme 71



Miranda *et. al.* [78] studied the photo-Fries rearrangement of 3,4-methylenedioxy-phenyl 3-methylbut-2-enoate (**184**). The irradiation of compound **184** through quartz in hexane with a medium pressure mercury lamp in the presence of potassium carbonate led to the formation of the two possible rearrangement products **185** and **186** (ratio 3:1). After chromatographic separation (HPLC) the hydroxyketones **185** and **186** were isolated in 22% and 8% yields, respectively. These were cyclized to 2,2-dimethyl-6,7-methylenedioxy-4-chromanone (**182**) and 2,2-dimethyl-5,6-methylenedioxy-4-chromanone (**187**) by means of a two phase system (hexane/10% aqueous sodium hydroxide) with nearly quantitative yield (Scheme 71).

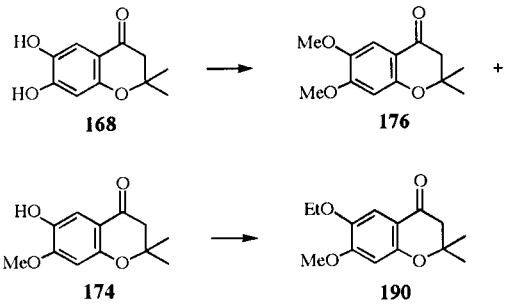
Banerji and Goomer [56,57] found that lithium enolate of 4,5-dimethoxy-2-hydroxyacetophenone (**188**) can be generated under mild conditions using lithium diisopropylamide in THF at -25°. The enolate was reacted with acetone (**12**) at -40° and the cross aldol condensation product (**189**, 86% yield) underwent facile cyclodehydration while refluxing in methanolic HCl (10 %) to give 6,7-dimethoxy-2,2-dimethyl-4-chromanone (**176**) in 90% yield (Scheme 72).

Scheme 72



7-Etoxy-6-methoxy-2,2-dimethyl-2*H*-chromene (precocene 3) has been known as the most powerful synthetic derivative of natural precocenes (see Chart 1). However, no satisfactory method was available to obtain precocene 3. To eliminate this difficulty Tímár and Jászberényi [65] elaborated a regioselective *O*-alkylation of 6,7-dihydroxy-2,2-dimethyl-4-chromanone (**168**). The reaction of **168** with methyl iodide furnished the 2,2-dimethyl-6-hydroxy-7-methoxy-4-chromanone (**174**) and 6,7-dimethoxy-2,2-dimethyl-4-chromanone (**176**) in 85% and 9% yields, respectively. Ethylation of compound **174** under the same conditions afforded the corresponding 2,2-dimethyl-6-ethoxy-7-methoxy-4-chromanone (**190**) in 85% yield. The flexibility of this approach has already been recognized and utilized for the synthesis of a large number of analogs of compound **190** by the use of different alkylating agents [65,69,79] (Scheme 73).

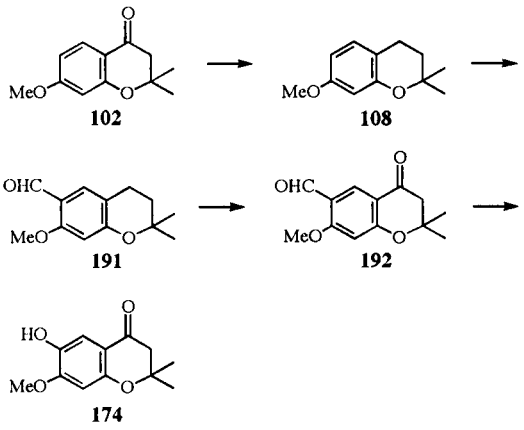
Scheme 73



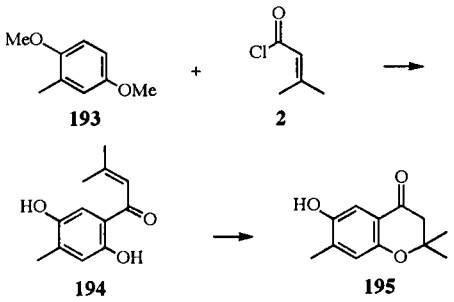
Kulkarni and Paradkar [80] followed a different strategy for the synthesis of 2,2-dimethyl-6-hydroxy-7-methoxy-4-chromanone (**174**) by introducing the hydroxy substitutent on the benzenoid part of the chromanone.The starting 2,2-dimethyl-7-methoxy-4-chromanone (**102**) was converted into 2,2-dimethyl-7-methoxychroman (**108**). Vilsmeier formylation of the chroman (**108**) led to the formation of 2,2-dimethyl-6-formyl-7-methoxychroman (**191**) which was then oxidized back to 2,2-dimethyl-6-formyl-7-methoxy-4-chromanone (**192**) by ceric ammonium nitrate. Further transformation of compound **192** using hydrogen peroxide and selenium dioxide in methylene dichloride furnished 2,2-dimethyl-6-hydroxy-7-methoxy-4-chromanone (**174**). Yields are missing for the whole synthetic sequence (Scheme 74).

In 1952 Cardani [81] reported the first preparation of 6-hydroxy-2,2,7-trimethyl-4-chromanone (**195**). The reaction of 1,4-dimethoxy-2-methylbenzene (**193**) with 3,3-dimethyl-acryloyl chloride (**2**) in the presence of aluminum chloride in benzene resulted in the formation of hydroxyketone **194** which was then separately cyclized in 2% aqueous sodium hydroxide to the compound **195**. No yield was reported (Scheme 75).

Scheme 74

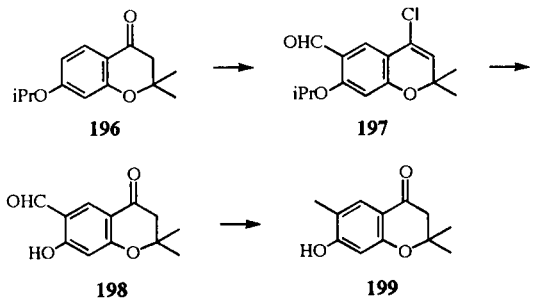


Scheme 75



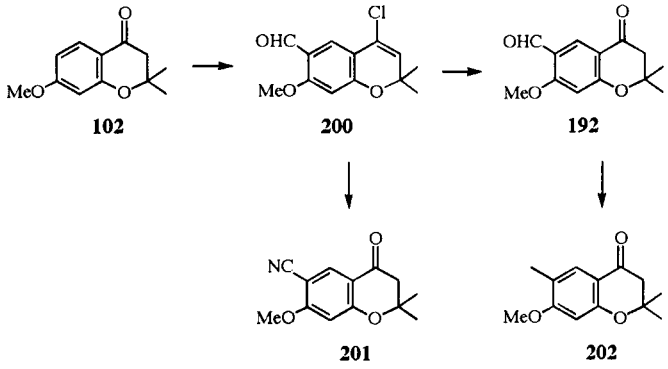
Eszenyi and Sebők [82] worked out a procedure for the synthesis of 7-hydroxy-2,2,6-trimethyl-4-chromanone (**199**), the regioisomer of compound **195** as a further development of the method published earlier by Eszenyi and Tímár [83]. Vilsmeier formylation of the 2,2-dimethyl-7-*iso*-propyloxy-4-chromanone (**196**) furnished 4-chloro-2,2-dimethyl-6-formyl-7-*iso*propyloxy-2*H*-chromene (**197**) in 94% yield. Treatment of compound **197** with 70% aqueous perchloric acid in nitromethane resulted in 2,2-dimethyl-6-formyl-7-hydroxy-4-chromanone (**198**, 78% yield). Catalytic hydrogenation of derivative **198** over palladium on activated carbon gave 7-hydroxy-2,2,6-trimethyl-4-chromanone (**199**) in 80% yield (Scheme 76). The synthesis of this chromanone (**199**) was also reported by Shinde and Usgaonkar [84].

Scheme 76



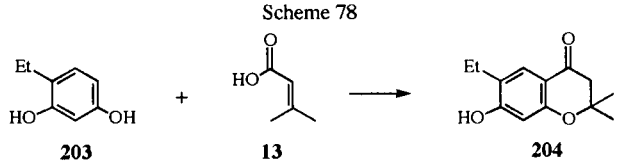
Eszenyi and Sebők [82] followed a similar approach to synthesize 6-cyano-2,2-dimethyl-7-methoxy-4-chromanone (**201**) and 7-methoxy-2,2,6-trimethyl-4-chromanone (**202**). Vilsmeier formylation of the 2,2-dimethyl-7-methoxy-4-chromanone (**102**) gave 4-chloro-2,2-dimethyl-6-formyl-7-methoxy-2*H*-chromene (**200**) in 78% yield. The latter compound was reacted with hydroxylamine in the presence of potassium carbonate in formic acid to give 6-cyano-2,2-dimethyl-7-methoxy-4-chromanone (**201**, 94% yield). Treatment of compound **200** with 70% aqueous perchloric acid in nitromethane at room temperature furnished 2,2-dimethyl-6-formyl-7-methoxy-4-chromanone **192** (60% yield). Catalytic hydrogenation of derivative **192** over palladium on activated carbon resulted in 7-methoxy-2,2,6-trimethyl-4-chromanone (**202**) in 70% yield (Scheme 77).

Scheme 77



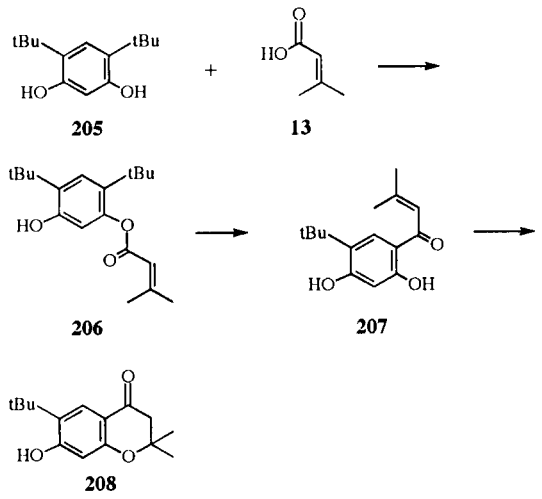
Steelink and Marshall [85] allowed to react 4-ethylresorcinol (**203**) and 3-methylbut-2-enoic acid (**13**) in polyphosphoric acid at 90° for 1 hour and prepared 2,2-dimethyl-6-ethyl-7-hydroxy-4-chromanone (**204**) in 35% yield. A considerable amount of base-insoluble tar formation was also observed. Camps *et al.* [86] performed the same reaction in methanesulfonic acid at 70° and isolated this 4-chromanone (**204**), however no yield was reported (Scheme 78).

Scheme 78



Sebők *et al.* [87] in the course of their research project in the field of precocene chemistry needed to synthesize a key intermediate, the 2,2-dimethyl-7-hydroxy-6-*tert*-butyl-4-chromanone (**208**). 2,6-Di-*tert*-butylresorcinol (**205**) was made to react with 3-methylbut-2-enoic acid (**13**) in the presence of zinc chloride in phosphorous oxychloride. The analysis of samples of the reaction mixture withdrawn at intervals during the reaction indicated the

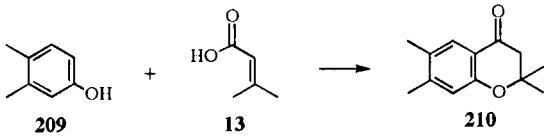
Scheme 79



sequence **206** →**207** →**208**. The structures of the intermediates **206** and **207** and the target product **208** were determined by nmr and ms methods [25,87]. Using this procedure 2,2-dimethyl-7-hydroxy-6-*tert*-butyl-4-chromanone (**208**) was prepared in 80% yield (Scheme 79).

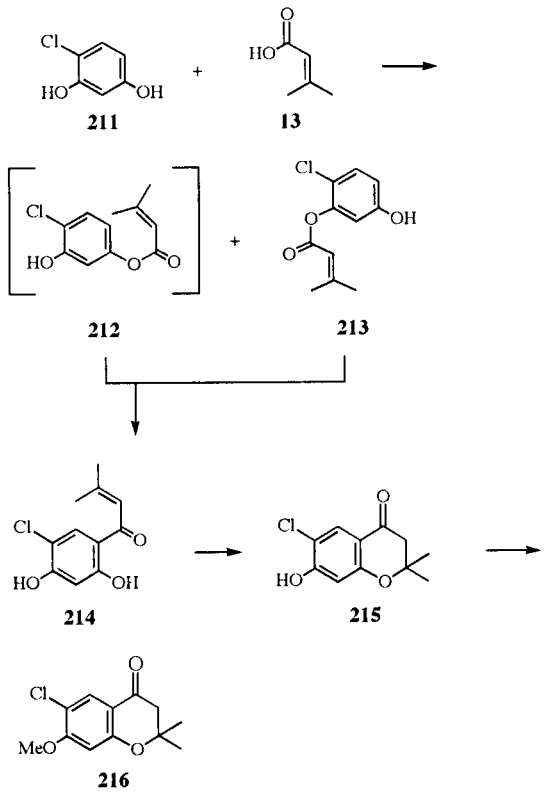
For structure-activity relationship studies there was a need to prepare 2,2,6,7-tetramethyl-4-chromanone (**210**). Sebők [88] allowed to react 3,4-dimethylphenol (**209**) with 3-methylbut-2-enoic acid (**13**) in the presence of zinc chloride in phosphorous oxychloride and the target compound **210** was obtained in 85% yield (Scheme 80).

Scheme 80



In 1985 Brooks *et al.* [89] gave an account on the synthesis of 71 precocene analogs. In the course of this work 6-chloro-2,2-dimethyl-7-hydroxy-4-chromanone (**215**) was prepared by the reaction of 4-chlororesorcinol (**211**) and 3-methylbut-2-enoic acid (**13**) in methanesulfonic acid at 70° and this 4-chromanone (**215**) was isolated in 62% yield. Later Sebők *et al.* [87] studied the same reaction in the presence of zinc chloride in phosphorous oxychloride (at room temperature for 10 hours) in detail. Tlc, gc and nmr investigations of samples of the reaction products withdrawn at intervals during the reaction, indicated the sequence **213**→**214**→**215**. It is noteworthy that the corresponding 4-chloro-3-hydroxyphenyl-3-methylbut-2-enoate (**212**) can also be obtained in an independent experiment. Thus, when 4-chlororesorcinol (**211**) was treated with 3,3-dimethylacryloyl chloride (**2**) in nitromethane at 25° for 30 minutes, evaporation and column chromatography gave **212** and **213** in a ratio of 1:1. The explanation of the finding that **212** was not isolated from the zinc

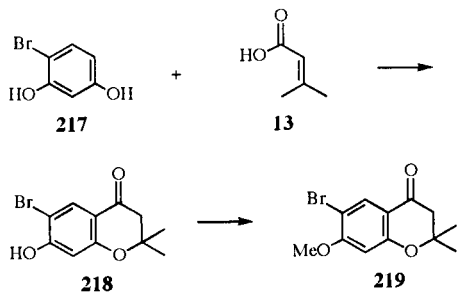
Scheme 81



chloride/phosphorous oxychloride system may be due to the fast rearrangement to the Fries product (**214**) obtained also from **213**. The 6-chloro-2,2-dimethyl-7-hydroxy-4-chromanone (**215**) was prepared in 79% yield and was methylated to the corresponding 6-chloro-2,2-dimethyl-7-methoxy-4-chromanone (**216**) almost quantitatively (Scheme 81).

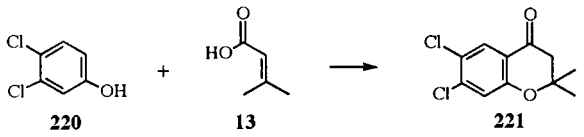
Steelink and Marshall [85] allowed to react 4-bromoresorcinol (**217**) and 3-methylbut-2-enoic acid (**13**) in polyphosphoric acid at 90° for 1 hour to obtain 6-bromo-2,2-dimethyl-7-hydroxy-4-chromanone (**218**). The latter compound was then methylated to obtain 6-bromo-2,2-dimethyl-7-methoxy-4-chromanone (**219**). Brooks *et al.* [89] also performed this reaction though no yield for this reaction can be found in their paper (Scheme 82).

Scheme 82



Kabbe and Widdig [23] reported the preparation of 6,7-dichloro-2,2-dimethyl-4-chromanone (**221**) in 63% yield by the reaction of 4,5-dichlo-2-hydroxyroacetophenone (**220**) with mesityl oxide (**11**) (Scheme 83).

Scheme 83

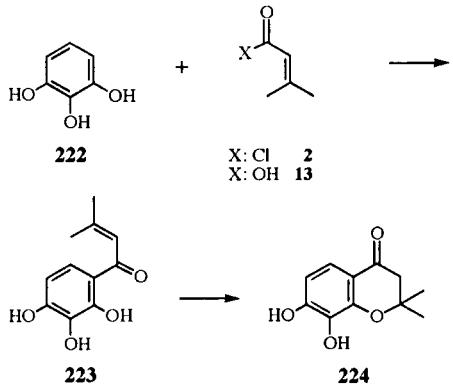


220 **13** **221**

9. 7,8-Disubstituted 2,2-Dimethyl-4-chromanones

In the course of the structure-activity relationship studies of natural precocenes [11] and their regioisomer analogs, increased attention was focused on the synthesis of 7,8- disubstituted 2,2-dimethyl-4-chromanones. These compounds are key intermediates for the preparation of the regioisomers of precocene 2 and precocene 3 as well as other analogs. There are several procedures for direct preparation and chemical transformation of 7,8-disubstituted 2,2-dimethyl-4-chromanones. The most frequently used method is the reaction of pyrogallol (**222**) with 3,3-dimethylacryloyl chloride (**2**) or 3-methylbut-2-enoic acid (**13**) in the presence of Lewis acids and different solvents under the conditions of the Friedel-Crafts reactions. In Table 9 details are given on the use of this type of reaction for the synthesis of 7,8-dihydroxy-2,2-dimethyl-4-chromanone (**224**) (Table 9, Scheme 84.)

Scheme 84



222 X: Cl **2** X: OH **13**

223 **224**

Table 9

Reported reactions for the synthesis of 7,8-dihydroxy-2,2-dimethyl-4-chromanone (**224**)

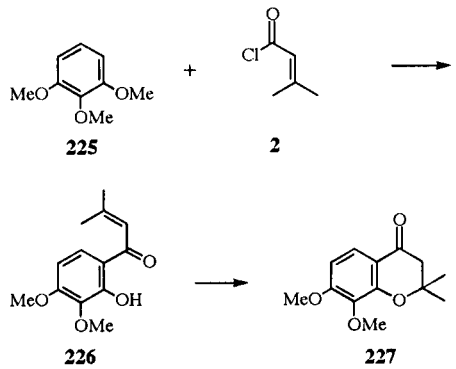
X[a]	Reagent	Conditions	Yield (%)	Reference
Cl	$AlCl_3/C_6H_5$-NO_2	25°, 5 days	24	[90]
HO	$ZnCl_2$(fused)/$POCl_3$	25°, 24 hours	no data	[51]
HO	$AlCl_3/POCl_3$	25°, 5 hours	30	[53]
HO	Polyphosphoric acid	40°, 5 hours	14	[73]
HO	CH_3SO_3H/P_2O_5	70°, 1 hour	no data	[86]
HO	$ZnCl_2$(unfused)/$POCl_3$	50°, 5 hours	80	[65]

[a] For X, see Scheme 84.

Data in Table 9 reveal that an efficient method was found by Tímár and Jászberényi [65] for the preparation of 7,8-dihydroxy-2,2-dimethyl-4-chromanone (**224**). Thus, pyrogallol (**222**) was allowed to react with 3-methylbut-2-enoic acid (**13**) in the presence of fused zinc chloride in phosphorous oxychloride at 25° for 2 hours. The intermediate *o*-hydroxyketone **223** was isolated in 80% yield and was subsequently cyclized in 5% aqueous sodium hydroxide (at 25° for 1 hour) to 7,8-dihydroxy-2,2-dimethyl-4-chromanone (**224**) near quantitatively. Alternatively, pyrogallol (**222**) can be reacted with 3-methylbut-2-enoic acid (**13**) in the presence of unfused zinc chloride in phosphorous oxychloride at 50° for 5 hours to obtain compound **224** in 80% yield (see also Scheme 84).

Nakayama *et al.* [91] reported that the reaction of 1,2,3-trimethoxybenzene (**225**) with 3,3-dimethylacryloyl chloride (**2**) in the presence of anhydrous aluminum chloride for 52 hours furnished 7,8-dimethoxy-2,2-dimethyl-4-chromanone (**227**). When the above reaction was allowed to proceed for a relatively short period of time, the unsaturated ketone **226** was obtained along with a small amount of **227**. Compound **226** was easily converted into **227** with hydrochloric acid in acetic acid (Scheme 85).

Scheme 85



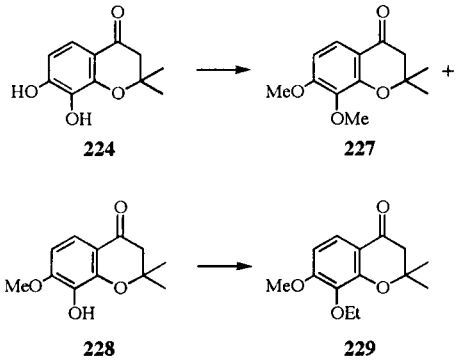
225 **2**

226 **227**

In order to obtain regioisomers of precocene 2 and precocene 3 and other analogs Tímár and Jászberényi [65] investigated the possibility of a regioselective *O*-alkylation of 7,8-dihydroxy-2,2-dimethyl-4-chromanone (**224**). It was found that the reaction of this substance (**224**) with methyl iodide furnished the 2,2-dimethyl-8-hydroxy-7-methoxy-4-chromanone (**228**) and 7,8-dimethoxy-2,2-dimethyl-4-chromanone (**227**) in 64% and 29% yields, respectively. Ethylation of compound **228** under the same conditions afforded the corresponding 2,2-dimethyl-8-ethoxy-7-methoxy-4-chromanone (**229**) in 86% yield. The flexibility of this approach has already been utilized for the synthesis a large number of analogs of compound **229** by the use of different alkylating agents [65,69] (Scheme 86).

Tímár *et al.* [76] recently found a procedure for the preparation of compounds **230** and **231**. The reaction of 7,8-dihydroxy-2,2-dimethyl-4-chromanone (**224**) with dibromomethane or 1,2-dibromoethane in the presence of potassium carbonate in *N,N*-dimethylformamide at 80°

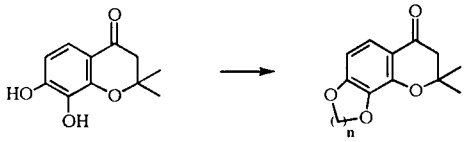
Scheme 86



224 227 228 229

resulted in the formation of 2,2-dimethyl-7,8-methylenedioxy-4-chromanone (**230**) or of 2,2-dimethyl-7,8-ethylenedioxy-4-chromanone (**231**) in 56% and 74% yields, respectively, (Scheme 87).

Scheme 87



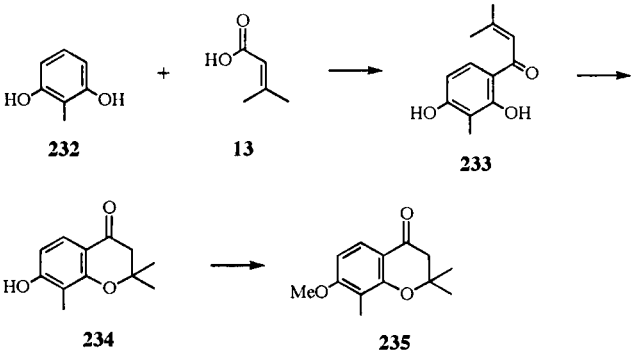
224 n:1 **230** n:2 **231**

The synthesis of 7-hydroxy-2,2,8-trimethyl-4-chromanone (**234**) was performed directly starting from 2-methylresorcinol (**232**) and 3-methylbut-2-enoic acid (**13**) in the presence of Lewis acids in phosphorus oxychloride or in methanesulfonic acid. Methylation of 7-hydroxy-2,2,8-trimethyl-4-chromanone (**234**) afforded 7-methoxy-2,2,8-trimethyl-4-chromanone (**235**) in excellent yield. Numerous other *O*-alkylated derivatives of **234** were also prepared [93] (Scheme 88). Table 10 contains detailed information on these reactions.

10. Trisubstituted 2,2-Dimethyl-4-chromanones

In 1959 Huls and Brunelle [5] published that the reaction of 1,2,3,5-tetramethoxy-benzene (**236**) and 3,3-

Scheme 88



232 13 233 234 235

Table 10

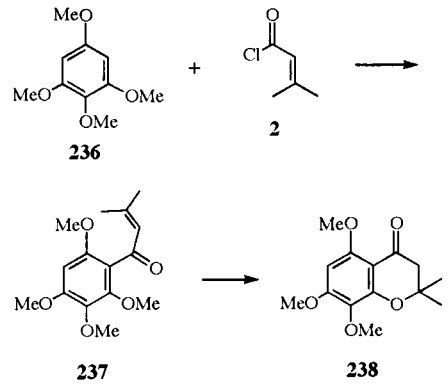
Reported reactions for the synthesis of 7-hydroxy-2,2,8-trimethyl-4-chromanone (**234**)

Reagent	Conditions	Product and yield (%)	Reference
$ZnCl_2$(fused)/$POCl_3$	25°, 12 hours	**234** (63)	[92]
CH_3SO_3H/P_2O_5	70°, 1 hour	**234** (no data)	[86]
$ZnCl_2$(fused)/$POCl_3$	25°, 1 hour	**233** (74)[a]	[93]
$ZnCl_2$(unfused)/$POCl_3$	50°, 3 hours	**234** (78)	[93]

[a] **233** is cyclized in alkali into **234** almost quantitatively.

dimethylacryloyl chloride (**2**) in the presence of anhydrous aluminum chloride in ether afforded the tetramethoxyacrylophenone **237**. However, when a mixture of ether and tetrachloroethane was used as the solvent, a 60% yield of 2,2-dimethyl-5,7,8-trimethoxy-4-chromanone (**238**) was isolated together with 12% of the uncyclized condensation product **237** (Scheme 89). It would appear that the formation of 2,2-dimethyl-5,6,7-trimethoxy-4-chromanone (**240**, see also Scheme 90) in the cyclization was equally possible. The structure of product **238** was confirmed as 5,7,8-trimethoxy compound by the use of ^{14}C isotopic labeling [6].

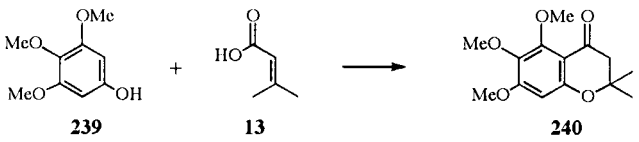
Scheme 89



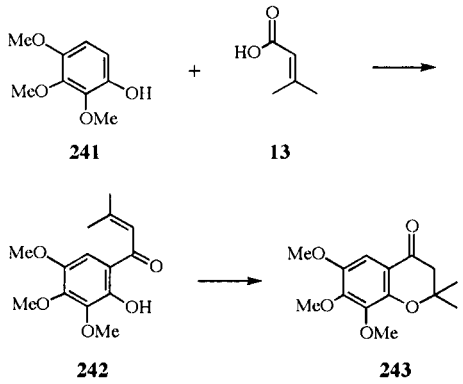
236 2 237 238

For structure-activity relationship studies of precocenes there was a need to prepare 2,2-dimethyl-5,6,7-trimethoxy-4-chromanone (**240**) and 2,2-dimethyl-6,7,8-trimethoxy-4-chromanone (**243**). Tímár [94], as an extension of the method [65], allowed to react 3,4,5-trimethoxyphenol (**239**) and 2,3,4-trimethoxyphenol (**241**) with 3-methylbut-2-enoic acid (**13**) in the presence of zinc chloride in phosphorous oxychloride and the target compounds **240** and **243** were obtained in 82% and 85% yields, respectively. In the case of the reaction of 2,3,4-trimethoxyphenol (**241**) with 3-methylbut-2-enoic acid (**13**) the unsaturated ketone **242** can also be isolated and subsequently cyclized in alkali into 4-chromanone (**243**) near quantitatively (Schemes 90 and 91).

Scheme 90

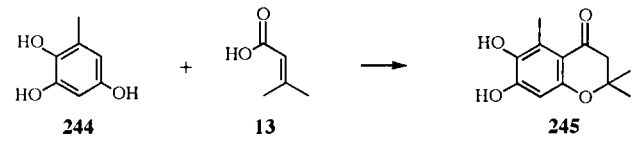


Scheme 91



Büchi and Williard [95] in the course of their work on total synthesis of *Mollicellin A* allowed to react 1-methyl-2,3,5-trihydroxybenzene (**244**) with 3-methylbut-2-enoic acid (**13**) in the presence of fused zinc chloride in phosphorous oxychloride. 6,7-Dihydroxy-2,2,5-trimethyl-4-chromanone (**245**) was obtained in 66% yield (Scheme 92).

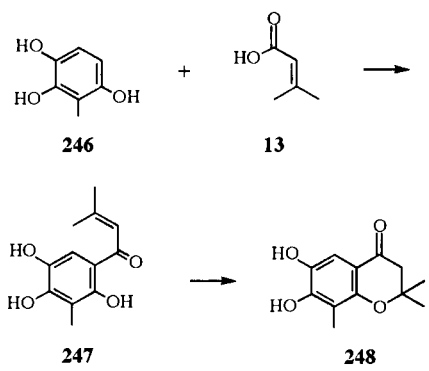
Scheme 92



Later Tímár *et al.* [96] reinvestigated and extended this reaction. Phenols **244** and **246** were allowed to react with 3-methylbut-2-enoic acid (**13**) in the presence of unfused zinc chloride in phosphorous oxychloride at 50° for 5 hours. 6,7-Dihydroxy-2,2,5-trimethyl-4-chromanone (**245**) as well as 6,7-dihydroxy-2,2,8-trimethyl-4-chromanone (**248**) were isolated in 85% and 80% yields, respectively. In the case of the reaction of 1-methyl-2,3,6-trihydroxybenzene (**246**) with 3-methylbut-2-enoic acid (**13**) in the presence of fused zinc chloride in phosphorous oxychloride the unsaturated ketone **247** was isolated in 80% yield, which was subsequently cyclized in sodium hydroxide solution near quantitatively to 6,7-dihydroxy-2,2,8-trimethyl-4-chromanone (**248**) (Schemes 92 and 93).

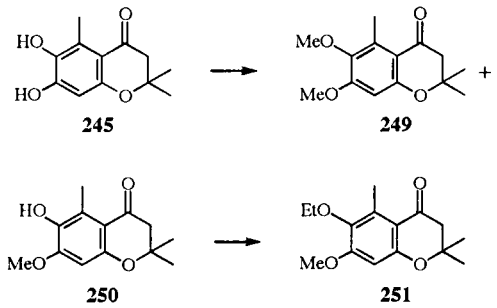
The possibility of a regioselective *O*-alkylation of 6,7-dihydroxy-2,2,5-trimethyl-4-chromanone (**245**) and 6,7-dihydroxy-2,2,8-trimethyl-4-chromanone (**248**) has also

Scheme 93

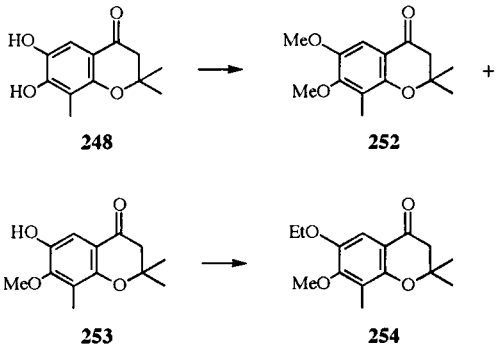


been investigated [96]. It was found that the reaction of these substances (**245** and **248**) with methyl iodide furnished the corresponding 6,7-dimethoxy-2,2,5-trimethyl-4-chromanone (**249**) and 6-hydroxy-7-methoxy-2,2,5-trimethyl-4-chromanone (**250**) as well as 6,7-dimethoxy-2,2,8-trimethyl-4-chromanone (**252**) and 6-hydroxy-7-methoxy-2,2,8-trimethyl-4-chromanone (**253**). Ethylation of compounds **250** and **253** under the same conditions afforded the corresponding 6-ethoxy-7-methoxy-2,2,5-trimethyl-4-chromanone (**251**) and 6-ethoxy-7-methoxy-2,2,8-trimethyl-4-chromanone (**254**). These high yielding reactions made possible the synthesis of a large number of precocene derivatives for structure-activity relationship studies [96] (Schemes 94 and 95).

Scheme 94

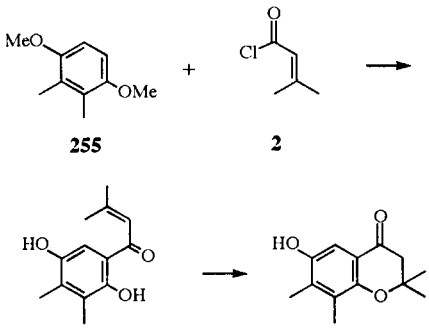


Scheme 95



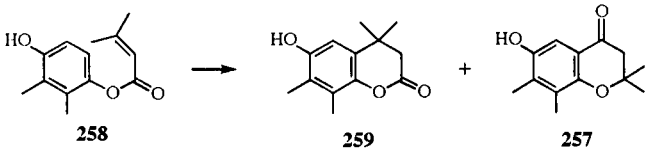
Cardani [81] reported that the reaction 1,4-dimethoxy-2,3-dimethylbenzene (**255**) with 3,3-dimethylacryloyl chloride (**2**) and aluminum chloride in carbon disulfide gave the intermediate acrylophenone (**256**) which was cyclized by dissolving it in dilute sodium hydroxide followed by acidification with hydrochloric acid to give 6-hydroxy-2,2,7,8-tetramethyl-4-chromanone (**257**). No yield was reported for these transformations (Scheme 96).

Scheme 96



King and Cohen [97] also prepared 6-hydroxy-2,2,7,8-tetramethyl-4-chromanone (**257**) in 12% yield together with the 3,4-dihydro-6-hydroxy-4,4,7,8-tetramethylcoumarin (**259**, 45% yield) while investigating the Fries rearrangement of phenolic ester **258** in the presence of sulfuric acid in benzene (Scheme 97).

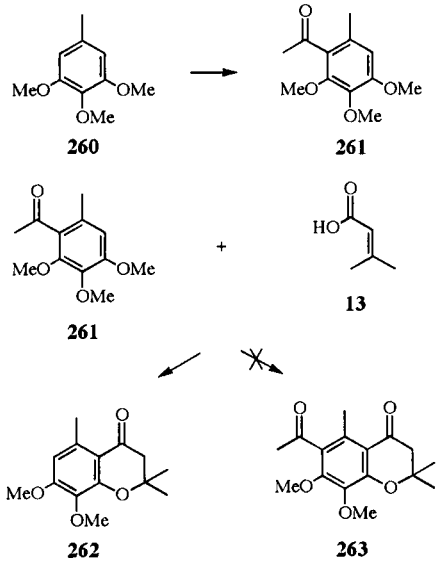
Scheme 97



Sebők [98] observed an interesting transformation when studying the reaction of 6-methyl-2,3,4-trimethoxyacetophenone (**261**), obtained by the acetylation of 3,4,5-trimethoxytoluene (**260**), with 3-methylbut-2-enoic acid (**13**) in the presence of zinc chloride in phosphorous oxychloride. Instead of the expected 6-acetyl-7,8-dimethoxy-2,2,5-trimethyl-4-chromanone (**263**), the 7,8-dimethoxy-2,2,5-trimethyl-4-chromanone (**262**) was obtained in 70% yield (Scheme 98).

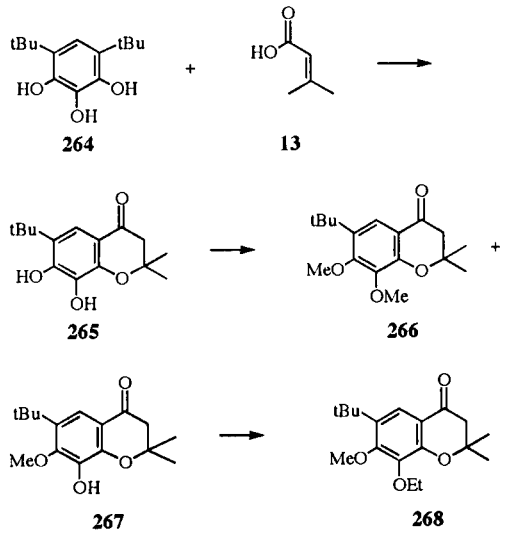
Sebők *et al.* [99] investigated the reaction of 4,6-*bis*-*tert*-butyl-pyrogallol (**264**) with 3-methylbut-2-enoic acid (**13**) in the presence of zinc chloride in phosphorous oxychloride and obtained 6-*tert*-butyl-7,8-dihydroxy-2,2-dimethyl-4-chromanone (**265**) in 70% yield. The regioselective *O*-alkylation of this compound (**265**) was also performed with methyl iodide. 6-*Tert*-butyl-2,2-dimethyl-8-hydroxy-7-

Scheme 98



methoxy-4-chromanone (**267**) and 6-*tert*-butyl-2,2-dimethyl-7,8-dimethoxy-4-chromanone (**266**) were obtained in 13% and 77% yields, respectively. Ethylation of compound **267** under the same conditions afforded the corresponding 6-*tert*-butyl-2,2-dimethyl-8-ethoxy-7-methoxy-4-chromanone (**268**) in 79% yield (Scheme 99).

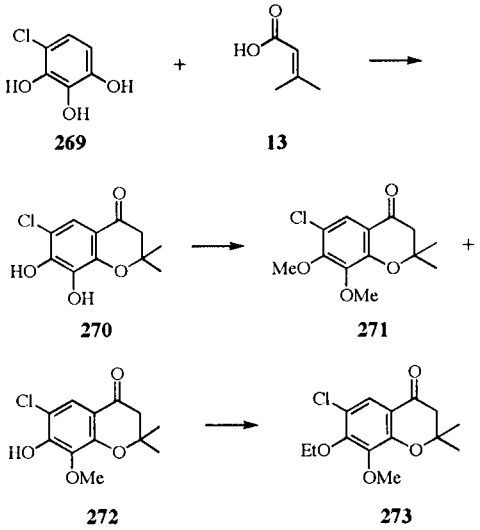
Scheme 99



Sebők *et al.* [99] also studied the reaction of 4-chloropyrogallol (**269**) with 3-methylbut-2-enoic acid (**13**) in the presence of zinc chloride in phosphorous oxychloride and 6-chloro-7,8-dihydroxy-2,2-dimethyl-4-chromanone (**270**) was obtained in 72% yield. The regioselective *O*-alkylation of this compound (**270**) was performed with methyl iodide. It is worthy to note, however, that the regioselectivity was

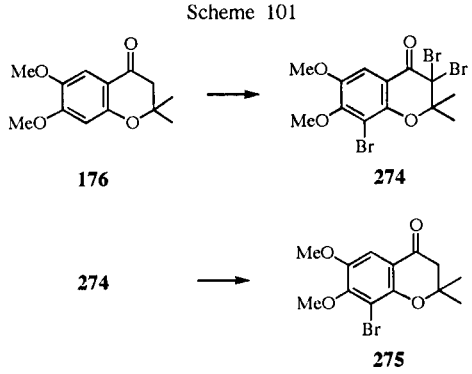
opposite to that observed in the 6-*tert*-butyl series (see Scheme 99) and 6-chloro-2,2-dimethyl-7-hydroxy-8-methoxy-4-chromanone (**272**) and 6-chloro-2,2-dimethyl-7,8-dimethoxy-4-chromanone (**271**) were obtained in 72% and 23% yields, respectively. Ethylation of compound **272** under the same conditions afforded the corresponding 6-chloro-2,2-dimethyl-7-ethoxy-8-methoxy-4-chromanone (**273**) in 90% yield (Scheme 100).

Scheme 100

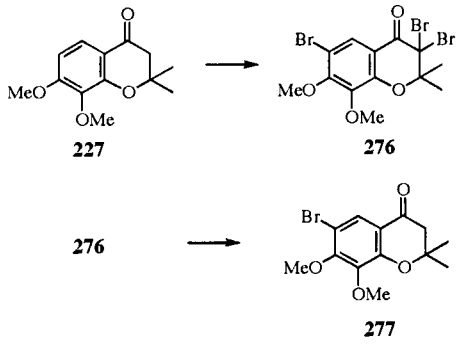


Tímár [100] adapted the method elaborated by Brown *et al.* [101] and prepared 8-bromo-2,2-dimethyl-6,7-dimethoxy-4-chromanone (**275**) as well as 6-bromo-2,2-dimethyl-7,8-dimethoxy-4-chromanone (**277**). The reaction of 6,7-dimethoxy-2,2-dimethyl-4-chromanone (**176**) or 7,8-dimethoxy-2,2-dimethyl-4-chromanone (**227**) with bromine in carbon tetrachloride furnished 6,7-dimethoxy-2,2-dimethyl-3,3,8-tribromo-4-chromanone (**274**) or 7,8-dimethoxy-2,2-dimethyl-3,3,6-tribromo-4-chromanone (**276**) in 53% and 85% yields, respectively. Treament of the latter compounds with an excess of zinc powder afforded the target chromanones **275** or **277** in 80% and 64% yields, respectively, (Schemes 101 and 102).

Scheme 101

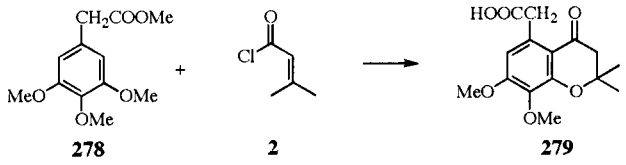


Scheme 102



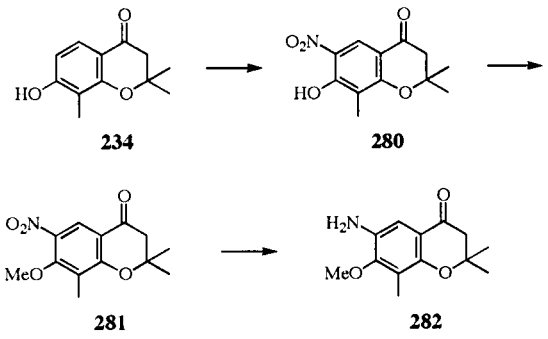
As an intermediate in the total synthesis of the mold metabolite, fuscin, 7,8-dimethoxy-2,2-dimethyl-4-chromanone-5-acetic acid (**279**) was prepared by Barton and Hendrikson [102] from methyl 3,4,5-trimethoxyphenyl acetate (**278**) and 3,3-dimethylacryloyl chloride (**2**) in the presence of aluminum trichloride (Scheme 103).

Scheme 103



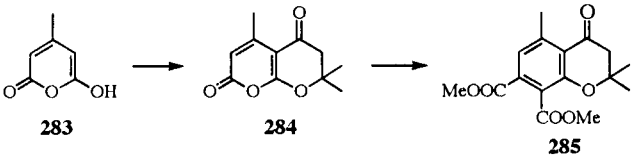
Lahey and Stick [92] in the course of their work for compounds expected to have anti-tumor activity performed the nitration of 7-hydroxy-2,2,8-trimethyl-4-chromanone (**234**) with nitric acid in ethanol and 7-hydroxy-6-nitro-2,2,8-trimethyl-4-chromanone (**280**) was obtained in 83% yield. The latter was smoothly methylated to give 7-methoxy-6-nitro-2,2,8-trimethyl-4-chromanone (**281**, 80% yield) which was subsequently hydrogenated over palladium on charcoal to obtain 6-amino-7-methoxy-2,2,8-trimethyl-4-chromanone (**282**) in excellent (95%) yield (Scheme 104).

Scheme 104



Burke *et al.* [103] discovered a novel transformation of pyrone to 4-chromanone. The two-step synthetic access to 4-chromanones was presaged by the observation that 4-methyl-6-hydroxy-2-pyrone (**283**) when treated with a catalytic amount of 4-(dimethylamino)-pyridine undergoes an amine catalyzed decarboxylative dimerization and is transformed to coumarochromanone (**284**) in 42% yield. It was supposed that the 2-pyrone moiety in prechromanone **284** could be reacted with an acetylenic dienophile to provide the desired 4-chromanones directly via a decarboxylative Diels-Alder reaction. Indeed, this intention was easily put to practice by heating prechromanone **284** in decalin solution with dimethyl acetylenedicarboxylate in a sealed tube to provide the 4-chromanone **285** in 76% yield (Scheme 105).

Scheme 105

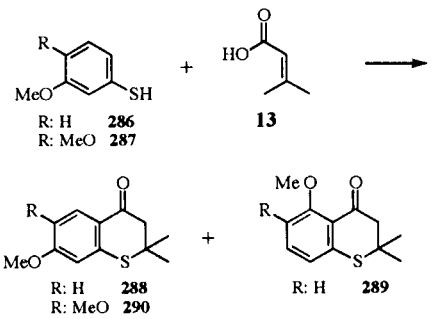


283 **284** **285**

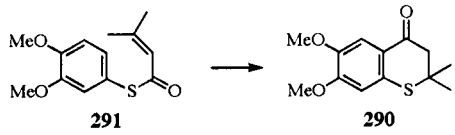
11. Miscellaneous

In 1983 Camps *et al.* [104] reported the first synthesis of precocene analogs with a sulfur atom replacing the pyranyl oxygen atom. The reaction of 3-methoxythiophenol (**286**) and 3-methylbut-2-enoic acid (**13**) in the presence of methanesulfonic acid at 70° for 30 minutes afforded a 6:1 mixture of thiochroman-4-ones **288** and **289** in 76% overall yield. These compounds were separated by flash column chromatography. On the other hand, direct reaction of 3,4-dimethoxythiophenol (**287**) and 3-methylbut-2-enoic acid (**13**) under the above conditions gave a poor yield (*ca.* 20%) of the desired thiochroman-4-one **290**, probably due to the instability of the starting thiophenol **287** which led to the formation of side products and also to extensive resinification. To overcome these drawbacks the Fries rearrangement of the thioester **291** was performed. Thus, treatment of **291** in methanesulfonic acid at 70° for 30 minutes afforded the thiochroman-4-one **290** in 60% yield (Schemes 106 and 107).

Scheme 106



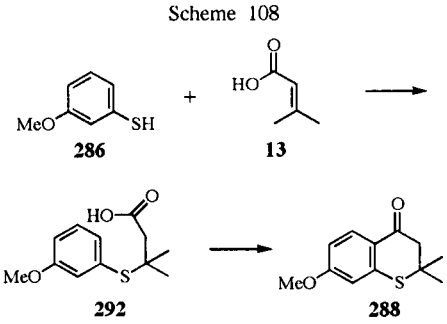
Scheme 107



291 **290**

Tércio *et al.* [105] published an alternative procedure utilizing the Michael addition of 3-methoxythiophenol (**286**) to 3-methylbut-2-enoic acid (**13**) in the presence of piperidine at 103-107° and 3-methoxyphenylthio-3-methylbutanoic acid (**292**) was prepared in 89% yield. Cyclization of compound **292** was accomplished in polyphosphoric acid at 50° to provide 2,2-dimethyl-7-methoxythiochroman-4-one (**288**) in 72% yield. In the course of their work a series of thiochroman-4-ones were also obtained (Scheme 108).

Scheme 108

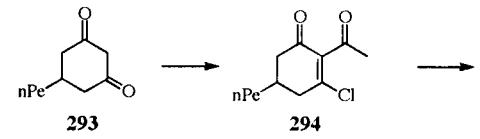


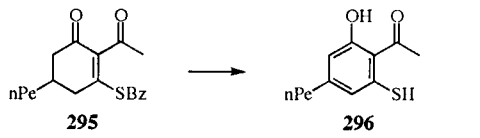
286 **13** **292** **288**

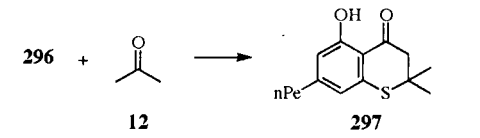
Arnoldi *et al.* [106] in the course of the study of the structure-activity relationship of the benzopyran-type potassium channel openers worked out a method for the preparation of thiochroman-4-one **297**. Thus, the acetylation of the enolate of 5-pentyl-1,3-cyclohexadienone (**293**), followed by Fries rearrangement with aluminum chloride and treatment with oxalyl chloride, gave chloro ketone **294**. Replacement of the halogen with a benzyl mercapto group afforded sulfide **295**, which was dehydrogenated with *N*-bromosuccinimide and triethylamine. Smooth debenzylation with aluminum tribromide gave thiol **296** which by reaction with acetone (**12**) and pyrrolidine afforded regiospecifically the expected thiochroman-4-one **297** in overall yield of 13% from **293** (Scheme 109).

Sebők *et al.* [59] reported on the first synthesis of 7-alkylthio-2,2-dimethyl-2*H*-chromenes, the thio analogs of natural and synthetic precocenes. In the course of this work 7-(*N*,*N*-dimethylcarbamoylthio)-2,2-dimethyl-6-methoxy-4-chromanone (**298**) was prepared and alkaline hydrolysis of this compound furnished 2,2-dimethyl-7-mercapto-6-methoxy-4-chromanone (**299**) which was then methylated to the corresponding 6-methoxy-7-methylthio-2,2-dimethyl-4-chromanone (**300**) (Scheme 110).

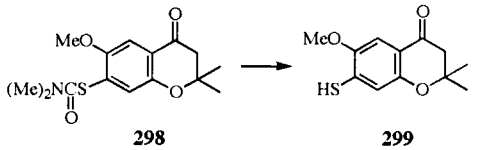
Scheme 109

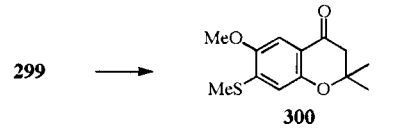






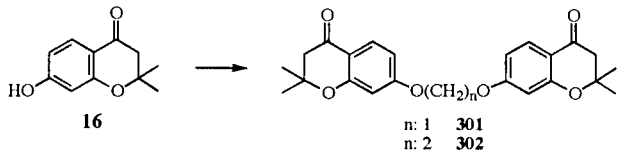
Scheme 110





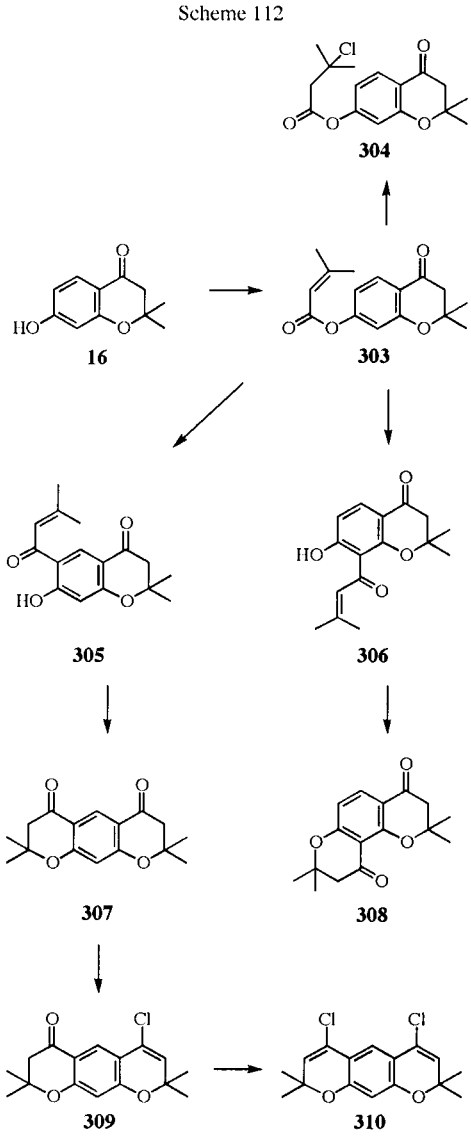
Tímár *et al.* [107] recently reported the synthesis of *bis*-(2,2-dimethyl-4-chromanone-7-oxy)-alkanes **301** and **302**. The synthesis is based on the reaction of 2,2-dimethyl-7-hydroxy-4-chromanone (**16**) with dibromomethane or 1,2-dibromoethane. The target compounds **301** and **302** were isolated in 82% and 67% yields, respectively. In the course of this work a series of *bis*-(2,2-dimethyl-4-chromanone-7-oxy)-alkane derivatives were also obtained [107] (Scheme 111).

Scheme 111



Eszenyi *et al.* [108] quite recently published a paper on the reaction of 2,2-dimethyl-7-hydroxy-4-chromanone (**16**) and 3-methylbut-2-enoic acid (**13**) in zinc chloride/phosphorus oxychloride. In the reaction 2,2-dimethyl-7-(3-methyl-2-butenoyloxy)-4-chromanone (**303**) was formed which was then transformed partly *via* hydrochloric acid addition to the saturated ester **304** and partly by *ortho/ortho'*-Fries rearrangement to the unsaturated ketones **305** and **306**. Fries rearrangement of **303** took place regioselectively and the ratio of **305** to **306** was 10:1. These ketones were then cyclized to the corresponding dipyrandiones **307** and **308**. As the reaction proceeded further, the formation of chlorodipyran **309** and dichlorodipyran **310** derivatives was observed (Scheme 112).

Scheme 112



In summary, in our present review most methods worked out for variously substituted 2,2-dimethyl-4-chromanones are compiled. Literature data were organized and discussed according to the substitution pattern of the aromatic ring. Yields were given in most cases to help to compare the utility of different synthetic procedures.

REFERENCES AND NOTES

[1] K.v. Auwers and E. Lämmerhirt, *Liebigs Ann. Chem.*, **421**, 1 (1920).

[2] A. Quilico, C. Cardani and L. Panizzi, *Gazz. Chim. Ital.*, **80**, 325 (1950).

[3] R. Huls, *Bull. Soc. Chim. Belg.*, **66**, 409 (1957).

[4] R. Huls, *Bull. Soc. Chim. Belg.*, **67**, 22 (1958).

[5] R. Huls and S. Brunelle, *Bull. Soc. Chim. Belg.*, **68**, 325 (1959).

[6] R. Warin, M. Renson and R. Huls, *Bull. Soc. Chim. Belg.*, **69**, 593 (1960).

[7] A. R. Alertsen, *Acta Polytech. Scand., Chem. Met. Ser.*, **13**, 1 (1961).

[8] R. Livingstone, D. Miller and S. Morris, *J. Chem. Soc.*, 3094 (1960).

[9] B. D. Tilak and Z. Muljiani, *Tetrahedron*, **24**, 949 (1968).

[10] N. I. Bruckner and N. L. Bauld, *J. Org. Chem.*, **37**, 2359 (1972).

[11] W. S. Bowers, T. Ohta, J. S. Cleere and P. A. Marsella, *Science*, **193**, 542 (1976).

[12] V. A. Ashwood, R. E. Buckingham, F. Cassidy, J. M. Evans, E. A. Faruk, T. C. Hamilton, D. J. Nash, G. Stemp and K. Willcocks, *J. Med. Chem.*, **29**, 2194 (1986).

[13] R. P. Hof, U. Quast, N.S. Cook and S. Blarel, *Circ. Res.*, **62**, 679 (1988).

[14] Anon., *Drugs of the Future*, **19**, 279 (1994).

[15] G. P. Ellis, Chromenes, Chromanones and Chromones, J. Wiley and Sons, New York, 1977, pp. 207-428.

[16] S. Skraup and E. Beng, *Ber.*, **60**, 942 (1927).

[17] S. Skraup and E. Beng, *Ber.*, **61**, 1665 (1928).

[18] K.v. Auwers and W. Mauss, *Ber.*, **61**, 416 and 2545 (1928).

[19] W. Baker, A. J. Floyd, J. F. W. McOmie, G. Pope, A.S. Weaving and J. H. Wild, *J. Chem. Soc.*, 2010 (1956).

[20] J. Cologne and R. Chambard, *Bull. Soc. Chim. France*, **20**, 573 (1953).

[21] S. Wawzonek, R. C. Nagler and L. J. Carlson, *J. Am. Chem. Soc.*, **76**, 1080 (1954).

[22] R. Livingstone, *J. Chem. Soc.*, 76 (1962).

[23] V. H-J. Kabbe and A. Widdig, *Angew. Chem.*, **94**, 254 (1982).

[24] P. Sebők, J. Jekő, T. Tímár and J. Cs. Jászberényi, *Tetrahedron Letters*, **33**, 2791 (1992).

[25] P. Sebők, J. Jekő, T. Tímár and J. Cs. Jászberényi, *Heterocycles*, **38**, 2099 (1994).

[26] P. Sebők, T. Tímár, T. Eszenyi and T. Patonay, *J. Org. Chem.*, **59**, 6318 (1994).

[27] J. D. Hepworth, T.K. Jones and R. Livingstone, *Tetrahedron*, **37**, 2613 (1981).

[28] J. Nickl, *Chem. Ber.*, **92**, 1989 (1959).

[29] H. Fukami and M. Nakajima, *Agr. Biol. Chem.*, **25**, 247 (1961).

[30] A. N. Starratt and A. Stoessl, *Can. J. Chem.*, **55**, 2360 (1977).

[31] A. Arnoldi, *Synthesis*, 856 (1984).

[32] F. Camps, J. Coll, O. Colomina and A. Messeguer, *J. Heterocyclic Chem.*, **22**, 363 (1985).

[33] M. A. Miranda, J. Primo and R. Tormos, *Heterocycles*, **27**, 673 (1988).

[34] F. Shawcross and H. Sard, *J. Heterocyclic Chem.*, **32**, 1393 (1995).

[35] M. Simonetta and C. Cardani, *Gazz. Chim. Ital.*, **80**, 750 (1950).

[36] T. Ohta and W. S. Bowers, *Chem. Pharm. Bull.*, **25**, 2788 (1977).

[37] J. Primo and R. Tormos, *Heterocycles*, **19**, 1819 (1982).

[38] A. Banerji and G. P. Kalena, *Synth. Commun.*, **19**, 159 (1989).

[39] G. Ariamala and K. K. Balasubramanian, *Tetrahedron Letters*, **29**, 3487 (1988).

[40] G. Ariamala and K. K. Balasubramanian, *Tetrahedron*, **45**, 309 (1989).

[41] G. Ariamala and K. K. Balasubramanian, *J. Chem. Soc. Chem. Commun.*, 34 (1988).

[42] J. D. Hepworth and R. Livingstone, *J. Chem. Soc.*, 2013 (1966).

[43] C. Cardani, *Gazz. Chim. Ital.*, **83**, 62 (1953).

[44] J. E. Baldwin, R. C. Thomas, L. I. Kruse and L. Silberman, *J. Org. Chem.*, **42**, 3846 (1977).

[45] D.R. Buckle, J. R. S. Arch, A. E. Fenwick, C. S. V. Houge-Frydrych, I. L. Pinto, D.G. Smith, S.G. Taylor and J. M. Tedder, *J. Med. Chem.*, **33**, 3028 (1990).

[46] F. Bohlmann and E. Vorwerk, *Chem. Ber.*, **114**, 147 (1981).

[47] A. J. Birch, M. Maung and A. Pelter, *Aust. J. Chem.*, **22**, 1923 (1969).

[48] W. Bridge, A. J. Crocker, T. Cubin and A. Robertson, *J. Chem. Soc.*, 1530 (1937).

[49] M. Miyano and M. Matsui, *Bull. Chem. Soc. Japan*, **31**, 397 (1958).

[50] M. Nakajima, H. Fukami, K. Konishi and J. Oda, *Agr.Biol. Chem.*, **27**, 700 (1963).

[51] P. R. Iyer and G. D. Shah, *Ind. J. Chem.*, **6**, 227 (1968).

[52] F. Camps, J. Coll, A. Messeguer, M. A. Pericas, S. Ricart, W.S. Bowers and D.M. Soderlund, *Synthesis*, 725 (1980).

[53] D. Sowmithran and K. J. R. Prasad, *Synthesis*, 545 (1985).

[54] T. Matsui, *Kogakubu Kenkyu Hokoku*, **30**, 141 (1984); *Chem. Abstr.*, **102**, 95441f (1985).

[55] T. Tímár, S. Hosztafi, J. Cs. Jászberényi, K. E. Kövér and Gy. Batta, *Acta Chim. Hung.*, **125**, 303 (1988).

[56] A. Banerji and N. C. Goomer, *Tetrahedron Letters*, **20**, 3685 (1979).

[57] A. Banerji and N. C. Goomer, *Ind. J. Chem.*, **20B**, 144 (1981).

[58] M.N. Kanvinde, S. A. Kulkarni and M.V. Paradkar, *Synth. Commun.*, **20**, 3259 (1990).

[59] P. Sebők, T. Tímár, T. Eszenyi and T. Patonay, *Synthesis*, 837 (1994).

[60] A. Lévai and T. Tímár, *Pharmazie*, **45**, 660 (1990).

[61] A. Lévai and T. Tímár, *Pharmazie*, **45**, 728 (1990).

[62] A. Lévai, G. Tóth, Á. Szőllősy and T. Tímár, *Monatsh. Chem.*, **121**, 403 (1990).

[63] W. Bridge, R. G. Heyes and A. Robertson, *J. Chem. Soc.*, 279 (1937).

[64] G. H. Stout and K. L. Stevens, *J. Org. Chem.*, **29**, 3604 (1964).

[65] T. Tímár and J. Cs. Jászberényi, *J. Heterocyclic Chem.*, **25**, 871 (1988).

[66] H. B. Bhat and K. Venkataraman, *Tetrahedron*, **19**, 77 (1963).

[67] A. Jefferson, I. Moore and F. Scheinmann, *J. Chem. Soc.(C)*, 151 (1967).

[68] S. W. George and A. Robertson, *J. Chem. Soc.*, 1535 (1937).

[69] T. Tímár, J. Cs. Jászberényi and S. Hosztafi, *Acta Chim. Hung.*, **126**, 487 (1989).

[70] T. Tímár, J. Cs. Jászberényi and S. Hosztafi, *Acta Chim. Hung.*, **125**, 457 (1988).

[71] K. E. Fahrenholtz, M. Lurie and R. W. Kierstead, *J. Am. Chem. Soc.*, **89**, 5934 (1967)

[72] K. v. Auwers and R. Döll, *Liebigs Ann. Chem.*, **421**, 86 (1920).

[73] P. Anastasis and P. E. Brown, *J. Chem. Soc. Perkin Trans. I*, 2013 (1982).

[74] W. Biernacki and W. Sobótka, *Polish J. Chem.*, **53**, 2275 (1979).

[75] W. Biernacki and W. Sobótka, *Polish J. Chem.*, **54**, 2239 (1980).

[76] T. Tímár, T. Eszenyi, P. Sebők and J. Jekő, *Heterocycl. Commun.*, **1**, 253 (1995).

[77] R. Canela and W.S. Bowers, *Anal. Quim.*, **83**, 113 (1987).

[78] M. A. Miranda, J. Primo and R. Tormos, *Heterocycles*, **32**,

1159 (1991).
[79] T. Tímár, J. Cs. Jászberényi and S. Hosztafi, *Acta Chim. Hung.*, **126**, 149 (1989).
[80] S. A. Kulkarni and M. V. Paradkar, *Synth. Commun.*, **22**, 1555 (1992).
[81] C. Cardani, *Gazz. Chim. Ital.*, **82**, 155 (1952).
[82] T. Eszenyi and P. Sebők, (unpublished results).
[83] T. Eszenyi and T. Tímár, *Synth. Commun.*, **20**, 3219 (1990).
[84] A. G. Shinde and R. N. Usgaonkar, *Ind. J. Chem.,Sect.B.*, **16**, 570 (1978).
[85] C. Steelink and G. P. Marshall, *J. Org. Chem.*, **44**, 1429 (1979).
[86] F. Camps, O. Colomina, J. Coll and A. Messeguer *Tetrahedron*, **38**, 2955 (1982).
[87] P. Sebők, T. Tímár, J. Cs. Jászberényi and J. Jekő, *Acta Chim. Hung.*, **126**, 471 (1989).
[88] P. Sebők, (unpublished results).
[89] G. T. Brooks, A. P. Ottridge, R. C. Jennings, D. W. Mace and B. A. Alexander, *Pestic. Sci.*, **16**, 571 (1985).
[90] J. H. Richards, A. Robertson and J. Ward, *J. Chem. Soc.*, 1610 (1948).
[91] M. Nakayama, S. Hayashi, M. Tsukayama, T. Horie and M. Masumura, *Chem. Lett.*, 315 (1972).
[92] F. N. Lahey and R. V. Stick, *Aust. J. Chem.*, **26**, 2307 (1973).
[93] T. Tímár, S. Hosztafi and J. Cs. Jászberényi, *Acta Chim. Hung.*, **125**, 617 (1988).
[94] T. Tímár, (unpublished results).
[95] G. Büchi and P. G. Williard, *Heterocycles*, **11**, 437 (1978).
[96] T. Tímár, P. Sebők, T. Eszenyi and J. Cs. Jászberényi *Heterocycles*, **38**, 2719 (1994).
[97] M.M. King and L.A. Cohen, *J. Am. Chem. Soc.*, **105**, 2752 (1983).
[98] P. Sebők, (unpublished results).
[99] P. Sebők, T. Tímár, J. Cs. Jászberényi and Gy. Batta, *Heterocycles*, **27**, 2595 (1988).
[100] T. Tímár, (unpublished results).
[101] P. E. Brown, W. Y. Marcus and P. Anastasis *J. Chem. Soc. Perkin Trans.I*, 1127 (1985).
[102] D.H.R. Barton and J.B. Hendrickson, *J. Chem. Soc.*, 1028 (1956).
[103] S.D. Burke, J.O. Saunders and C.W. Murtiashaw, *J. Org. Chem.*, **46**, 2425 (1981).
[104] F. Camps, O. Colomina, J. Coll and A. Messeguer *J. Heterocyclic Chem.*, **20**, 1115 (1983).
[105] J. Tércio, B. Ferreira, V. Catani, and J.V. Comasseto, *Synthesis*, 149 (1987).
[106] A. Arnoldi, A. Bonsignori, P. Melloni, L. Merlini, M.L. Quadri, A.C. Rossi and M. Valsecchi, *J. Med. Chem.*, **33**, 2865 (1990).
[107] T. Tímár, P. Sebők, T. Eszenyi and J. Jekő, *Heterocycl. Commun.*, **2**, 91 (1996).
[108] T. Eszenyi, T. Tímár, P. Sebők and J. Jekő, *Heterocycl. Commun.*, **5**, 45 (1999).