Theses of doctoral (Ph.D) dissertation

SYNTHESIS AND CHEMICAL TRANSFORMATIONS OF SUBSTITUTED 2,2-DIMETHYL-2*H*-1-BENZOPYRANS; DEVELOPMENT OF A NOVEL AND EFFICIENT COLUMN CHROMATOGRAPHY METHOD

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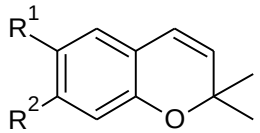
1. Introduction, subjects and aims of the dissertation

Pest insects can damage agricultural crops, consume and/or damage harvested food, or transmit diseases to humans and animals. The past 30 years has witnessed a dramatic reemergence of epidemic vector-borne diseases throughout much of the world.

Synthetic insecticides were extremely entrenched in 'modern' agricultural production. They induce widespread environmental contamination, toxicity to non-target organisms, development of resistance against insecticides, and negative effects on animal and human health. Consequently, there was an urgent need to explore and utilize naturally occurring products or their synthetic analogues for combating pests.

Insect growth regulators (IGR's) are chemical compounds that alter growth and development in insects. They do not directly kill insects, but interfere with the normal mechanisms of development, resulting in insects dying before they reach adulthood.

Precocene 1 and 2 (**1a,b**) isolated from natural sources are known insect antijuvenile hormones (AJH's). They induce precocius metamorphosis and have nematocidal activity. Several analogs of natural precocenes have been synthesized and the 7-ethoxy-6-methoxy-2,2-dimethyl-chromene (Precocene 3, **1c**) was found to be the most active synthetic precocene derivative (Figure 1).



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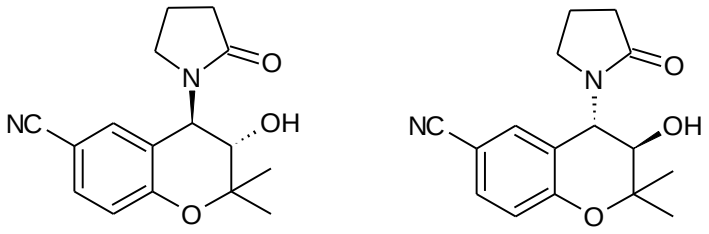
1a: Precocene 1 (P1): R^1 = H, R^2 = MeO; **1b**: Precocene 2 (P2): R^1 = MeO, R^2 = MeO;
1c: Precocene 3 (P3): R^1 = MeO, R^2 = EtO

Figure 1

As of 2000, nearly one billion people or ~26% of the adult population of the world had suffered in hypertension. That incidence level drove/drives intense research activities worldwide on new, more effective antihypertensive agents. Cromakalim [racemate: 3S, 4R (**2a**); 3R, 4S (**2b**)], the leading compound of the benzopyran type K^+ channel activators (or potassium channel openers, PCO's) has been found to exert a marked antihypertensive activity (Figure 2).



2a **2b**

Figure 2

Alkaloida Chemical Company (Tiszavasvári, Hungary) started intensive research on development of ’biorational pesticide’ with new mode of actions in the field of 2,2-dimethyl-2*H*-1-benzopyrans in 1979. Research on the development of new antihypertensive agents in the same field began in 1988. Majority of the research work in my dissertation is connected to these two projects, some of the results were previously retained due to IP considerations.

The general aims of the dissertation are the following ones:

a) Synthesis and chemical transformations (both on aromatic ring and at the C3-C4 bond) of substituted 2,2-dimethyl-2*H*-chromenes with potential insecticide/antihypertensive properties,

b) Synthesis and chemical transformations (both on aromatic ring and at the C3-C4 bond) of substituted 2,2-dimethyl-4-chromanones with potential insecticide/antihypertensive properties (Figure 3).

substituted 2,2-dimethyl-2*H*-chromenes substituted 2,2-dimethyl-4-chromanones

Figure 3

c) Development of a novel and efficient column chromatography method for the fast and effective separation of mixtures of substituted 2,2-dimethyl-1-*2H*-benzopyrans prepared.

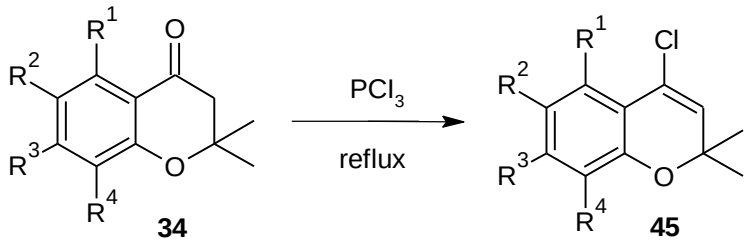
2. Methods applied

Both macro- and semi-micro methods of the preparative organic chemistry were used throughout this work. The reactions were monitored by thin-layer chromatography, the products of the reactions were purified by crystallization or by column chromatography. In addition to classical analytical techniques, such as melting point measurements and microanalyses, recording of ^{1}H-NMR, ^{13}C-NMR, IR and MS spectra were used for identification and characterization of the prepared and isolated compounds.

3. New scientific results of the dissertation

3.1 Chlorination 2,2-dimethyl-4-chromanones

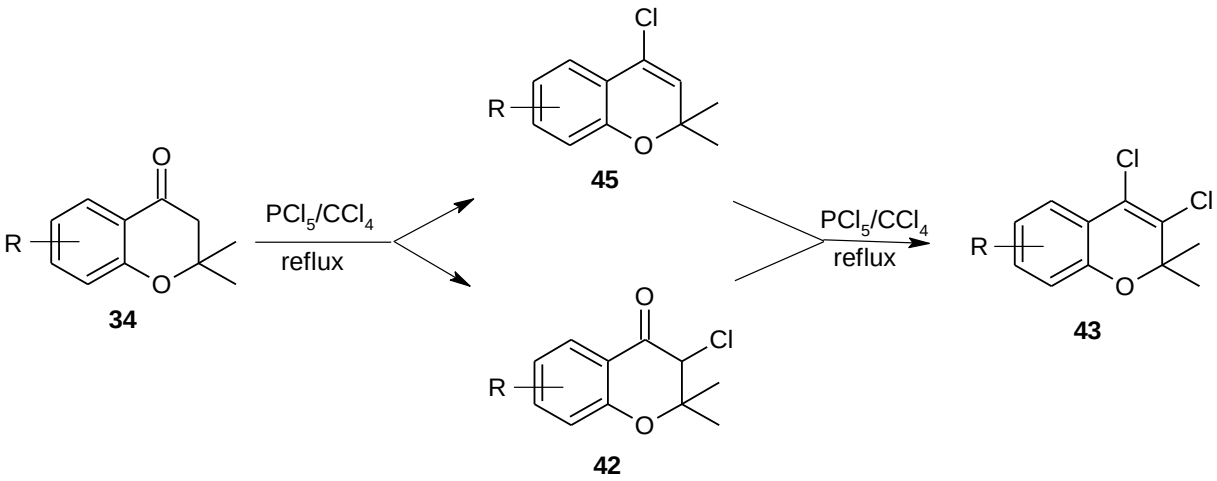
We examined the reactions of substituted 2,2-dimethyl-4-chromanones **34** with PCl_3 to prepare different alkoxy substituted derivatives of 4-chloro-2,2-dimethyl-2*H*-chromenes **45** because it provides simple reaction conditions in line with the industrial requirements. The target compounds **45** were obtained with moderate to good yields (Scheme 1).



R^1, R^2, R^3, R^4 = H, Cl, EtO, MeO, PropargylO
reaction time: 8-12 h; yield: 27-75%;
Scheme 1

We observed that 4-chloro-2,2-dimethyl-2*H*-chromenes **45** having electron-withdrawing groups on their aromatic rings are stable against acidic hydrolysis during the work-up procedure, meanwhile, products with electron-donating group on their aromatic rings undergo fast hydrolysis to the corresponding 4-chromanones.

We reinvestigated the reaction of substituted 2,2-dimethyl-4-chromanones **34** with PCl_5 and confirmed an extended pathway outlined in Scheme 2.



R = 7-MeO, 7-AcO, 7,8-$(AcO)_2$, 7-AcO-6-*t*Bu, 6-AcO-7-*i*PrO, 6-AcO-7-MeO
yield: 3-85%
Scheme 2

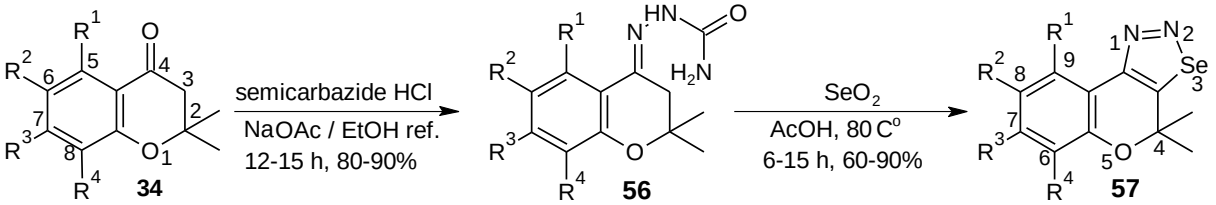
We found that the acetoxy substituent at different positions on the aromatic ring has remarkable influence on the product distribution. Based on this observation one can synthetize such acetoxy derivates of 4-chloro-2*H*-chromenes **45** which are difficult to be prepared by the method (using PCl_3) described earlier. These chlorobenzopyran derivatives **45, 42** and **43** are versatile intermediates for a wide variety of further transformations in the field of benzopyranoid chemistry.

3.2 Synthesis of 1,2,3-selenadiazolo-benzopyran derivatives from 2,2-dimethyl-4-chromanones

We chose Lalezari's method method to prepare the new 1,2,3-selenadiazolo annellated benzopyran derivatives (Scheme 3) with modified $\Delta^{3,4}$ double bond.

We reported the synthesis and the detailed characterization of 4,4-dimethylchromeno[4,3-d]selenadiazole derivatives **57** which represents a new ring system. First, 4-chromanones **34** were converted into their corresponding semicarbazones **56** by a traditional method and then cyclized into 1,2,3-selenadiazole derivatives **57** by oxidative ring closure with selenium dioxide.

We identified and described two typical fragmentation pathways of **57** during their mass spectrometry.

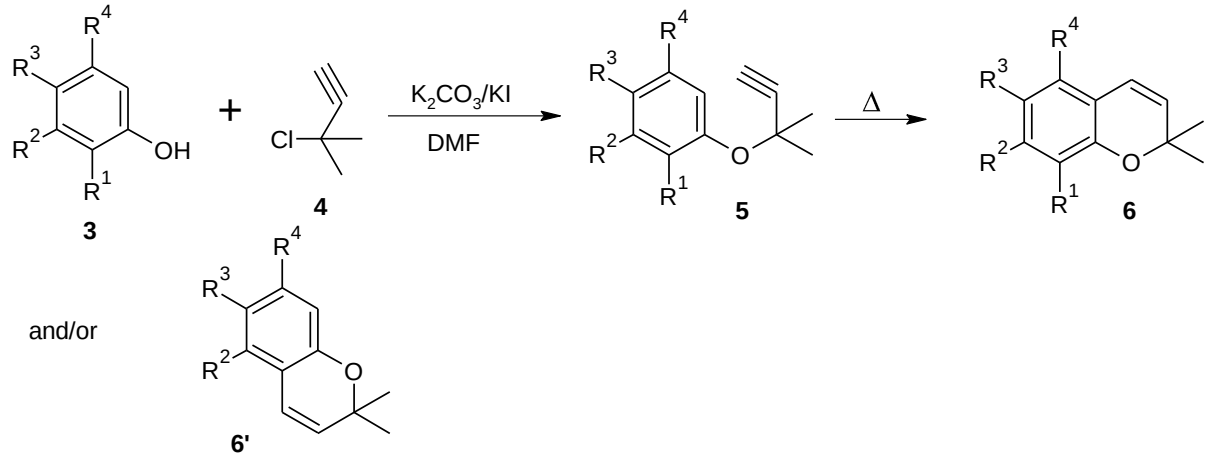


R^1, R^2, R^3, R^4 = H, Me, MeO, EtO, PropargylO

Scheme 3

3.3 Preparation and thermal cyclization of aryl propargyl ethers

We prepared several 2,2-dimethyl-2*H*-chromene derivatives **6**, **6'** *via* the following well-known route (Scheme 4).



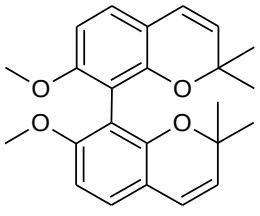
R^1, R^2, R^3, R^4 = H, Cl, Me, MeO, NO_2

yield: 65-87% for cyclization

Scheme 4

We found that the cyclization of the *meta*-substituted aryl-propargyl ethers proceeded to yield 5-substituted-2,2-dimethyl-2*H*-chromenes **6'** with high isomeric ratios similar to our findings presented earlier.

We also observed the formation of a minor product (**60**), its structure was elucidated NMR spectroscopic methods (Figure 4)



60

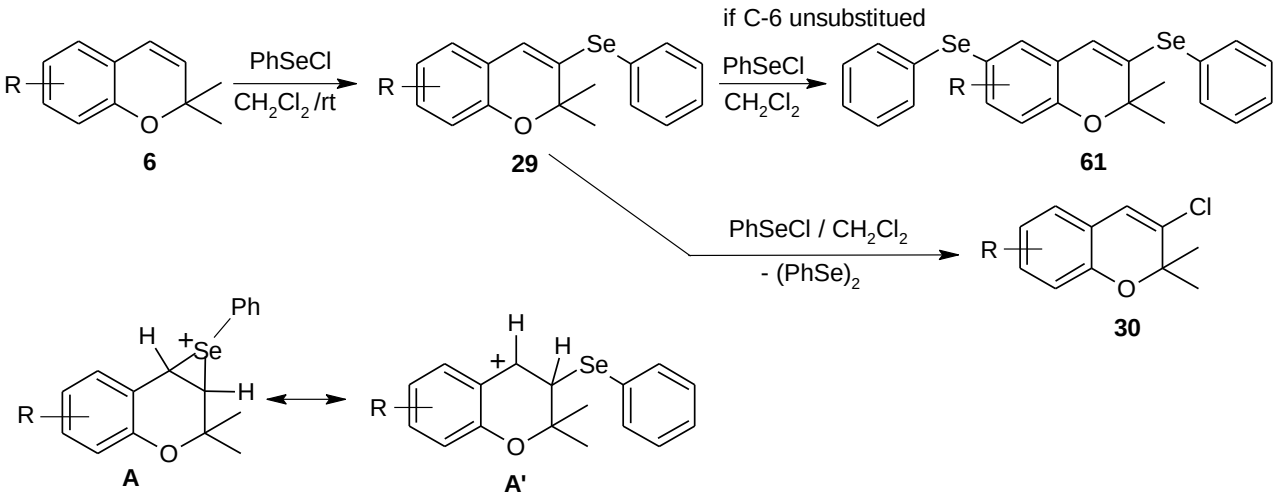
Figure 4

3.4 Reaction of 2,2-dimethyl-2*H*-chromenes with phenylselenyl chloride

We utilized the reaction of 2,2-dimethyl-2*H*-chromenes **6** with phenylselenyl chloride to prepare phenylselenyl derivatives of 2,2-dimethyl-*2H*-chromenes and derivatives of 3-chloro-2,2-dimethyl-*2H*-chromenes (Scheme 5). Instead of the desired 4-chloro-2,2-dimethyl-3-phenylselenyl-2*H*-benzopyrans, 2,2-dimethyl-3-phenylselenyl-2*H*-benzopyrans **29** were obtained in moderate-to-good yields (Scheme 5) in line with our preliminary experiments.

We suggested that the formation of derivatives **29** can be rationalized on the basis of a proton-loss from the stable benzyl-type carbocation **A**' instead of the attack of the chloride ion. The carbocation **A**' is formed in the first step of the reaction *via* electrophilic attack of the phenylselenyl group.

To our best knowledge this is the only synthetically useful method of the synthesis of 3-chloro-2,2-dimethyl-2*H*-benzopyrans **30**. These 3-chloro derivatives may be useful building blocks for substitutions or cross-coupling reactions.



R = 7-MeO, 6,7-$(MeO)_2$, 7,8-$(MeO)_2$, 7-EtO-6-MeO

Scheme 5

In this way we completed our chloro derivative series such as

- ✓ 3,4-dichloro-2,2-dimethyl-2*H*-chromenes **43**
- ✓ 4-chloro-2,2-dimethyl-2*H*-chromenes **45**
- ✓ 3-chloro-2,2-dimethyl-*2H*-chromenes **30**

3.5 Development of TLC Mesh Column Chromatography: Facile Combination of Vacuum-Driven and Low-Pressure Methods

We developed a combined TLC mesh column chromatographic system which unifies the advantages of the vacuum-driven and low-pressure methods and can be considered as an improvement of Taber's method. Our procedure was found to be efficient for separations of mixtures showing $\Delta Rf \geq 0.05$ by TLC. In comparison with Taber's low-pressure method we achieved the same or even better separation.

3.6 Biological results

Selected compounds of **57** were tested for non-specific toxic activities on *P. brassicae* and *L. decemlineata* larvae in a comparative study. We found that 1,2,3-selenadiazolo derivatives of P1 and P2 were much more effective on insect larvae than P1, P2, respectively.

This finding clearly shows the pertinence of our working hypothesis on the role of an annelated ring system in the insecticide effect.

We found that the 6,7-dimethoxy Cromakalim analogue (Figure 5) had the most effective blood-pressure lowering effect amongst the analogues synthesized. This observation challenged the prevailing 'dogma' in structure-activity model for Cromakalim analogues.

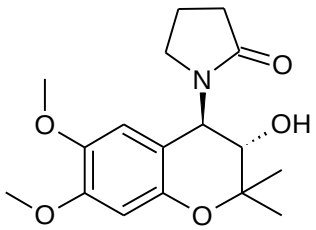
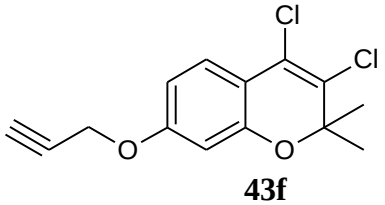


Figure 5

4. Exploitation of the results

3,4-Dichloro-7-propargyloxy-2,2-dimethyl-2*H*-chromene (**43f**), our lead compound (Figure 6) among the derivatives of 3,4,-dichloro-2,2-dimethyl-2*H*-chromene showed synergistic effect when used in conjuction with certain pyrethroid insecticides.



43f
Figure 6

Chinoin Inc. bought the patent and manufactured the compound, it was in commercial use for ten years.

5. List of Publications

5.1 Publications included in the dissertation

1) Zsótér, Zs.; Eszenyi, T.; Tímár, T.: TLC Mesh Column Chromatography: Facile Combination of Vacuum-Driven and Low-Pressure Methods, *J. Org. Chem. 59*, 672 (**1994**) *Impact factor = 3.193*

2) Eszenyi, T.; Zsótér, Zs.; Tímár, T.; Sebők, P: On the Formation of 3,4-Dichloro-2,2-dimethyl-2*H*-chromenes from 2,2-Dimethyl-4-chromanones, *Heterocycl. Commun. 4*, 155 (**1998**) *Impact factor = 0.469*

3) Zsótér, Zs.; Tímár, T.; Kónya, K; Patonay, T.; Jekő, J.: Facile synthesis of novel selenium-containing benzopyran derivatives, *J. Heterocycl. Chem.* (**2014**) (in press)
Impact factor = 1.224
Cumulated IF of the papers published/in press: 4.886

5.2 Other publications not included in the dissertation

1) Tóth, Z.; Zsótér, Zs.; Beck, M.T.: Testing the Photocatalytic Activity of Cyanogen- and Thiocyanogen-based Inorganic Polimers, *React. Kinet. Catal. Lett*. *47*, 29 (**1992**)
Impact factor= 0.334

2) Pados, Gy.; Kiss, Z.; Zsótér, Zs.; Karádi, I.; Paragh, Gy.: LDL-koleszterin, LDL-koleszterin kalkulátor, *Háziorvos Továbbképző Szemle*, *13*, 569 (**2008**)

Notes: