Synthesis and reactivity of styrylchromones

Artur M. S. Silva,*[a] Diana C. G. A. Pinto,[a] José A. S. Cavaleiro,[a] Albert Levai,[b] and Tamás Patonay[b]

[a] *Department of Chemistry, University of Aveiro, 3810-193 Aveiro, Portugal, and*
[b] *Department of Organic Chemistry, University of Debrecen, H-4010 Debrecen, Hungary*
E-mail: arturs@dq.ua.pt

Dedicated to Professor Sándor Antus, University of Debrecen, Hungary, on the occasion of his 60th birthday

(received 30 Jan 04; accepted 16 Feb 04; published on the web 17 Feb 04)

Abstract

2-Styrylchromones, although scarce in nature, constitute a group of oxygen heterocyclic compounds which have shown significant biological activities. Their transformation and the transformation of their 3-isoanalogues into other biologically active compounds have been exploited. This short review describes the most recent work on the synthesis, biological evaluation and transformation of 2- and 3-styrylchromones.

Keywords: 2-Styrylchromones, 3-styrylchromones, biological activity, Wittig reactions, Diels-Alder reactions, 1,3-dipolar cycloadditions, microwave irradiation

Contents

Introduction

Chromones and their derivatives of different oxidation level are well known naturally occurring oxygen-containing heterocyclic compounds which perform important biological functions in Nature. It is known that certain natural and synthetic derivatives possess important biological activities, such as anti-tumor, anti-hepatotoxic, antioxidant, anti-inflammatory, anti-spasmolytic, oestrogenic and antibacterial activities.[1-5] These applications have stimulated a continuous search for the synthesis of new compounds in this field and led already to the appearance of some drugs on the market.[6]

2-Styrylchromones are one of the scarcest classes of natural chromones. Hormothamnione **1** and 6-desmethoxyhormothamnione **2** are the first and to the best of our knowledge the only naturally occurring styrylchromones isolated from the marine crytophyte *Chrysophaeum taylori* (Figure 1).[7,8] Hormathamnione **1** is exceptionally cytotoxic to P388 lymphocytic leukemia and HL-60 promyelocytic leukemia cell lines *in vitro* and appears to be a selective inhibitor of RNA synthesis.[7] 6-Desmethoxyhormothamnione **2** showed cytotoxicity to 9 KB cell lines.[8] These pharmacological activities and potential medicinal uses in addition to the fact that the isolation and purification of these 2-styrylchromones **1** and **2** are difficult, in view of very low concentration in the rare algae, have stimulated even more extensive studies related to their synthesis.[9]

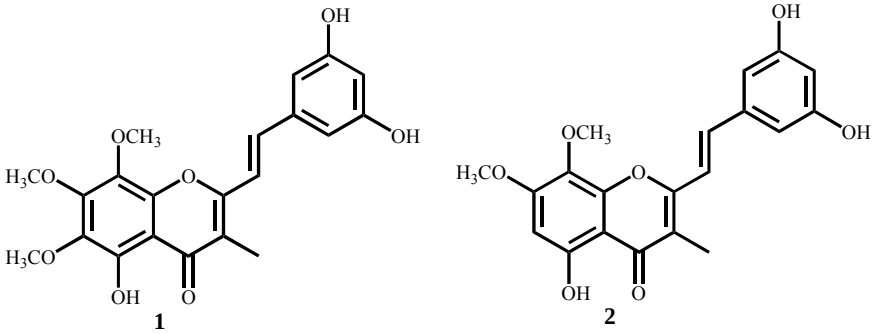


Figure 1

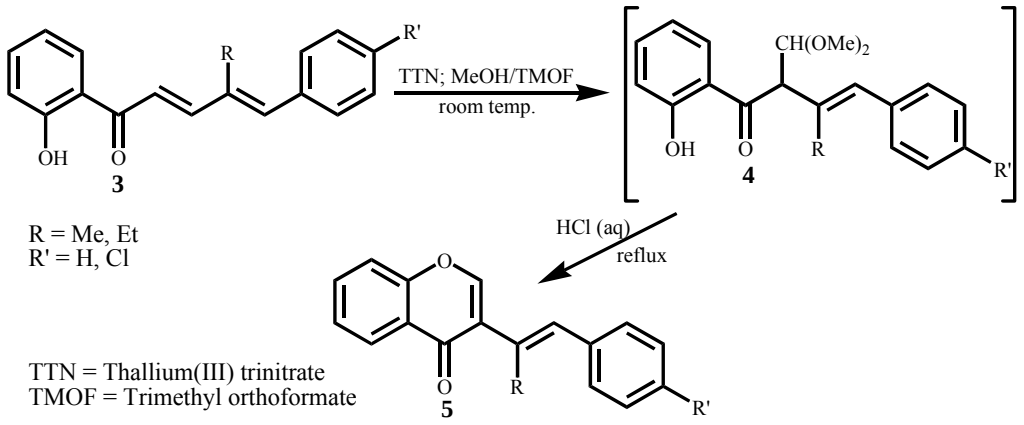
Although 2-styrylchromones constitute a small family of naturally occurring compounds, their synthesis has been extensively studied. A previous review[10] summarized the literature on the chemistry of 2-strylchromones and their 3-isoanalogues with emphasis on successful synthetic strategies and reactivity in Diels-Alder and photo-oxidative reactions. This review aims, therefore, to cover the work on the synthesis, biological evaluation and transformation of both 2- and 3-styrylchromones since 1993.

1. Preparation of styrylchromones

1.1.Synthesis of 3-styrylchromones

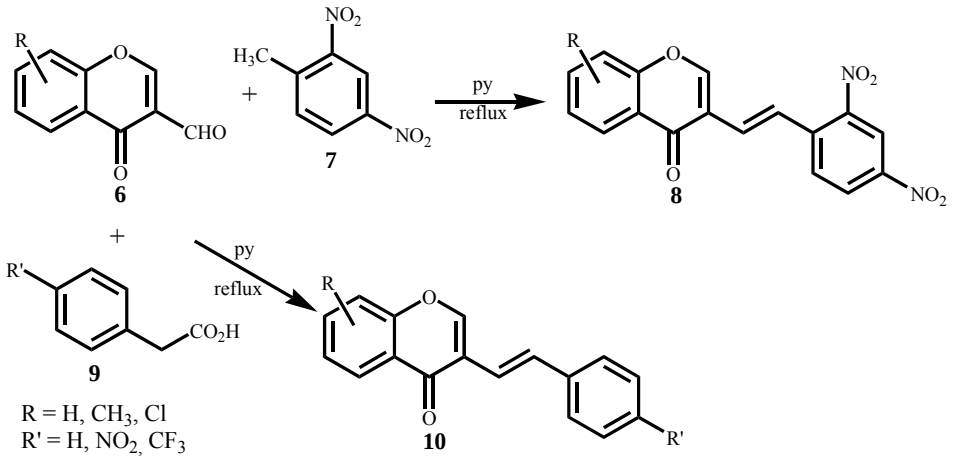
Despite the structural analogy of the 3-styrylchromones with isoflavones and their relationship with the well-studied 2-styrylchromones there has been limited interest in their study. The first example regarding the formation of only one derivative of these chromones was published in

1987[11] and since then there were no significant developments. It was necessary to wait ten years for another publication on the establishment of a new synthesis of several new derivatives.[12] This synthetic route is analogous to the oxidative rearrangement of 2'-hydroxychalcones to isoflavones.[13] In fact the treatment of (*E,E*)-2'-hydroxycinnamylideneacetophenones **3** with thallium(III) trinitrate involves a cinnamyl group transposition from C-β to C-α, resulting in the formation of intermediates 3-alkyl-4-aryl-1-(2-hydroxyphenyl)-2-dimethoxymethyl-3-buten-1-ones **4**. Treatment of acetals **4** with diluted hydrochloric acid gave the corresponding 3-styryl-chromones **5** (Scheme 1). This method gave rise stereoselectively to the (*E*)-isomers and is the only known strategy which does not use a chromone as starting material, but has some limitations, it uses very toxic reagents, such as thallium(III) trinitrate, and only 3-(α-alkylstyryl)chromones could be obtained.[12]



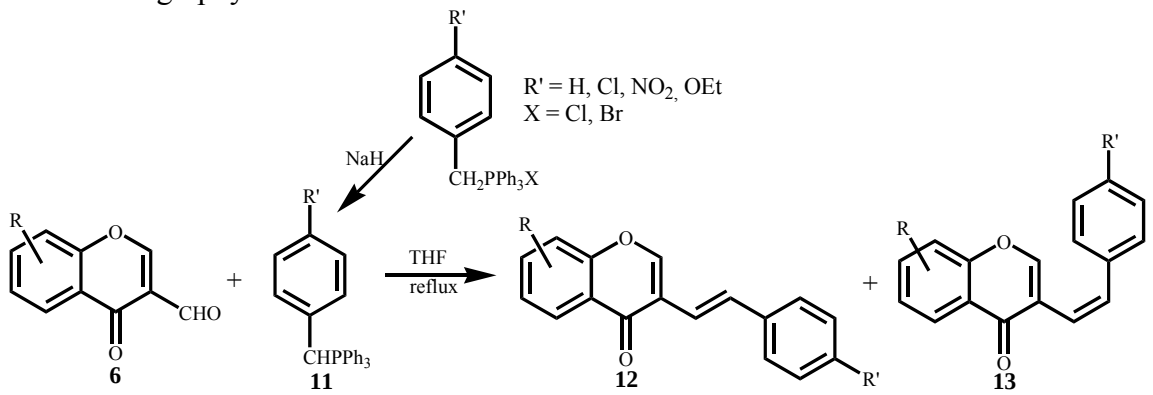
Scheme 1

The use of 3-formylchromones in the synthesis of heterocyclic systems has attracted the attention of many researchers, since their convenient synthesis was reported in the 1970's.[14] Very recently, the reactivity of the electrophilic 3-formyl group was successfully exploited in the synthesis of 3-styrylchromones, as well.[15-18] The first publication on this issue appeared in 2002[15] and consists of the condensation of 3-formylchromones **6** with 2,4-dinitrotoluene **7** in pyridine (Scheme 2). New and simple 3-styrylchromones **8** have been obtained with this synthetic approach. A modification on this method[16,17] which consists of the condensation of 3-formyl-chromones **6** with phenylacetic acids **9** followed by decarboxylation reaction, allowed the synthesis of new 3-styrylchromone derivatives **10** and gave only the (*E*) isomer.[17]



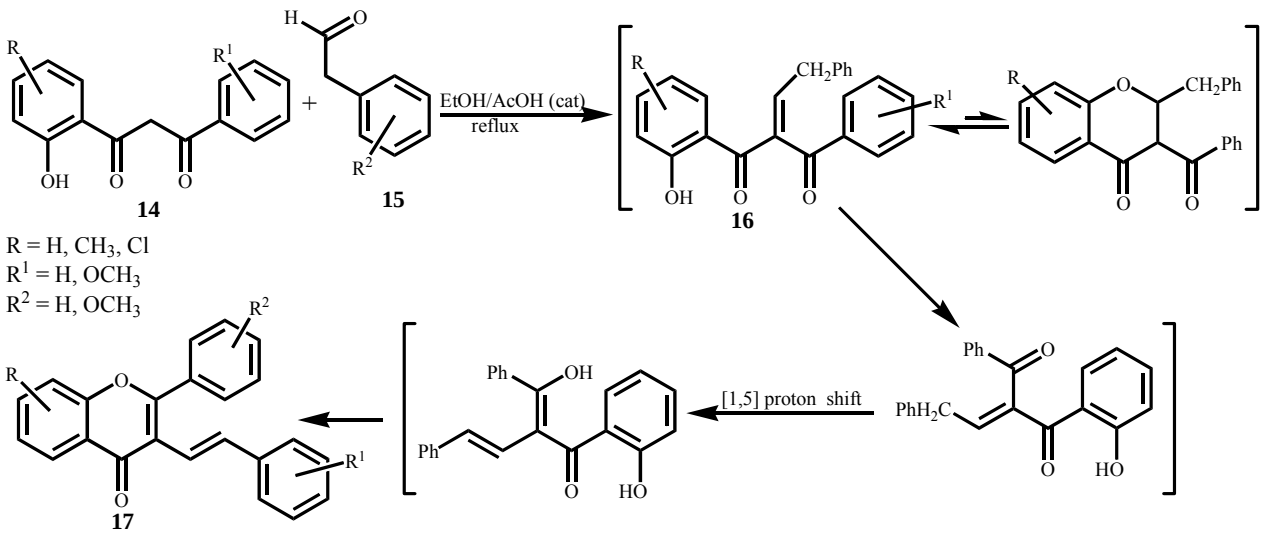
Scheme 2

The third synthetic method for 3-styrylchromones involves the Wittig reaction of 3-formylchromones **6** with benzylic ylides **11** (Scheme 3).[18] This new approach seems to be of general use and gave a diastereomeric mixture of (*E*) and (*Z*)-3-styrylchromones **12** and **13**, the (*Z*)-isomer being the most abundant one. The obtained diastereomers have been separated by thin-layer chromatography.



Scheme 3

In 1999 Samat and coworkers reported the synthesis of novel 3-styrylchromones **17** which can also be regarded as 3-styrylflavones.[19] These compounds have been obtained from the reaction of 1-(2-hydroxyphenyl)-3-phenylpropan-1,3-diones **14** and phenylacetaldehydes **15** under a mild acid-catalyzed condition (acetic acid), (Scheme 4). The proposed possible mechanism involves an acid-catalyzed aldol reaction of **14** with aldehydes **15**, leading to diketo-compounds **16** which after [1,5]-benzylic proton migration cyclize into the obtained 3-styryl-chromones **17**. The structure of these novel 3-styrylchromones **17** was established by X-Ray analysis.[19]



Scheme 4

1.1 Synthesis of 2-styrylchromones

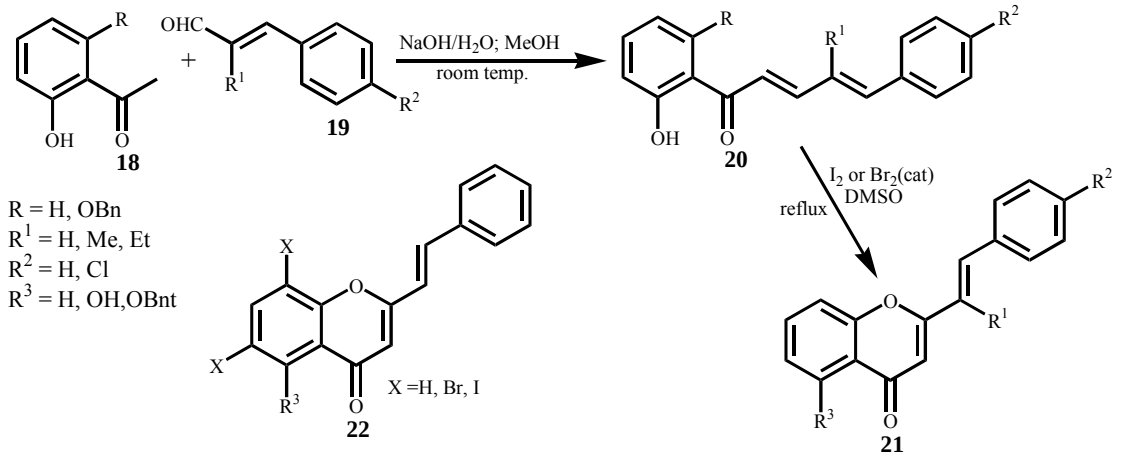
In the previous paragraphs new synthetic approaches used in the synthesis of 3-styrylchromones were described. In the case of their 2-isoanalogues, which were prior extensively studied; there were since 1993[10] some publications with innovating strategies. The reports found in literature deal with improvements of the most promising approaches, such as: 1) aldol condensation / oxidative cyclization[20-26] and 2) Baker-Venkataraman rearrangement.[26-31]

Taking into consideration the important biological activities described for 2-styryl-chromones (*vide infra*), it is advantageous if these compounds could be available by simple and efficient synthetic transformations. For that reason almost all reports on the synthesis of new 2-styrylchromones include their transformation and/or biological activities evaluations.

1.1.1 Aldol condensation / oxidative cyclization

This two-step approach involves an aldol reaction followed by an oxidative cyclization. The base-catalyzed aldol reaction of cinnamaldehydes **19** with 2′-hydroxy-acetophenones **18** in methanolic solutions affords (*E*,*E*)-2′-hydroxycinnamylidene-acetophenones **20** (Scheme 5). Much more attention was paid to the oxidative cyclisation of **20** into (*E*)-2-styrylchromones **21** and several oxidative reagent systems were proposed.[10,21-26] The most successful one uses DMSO and a catalytic amount of iodine (Scheme 5).[25] We proved that bromine can also be successfully used for this oxidative step and that the amount of the halogen used (I_2 or Br_2) and the refluxing time are very important parameters in the reaction results. Treatment of 2′-hydroxycinnamylideneacetophenones **20** with one molar equivalent of halogen, in refluxing DMSO for 30 min., allowed both the oxidative cyclization into 2-styrylchromones and the halogenation of their most activated positions. This method constitutes a new synthetic route for halogenated 2-styrylchromones **22**.[22,24] When 2′-benzyloxy-6′-hydroxycinnamylidene-acetophenones **20** (R = OBn) were reacted in the presence of a catalytic amount of halogen the

reaction of longer period (2 hours) resulted in not only the expected oxidative cyclizations but a debenzylation leading to 5-hydroxy-2-styrylchromones **21** (R^3 = OH).[20,24]



Scheme 5

1.1.2 Baker-Venkataraman rearrangement

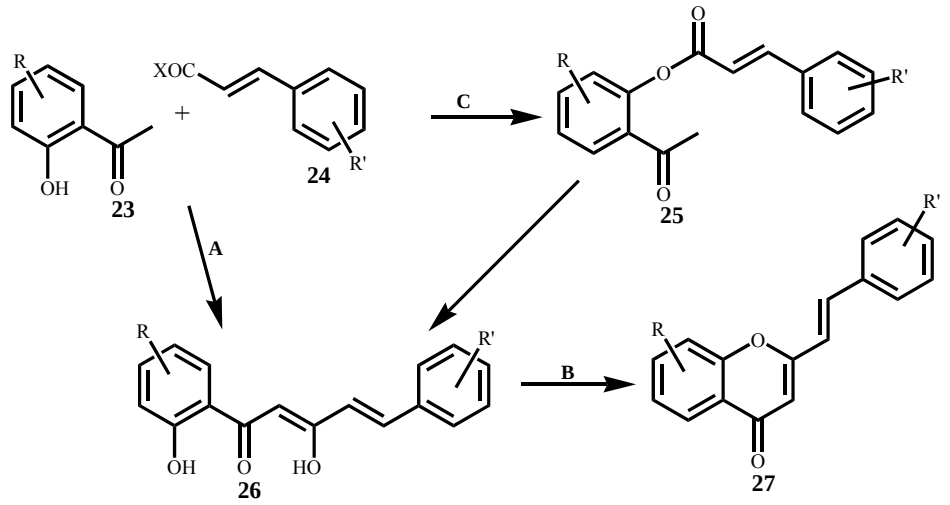
The most common procedures in the Baker-Venkataraman rearrangement (Scheme 6) consist of the *O*-acylation of a 2′-hydroxyacetophenone **23** followed by a base-catalyzed rearrangement of the formed ester **25** into 5-aryl-3-hydroxy-1-(2-hydroxyaryl)-2,4-pentadien-1-ones **26** (structures involved in the keto-enol equilibrium). The last step of the synthesis is the cyclodehydration of these diketones into the desired 2-styrylchromones **27**.[10] The main reported modifications on this method consists of changes in the reagent systems used and/or in the elimination of one procedure step.

One of the first publications since 1993 on the synthesis of 2-styrylchromones, using this procedure, reports a two-step modification.[28] The authors indicated that refluxing 2′-hydroxy-3′-allylacetophenones **23** (R = 3′-allyl) with cinnamoyl chlorides **24** (X =Cl) in potassium carbonate/acetone medium yields directly 1-(3-allyl-2-hydroxyaryl)-5-aryl-3-hydroxy-2,4-pentadien-1-ones **26** which were then cyclized in acid medium into 2-styrylchromones **27** (Scheme 6, steps **A** and **B.i**). More recently, the same research group has synthesized some 2-(2′-vinylthiophene)chromones **30** (2-styrylchromone-type compounds) in one step, by condensation of appropriate 2′,4′-dihydroxyacetophenones **28** and thiophene-2-acroyl chloride **29** (Scheme 7).[32]

Another important modification of the Baker-Venkataraman method was the improvement in the cyclodehydration step, which was originally performed in strong acidic conditions. However, it was also reported that several 2-styrylchromones **27** could be obtained by a three-step procedure where the cyclodehydration of 5-aryl-3-hydroxy-1-(2-hydroxyaryl)-2,4-pentadien-1-ones **26** was achieved with *p*-toluenesulfonic acid or with a catalytic amount of iodine in hot DMSO (90-100°C) (Scheme 6, step **B.ii**).[29,31]

The *O*-acylation is generally an easy step, but in some cases the use of classical procedures to the synthesis of 5-hydroxy-2-styrylchromones **27** (R = 5-OH), the nucleus which is present in the natural derivatives, the *O*-acylation was found to be difficult. Recent work[30] reports that this step

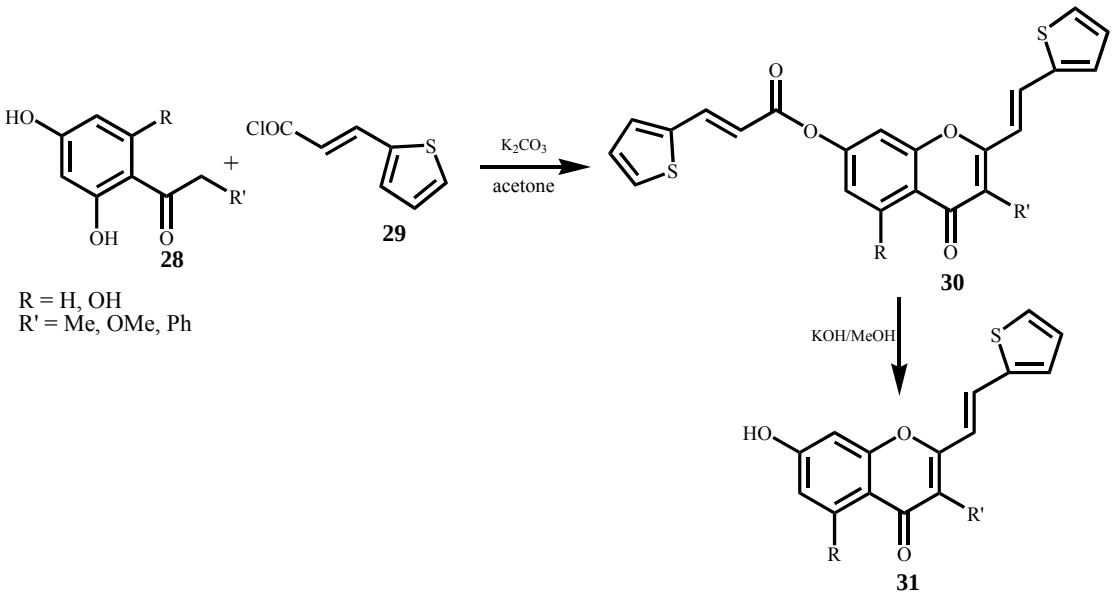
can be successfully achieved. Treatment of the appropriate 2′,6′-dihydroxyacetophenone **23** (R = 6′-OH) with cinnamic acids **24** (X = OH) in the presence of *N*,*N*-dicyclohexyl-carbodiimide (DCC) and a catalytic amount of 4-pyrrolidinopyridine (Scheme 6, step **C**).



A: K_2CO_3, acetone, reflux 12 h; X = Cl
B: i) H_2SO_4, reflux 3 h
ii) *p*-toluenesulfonic acid or I_2, DMSO, 90-100 °C, 2-3 h
C: DCC, 4-pyrrolidinopyridine, CH_2Cl_2, room temp.; X = OH

R = H, OH
R' = H, Me, OMe, OBn, Cl, NO_2

Scheme 6



R = H, OH
R' = Me, OMe, Ph

Scheme 7

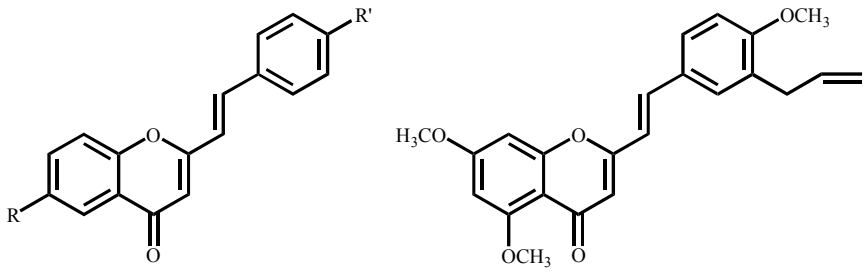
2. Biological evaluation of 2- and 3-styrylchromones

The significant anti-allergic activity of 2-styrylchromones has been recognized more than twenty years ago[33] and since then their synthesis and biological evaluations of these compounds have been the subject of several studies, which were also stimulated by the discovery of the natural

derivatives and of their biological activity.[7,8] This paper does not intend to describe exhaustively biological properties, only the most recent and significant reports on the effects of styrylchromones are listed here.

Human rhinoviruses (HRVs) are the most frequent cause of the common cold and therefore responsible for several chronic conditions, such as asthma and sinusitis. Consequently HRV has become a target for antiviral research. Desideri and coworkers focused their interest on study of the anti-rhinovirus activity of 2-styrylchromones.[34] They selected two serotypes of human rhinovirus, 1B and 14, and tested several 2-styrylchromones (**32**, Figure 2). From their study one can conclude that styrylchromones can be considered as promising new antiviral compounds.

It has also been proved that 3′-allyl-4′,5,7-trimethoxy-2-styrylchromone (**33**, Figure 2) can inhibit the phosphorylative system and the electron transfer via the respiratory chain of rat liver mitochondria.[30] This interaction indicates that 3′-allyl-4′,5,7-trimethoxy-2-styrylchromone can show potential anticancer activity.



32 **33**

R = H, Cl
R' = H, Cl, CH_3, OCH_3, OH, NO_2, NH_2

Figure 2

Quercetin (3,5,7,3′,4′-pentahydroxyflavone) (**34**, Figure 3) is a natural compound with a widespread occurrence and appears to help the fight against a host of disorders, from asthma to cancer and heart diseases. As an antioxidant, it combats the destructive "free radical" species that play an “important role” in many human diseases. Quercetin is just the most famous example, since several flavonoids have the capacity to act as antioxidants.[36,37] Taking into account these important properties and the similarity of 2-styrylchromones with flavones, several polyhydroxylated 2-styrylchromones **35, 36** have been studied to demonstrate their potential biological applications experimentally.[38-40] In one of these studies certain hydroxylated -2-styrylchromones **36** have been demonstrated to act as potent xanthine oxidase inhibitors.[38] The study indicated that more attention should be devoted to these 2-styrylchromones to evaluate their potential use as agents in the treatment of diseases related to xanthine oxidase activity (*e.g.* gout, hypertension and hepatitis). Recently, the same polyhydroxylated 2-styrylchromones **35, 36** were found to be potent hepatoprotectors against *tert*-butyl-hydroperoxide[39] and their inhibitory effect on the Cu^{2+}-induced oxidation of isolated human serum low-density lipoproteins, a well-established *in vitro* model of lipid peroxidation, was also studied in order to explore their antioxidant properties.[40]

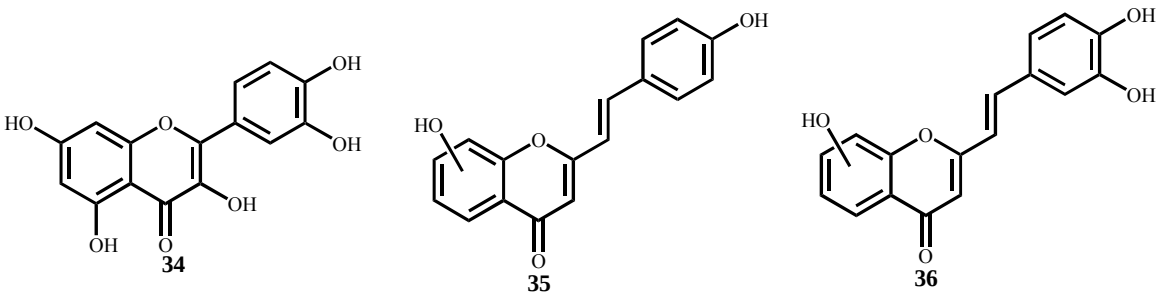


Figure 3

Biological activities of 3-styrylchromones have hardly been studied; to our knowledge only one paper reported biological evaluations of this type of compounds.[15] Some 2′,4′-dinitro-3-styrylchromones **8** (Figure 4) were screened for their antibacterial activities against *E. coli* and *S. albus* and their fungicidal activities against *A. niger* and *A. teniussiama*. All compounds showed moderate bactericidal activities and moderate to excellent fungicidal activities.

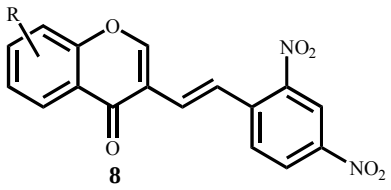
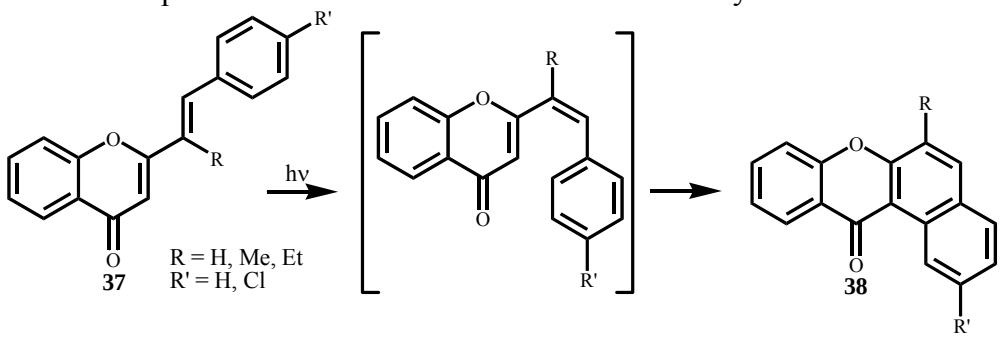


Figure 4

3. Reactivity of 2- and 3-styrylchromones

It has been known since 1954 that 2-styrylchromones can participate in pericyclic reactions as dienes whilst photo-oxidative cyclizations into 12*H*-benzo[*a*]xanthen-12-one was demonstrated more than twenty years later.[10] Since 1993 different types of reactivity have been studied, such as their use as dienophiles and dipolarophiles in cycloaddition reactions to synthesize new potential biological active heterocyclic compounds.

Although the photo-oxidative cyclization of 2-styrylchromones **37** is not a new reaction in 1993 we reported a new, less dangerous and more efficient methodology (Scheme 8).[23,25,41] The major improvements were: i) the use of chloroform as solvent instead of benzene; ii) the use of daylight instead of UV light; iii) the use of borosilicate glass vessels instead of quartz vessels, and, as a result the expected xanthones **38** were obtained in better yields.



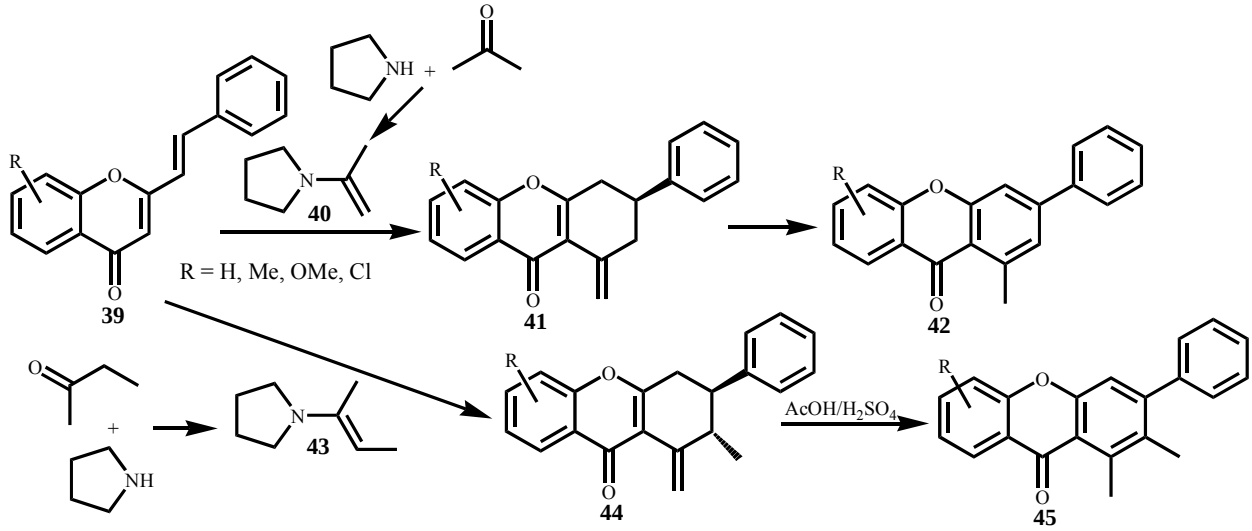
Scheme 8

3.1.Styrylchromones as dienes

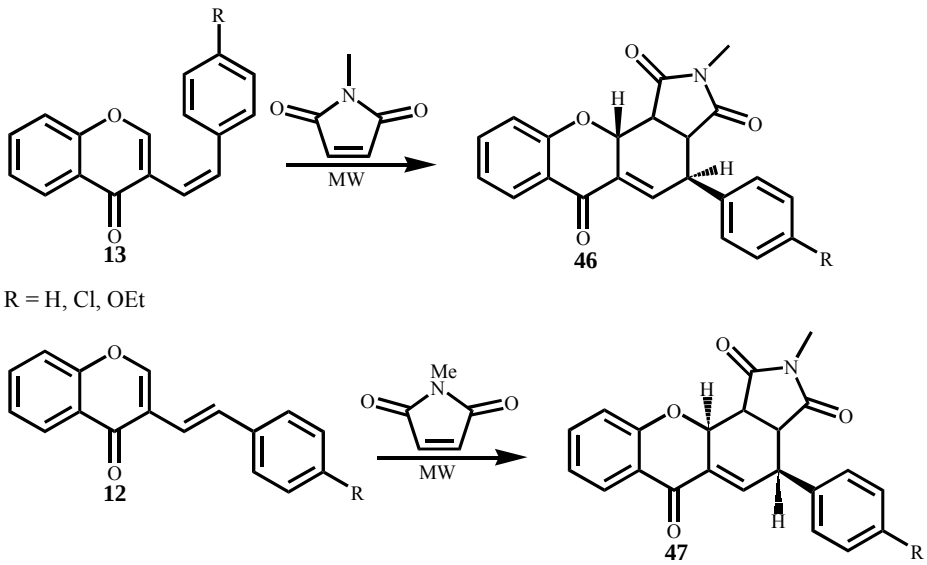
The transformation of 2-styrylchromones into other heterocyclic compounds by pericyclic reactions started with their use as dienes in Diels-Alder reactions.[10] More recently, a novel approach to the synthesis of xanthones **42** was reported utilizing the [4+2] cycloaddition reactions of 2-styrylchromones **39** with pyrrolidine enamine **40**, formed *in situ* from pyrrolidine and acetone (Scheme 9).[42] The proposed mechanism involves the tetrahydroxanthones **41** as the initial products of pyrrolidine elimination from the Diels-Alder adducts. Adducts **41** are the precursors of the fully aromatized compounds **42**, *via* migration of the exocyclic double bond and a subsequent dehydrogenation of the C-ring. This mechanism was confirmed by replacing acetone with 2-butanone in the generation of the enamine dienophile **43**. In this case the tetrahydroxanthones **44** were the major reaction products and there was neither rearrangement and aromatization, however 1-methylidene-2-methyltetrahydroxanthones **44** were easily converted into the desired 1,2-dimethylxanthone **45** by treatment with strong acid (Scheme 9).

The transformation of 3-styrylchromones into other heterocyclic compounds is scarce; as far as we are aware there is only one publication on their reactivity as dienes. The Diels-Alder reactions of 3-styryl-chromones were investigated using very reactive dienophiles, such as *N*-methyl and *N*-phenyl-maleimide, under microwave irradiation.[43] Using *N*-methylmaleimide, (*Z*)-3-styrylchromones **13** gave the expected *endo* cycloadducts tetrahydroxanthones **46** were obtained, while only *exo* cycloadducts **47** were observed with the (*E*)-diastereomers **12** (Scheme 10).

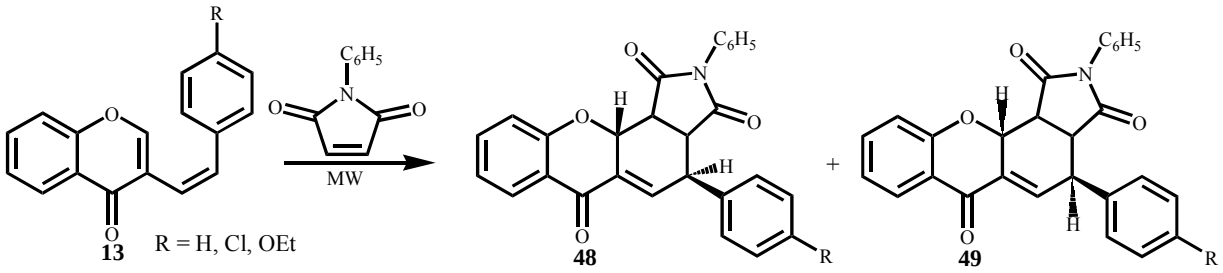
The reaction of *N*-phenylmaleimide with (*Z*)-3-styrylchromones **13** gave a mixture of the *endo* and *exo* cycloadducts **48** and **49**, the *endo* cycloadducts being the most abundant ones (Scheme 11). The reaction of *N*-phenylmaleimide with (*E*)-3-styrylchromones **12** yielded only the *exo* cycloadducts **49**. It was postulated that due to the lower reactivity of *N*-phenylmaleimide, compared with *N*-methylmaleimide, a part of (*Z*)-3-styrylchromones could isomerise into (*E*)-3-styrylchromones under microwave irradiation which reacted with *N*-phenylmaleimide giving the *exo* cycloadducts **49**.



Scheme 9



Scheme 10

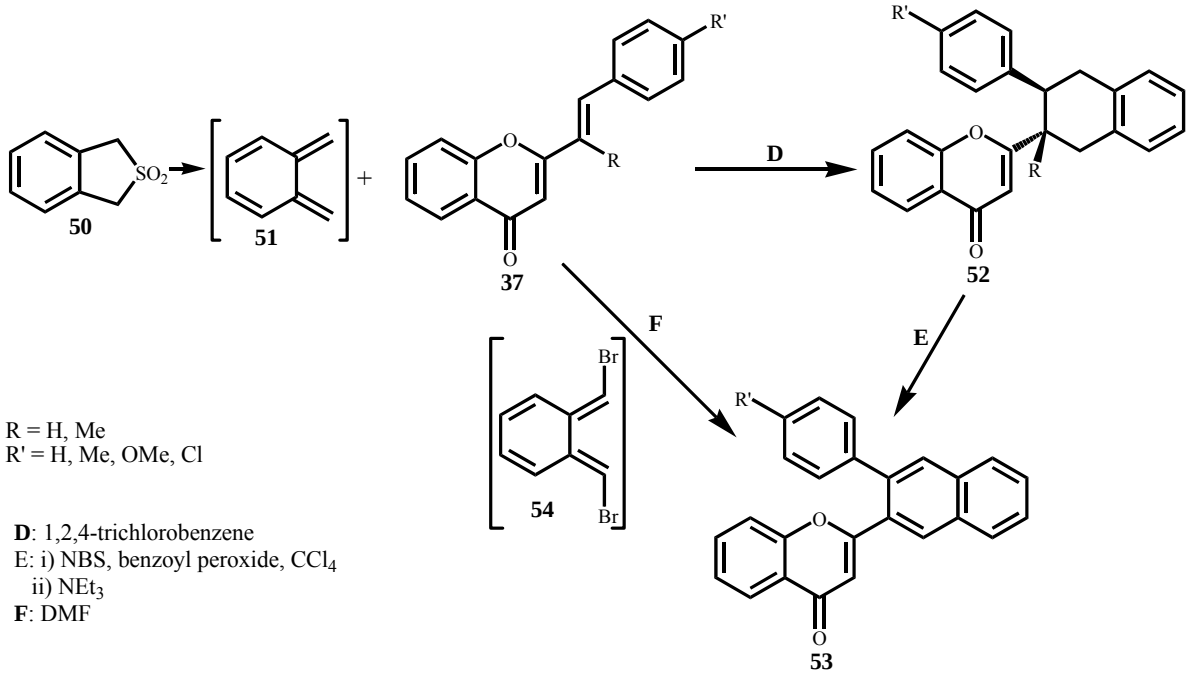


Scheme 11

3.2.Styrylchromones as dienophiles

In the previous section the use of 2-styrylchromones as dienes in Diels-Alder reactions was reported; hereby their use as dienophiles will be reviewed. As far as we are aware only one paper was published on this subject.[44]

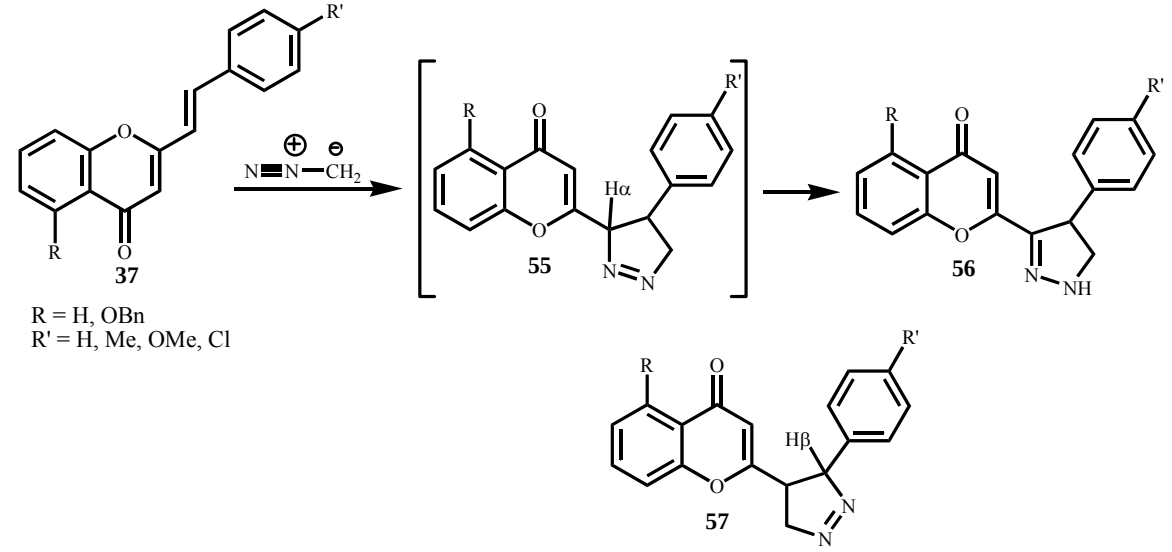
2-Styrylchromones **37** reacted with *ortho*-benzoquinodimethane **51** (highly reactive diene generated *in situ* by thermal extrusion of SO_2 from sulfone **50**) to give chromones **52** (Scheme 12). In some cases, when there was no substitution at C-α of 2-styrylchromones **37** (R = H), the obtained cycloadducts **52** could be dehydrogenated into 2-[2-(3-arylnaphthyl)]chromones **53**, novel benzoflavone-type compounds. These oxidations were achieved by benzylic bromination with *N*-bromosuccinimide in the presence of benzoyl peroxide and followed by dehydrobromination of the products with triethylamine. To circumvent the bromination step, the *ortho*-benzoquinodibromomethane **54**, generated *in situ* from α,α,α',α'-tetrabromo-*o*-xylene, was used and the 2-[2-(3-arylnaphthyl)]chromones **53** were prepared in one-pot reaction. However, in the case of 4′-methoxy-2-styrylchromone (R = H and R′ = OCH_3), chromone **53**, was obtained in poor yield, due to the electron-donating substituent on the 2-styrylchromone B ring which decreases the reactivity of their Cα=Cβ double bond.



Scheme 12

3.3.Transformation into pyrazolines

2-Styrylchromones behave as dipolarophiles in the reaction with diazomethane, one of the most frequently used 1,3-dipoles in the preparation of pyrazolines. 2-Pyrazolines **56** were obtained as the main products in the reactions of 2-styrylchromones **37** with diazomethane, whereas the regioisomers 1-pyrazolines **57** were obtained as minor products (Scheme 13).[29] Detailed studies performed ten years ago concluded that 1-pyrazolines similar to adduct **55** were formed as primary product and then rearranged to the more stable 2-pyrazoline isomers.[45] In our case these isomerisations took place only in the case of compounds **55** because Hα is acidic whereas Hβ of their regioisomers **57** is not.

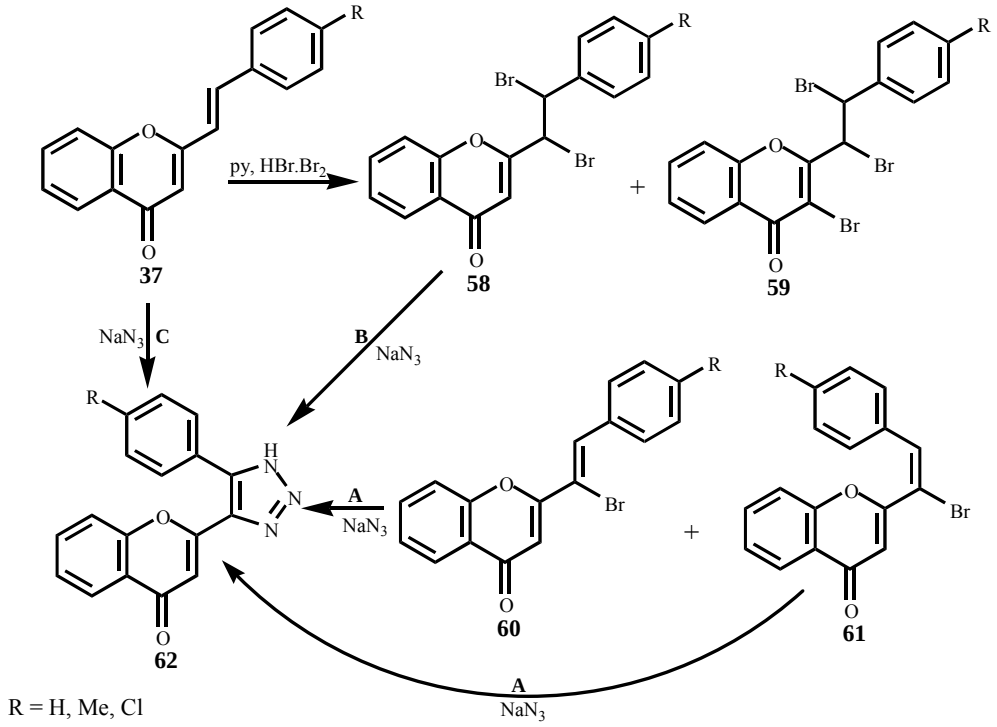


Scheme 13

3.4.Transformation into 1,2,3-triazoles

In the previous paragraph it was described the capacity of the Cα=Cβ double bond of 2-styrylchromones to react with diazomethane in 1,3-dipolar cycloaddition reactions. In this section we will demonstrate the usefulness of the styryl double bond activated by the strongly electron-withdrawing chromonyl unit in the synthesis of 1,2,3-triazoles.[46,47] The studies started with the bromination / dehydrobromination reactions of 2-styrylchromones in order to prepare 2-(α-bromostyryl)-chromones **60** and/or **61** (Scheme 14). The results on the bromination studies indicated that using two molar equivalents of pyridinium tribromide only the brominated compounds **58** and **59** were obtained. 2-(1,2-Dibromo-2-phenylethyl)chromones **58** were dehydrobrominated by treatment with triethylamine and the isomeric (*Z*) and (*E*)-2-(α-bromostyryl)chromones **60** and **61** were obtained. The desired 1,2,3-triazoles **62** were achieved by treating chromones **60** and **61** with an excess of sodium azide (Scheme 14, step **A**).[46]

Further studies on the synthesis of these 1,2,3-triazoles **62** have shown that the bromination and dehydrobromination steps could be avoided since 4(5)-aryl-5(4)-(2-chromonyl)-1,2,3-triazoles **62** can be directly prepared in a one-pot reaction from 2-(1,2-dibromo-2-phenylethyl)chromones **58** (Scheme 14, step **B**) or even from 2-styrylchromones **37** (Scheme 14, step **C**).[47]



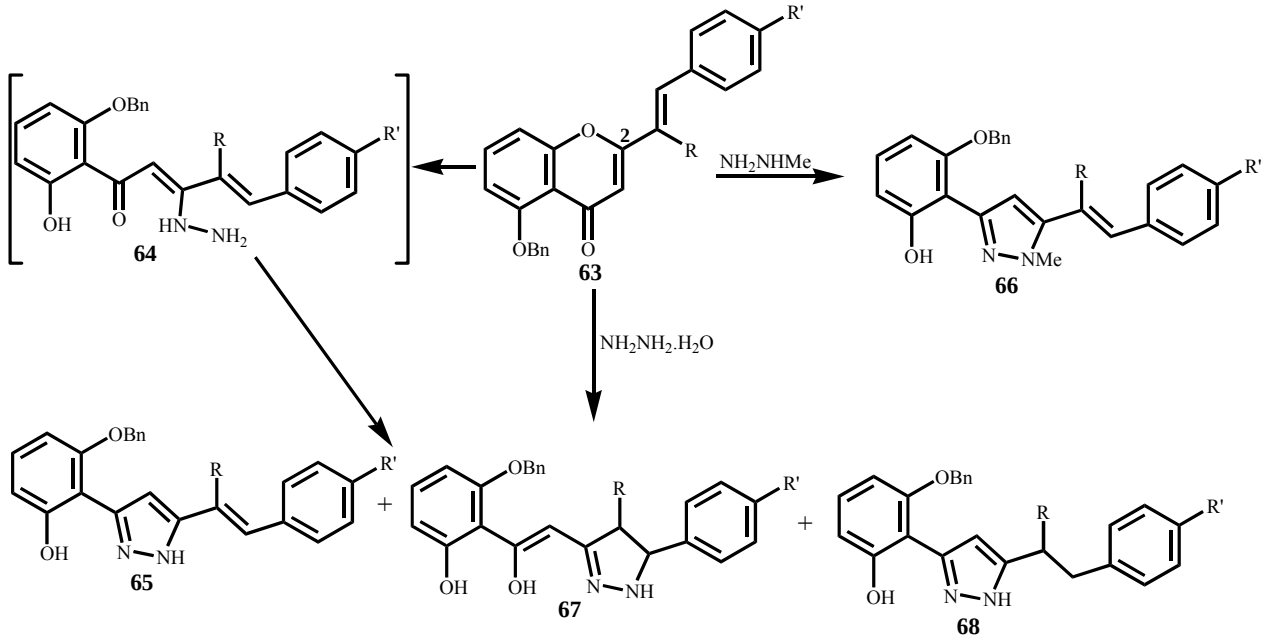
Scheme 14

3.5.Transformation into pyrazoles

It was recognized more than fifty years ago that chromones can react with hydrazine hydrate to give 5(3)-(2-hydroxyphenyl)pyrazoles. Thirty years later the structures of these reaction products were confirmed as pyrazoles and the reaction mechanism was explained.[48] In 1997 we published

the first studies on the reactions of 2-styrylchromones with hydrazines which resulted in the formation of 3-(2-hydroxyphenyl)-5-styrylpyrazoles.[49] Few years later, full detailed results on the reactions of 2-styrylchromones **63** with hydrazine hydrate[26] and with methylhydrazine[50] have been reported.

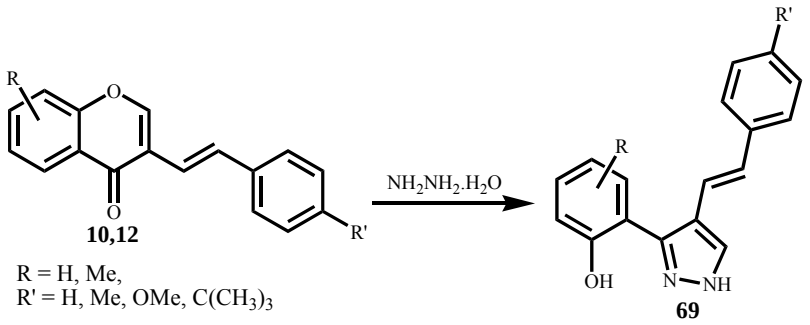
In the reaction of 2-styrylchromones **63** with methylhydrazine, 3-(2-benzyloxy-6-hydroxyphenyl)-1-methyl-5-styrylpyrazoles **66** have been obtained as the only detectable products (Scheme 15). However, in the reactions of 2-styrylchromones **63** with hydrazine hydrate not only the expected 3-(2-benzyloxy-6-hydroxyphenyl)-5-styrylpyrazoles **65** but also 2-pyrazolines **67** and pyrazoles **68** were obtained (Scheme 15). The formation of by-products **68** can be envisaged by reduction of the major reaction products **65** by diazene (N_2H_2), formed by oxidation of hydrazine. The study revealed that the quantities of the pyrazoles **68** increased with the increasing amount of hydrazine hydrate and/or with refluxing time longer than necessary for the disappearance of the starting chromone. The formation of 2-pyrazolines **67** can be explained on the basis of the reaction mechanism. First there is a nucleophilic attack at C-2 of 2-styrylchromones **63** and subsequent ring opening **64**, followed by conjugate addition of hydrazine to the former C-β of the 2-styrylchromone. Obviously, the nucleophilic attack at the carbonyl group giving the major product 3-(2-benzyloxy-6-hydroxyphenyl)-5-styrylpyrazoles **65** is much more favorable.



R = H, Me,
R' = H, Me, OMe, $C(CH_3)_3$

Scheme 15

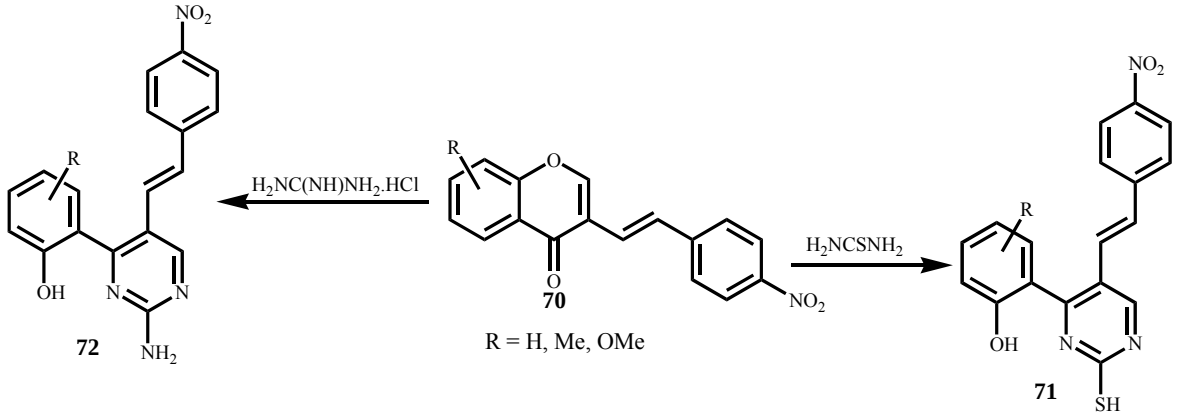
The same reaction has been recently applied to 3-styrylchromones and it seems that these compounds are also good starting material in the synthesis of styrylpyrazoles. 4-Styryl-3-(2-hydroxyphenyl)pyrazoles **48** have been synthesized from the reactions of 3-styrylchromones **10**,**12** with hydrazine hydrate (Scheme 16).[51]



Scheme 16

3.6.Transformation into pyrimidines

One of the last publications concerning the reactivity of styrylchromones deals with transformation of 3-styrylchromones into styrylpyrimidines[16] as another example involving the ring opening of the chromone nucleus (Scheme 17). The reaction of 3-styrylchromones **70** with thiourea or guanidine afforded 2-thio-4-(2-hydroxyphenyl)-5-styrylpyrimidines **71** and 2-amino-4-(2-hydroxyphenyl)-5-styrylpyrimidines **72**, respectively.



Scheme 17

Closing remarks

Results compiled and discussed in this review unquestionably prove that styrylchromones became versatile and important oxygen heterocycles. Their proved biological activities and their utility in the synthesis of other heterocyclic compounds emphasize their importance. This paper highlights that work on their transformation has been done and several transformations can give rise to important targets. It is also evident that biological evaluations, especially in the case of 3-styrylchromones should be further considered.

Acknowledgments

Our thanks are due to the University of Aveiro, "Fundação para a Ciência e Tecnologia" and FEDER for funding the Organic Chemistry Research Unit and the project POCTI/QUI/38394/2001. Financial support of Hungarian-Portuguese Intergovernmental Science and Technology Cooperation Programme (Project No. P-2/01) is highly appreciated.

References

1. McClure, J. W. *The Flavonoids;* Harborne, J. B.; Mabry, T. J.; Mabry, H., Eds; Chapman and Hall: London, 1975; p 970.
2. Atassi, G.; Briet, P.; Berthelon, J.-P.; Collonges, F. *J. Med. Chem., - Chim. Ther.* **1985**, *20*, 393.
3. Middleton Jr., E.; Kandaswami, C. *The Flavonoids Advances in Research Since*; *1986* Harborne, J. B., Ed.; Chapman and Hall: London, 1994, p 619.
4. Bruneton, J. *Pharmacognosy, Phytochemistry and Medicinal Plants*; English Translation by Hatton, C. K.; Lavoisier Publishing: Paris, 1995; p 265.
5. Harborne, J. B.; Williams, C. A. *Phytochemistry* **2000**, *55*, 481.
6. Wagner, H.; Lacaille-Dubois, M.-A. *Flavonoids and Bioflavonoids 1995 – Proceedings of the International Bioflavonoid Symposium* Antus, S.; Gábor, M.; Vetschera, K., Eds; Akadémiai Kiadó: Budapest, 1996; p 53.
7. Gerwick, W. H.; Lopez, A.; Van Duyne, G. D.; Clardy, J.; Ortiz, W.; Baez, A. *Tetrahedron Lett.* **1986**, *27*, 1979.
8. Gerwick, W. H. *J. Nat. Prod.* **1989**, *52*, 252.
9. Jain, N.; Gambhir, G.; Krishnamurty, H. G. *Indian J. Chem.* **2001**, *40B*, 278.
10. Price, W. A.; Silva, A. M. S.; Cavaleiro, J. A. S. *Heterocycles* **1993**, *36*, 2601.
11. Davies, S. G.; Mobbs, B. E.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans I* **1987**, 2597.
12. Silva, A. M. S.; Cavaleiro, J. A. S.; Elguero, J. *Liebigs Ann./Recueil* **1997**, 2065.
13. Prakash, O. *Aldrichimica Acta* **1995**, *28*, 63.
14. Sabitha, G. *Aldrichimica Acta* **1996**, *29*, 15.
15. Sonawane, S. A.; Chavan, V. P.; Shingare, M. S.; Karale, B. K. *Indian J. Heterocycl. Chem.* **2002**, *12*, 65.
16. Karale, B. K.; Gill, C. H.; Shingare, M. S. *Indian J. Heterocycl. Chem.* **2003**, *12*, 267.
17. Silva, V. L. M.; Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S. *"5th Organic Chemistry Meeting of the Portuguese Chemical Society and 1st Portuguese-Japanese Symposium"*, Aveiro, July 2003, *PO102*, p 148.
18. Sandulache, A.; Silva, A. M. S.; Pinto, D. C. G. A.; Almeida, L. M. P. M.; Cavaleiro, J. A. S. *New J. Chem.* **2003**, *27*, 1592.
19. Lokshin, V.; Heynderickx, A.; Samat, A.; Pèpe, G.; Guglielmetti, R. *Tetrahedron Lett.* **1999**, *40*, 6761.
20. Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S. *Tetrahedron Lett.* **1994**, *35*, 5899.
21. Singli, M.; Grover, S. K. *Indian J. Chem.* **1994**, *33B*, 1083.

22. Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S. *Tetrahedron Lett.* **1994**, *35*, 9459.
23. Silva, A. M. S.; Tavares, H. R.; Cavaleiro, J. A. S. *Heterocycl. Commun.* **1996**, *2*, 251.
24. Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S. *J. Heterocycl. Chem.* **1996**, *33*, 1887.
25. Silva, A. M. S.; Pinto, D. C. G. A.; Tavares, H. R.; Cavaleiro, J. A. S.; Jimeno, M. L.; Elguero, J. *Eur. J. Org. Chem.* **1998**, 2031.
26. Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S.; Foces-Foces, C.; Llamas-Sainz, A. L.; Jagerovic, N.; Elguero, J. *Tetrahedron* **1999**, *55*, 10187.
27. Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S. *Heterocycl. Commun.* **1996**, *2*, 145.
28. Reddy, B. P.; Krupadanam, G. L. *J. Heterocycl. Chem.* **1996**, *33*, 1561.
29. Pinto, D. C. G. A.; Silva, A. M. S.; Almeida, L. M. P. M.; Cavaleiro, J. A. S.; Levai, A.; Patonay, T. *J. Heterocycl. Chem.* **1998**, *35*, 217.
30. Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S. *New J. Chem.* **2000**, *24*, 85.
31. Santos, C. M. M.; Silva, A. M. S.; Cavaleiro, J. A. S. *Eur. J. Org. Chem.* **2003**, 4575.
32. Miya, M. B.; Ramadas, S.; Krupadanam, G. L. D. *Indian J. Chem.* **1998**, *37B*, 579.
33. Doria, G.; Romeo, C.; Forgione, A.; Sberze, P.; Tibolla, N.; Corno, M. L.; Cruzzola, G.; Cadelli, G. *Eur. J. Med. Chem. - Chim. Ther.* **1979**, *14*, 347.
34. Desideri, N.; Conti, C.; Mastromarino, P.; Mastropaolo, F. *Antiviral Chem. Chemother.* **2000**, *11*, 373.
35. Peixoto, F.; Barros, A. I. R. N. A.; Silva, A. M. S. *J. Biochem. Mol. Toxicol.* **2002**, *16*, 220.
36. Bors, W.; Heller, W.; Michel, C.; Stettmaier, K. *Handbook of Antioxidants* Cadenas, E.; Packer, L., Eds; Marcel Dekker: New York, 1996, p 409.
37. *Flavonoids in Health and Disease*; Rice-Evans, C. A.; Packer, L., Eds; Marcel Dekker: New York, 1998.
38. Fernandes, E.; Carvalho, F.; Silva, A. M. S.; Santos, C. M. M.; Pinto, D. C. G. A.; Cavaleiro, J. A. S.; Bastos, M. L. *J. Enz. Inhib.* **2002**, *17*, 45.
39. Fernandes, E.; Carvalho, M.; Carvalho, F.; Silva, A. M. S.; Santos, C. M. M.; Pinto, D. C. G. A.; Cavaleiro, J. A. S.; Bastos, M. L. *Arch. Toxicol.*, **2003**, *77*, 500.
40. Filipe, P.; Silva, A. M. S.; Morlière, P.; Brito, C. M.; Patterson, L. K.; Hug, G. L.; Silva, J. N.; Cavaleiro, J. A. S.; Mazière, J.-C.; Freitas, J. P.; Santus, R. unpublished results.
41. Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S.; Almeida, L. M. P. M.; Tavares, H. R.; Patonay, T.; Lévai, A. *Proceedings of the 7th Blue Danube Symposium on Heterocyclic Chemistry*, 1998, *Compact Disc.*
42. Kelkar, A. S.; Letcher, R. M.; Cheung, K.-K.; Chiu, K.-F.; Brown, G. D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3732.
43. Pinto, D. C. G. A.; Silva, A. M. S.; Carrillo, J. R.; Díaz-Ortiz, A.; de la Hoz, A.; Cavaleiro, J. A. S. *Synlett* **2003**, 1415.
44. Silva, A. M. S.; Silva, A. M. G.; Tomé, A. C.; Cavaleiro, J. A. S. *Eur. J. Org. Chem.* **1999**, 135.
45. Tóth, G.; Levai, A.; Szollósy, A.; Duddeck, H. *Tetrahedron* **1993**, *49*, 863, and references cited therein.
46. Silva, A. M. S.; Vieira, J. S.; Cavaleiro, J. A. S.; Patonay, T.; Levai, A.; Elguero, J. *Heterocycles* **1999**, *51*, 481.

47. Silva, A. M. S.; Vieira, J. S.; Brito, C. M.; Cavaleiro, J. A. S.; Patonay, T.; Levai, A.; Elguero, J. *Monatsh. Chem.* **2003**, in press.
48. Takagi, K.; Tanaka, M.; Murakami, Y.; Morita, H.; Aotsuka, T. *Eur. J. Med. Chem. - Chim. Ther.* **1986**, *21*, 65.
49. Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S. *Heterocycl. Commun.* **1997**, *3*, 433.
50. Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S. *J. Heterocycl. Chem.* **2000**, *37*, 1629.
51. Silva, V. L. M.; Silva, A. M. S.; Pinto, D. C. G. A.; Cavaleiro, J. A. S. *10th Blue Danube Symposium on Heterocyclic Chemistry*, Vienna, September, 2003, *PO167*.