

2-STYRYLCHROMONES: BIOLOGICAL ACTION, SYNTHESIS AND REACTIVITY

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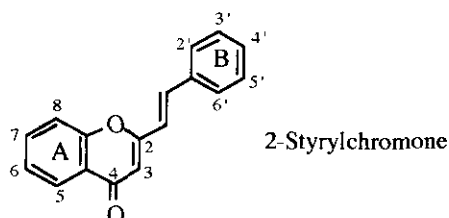
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Abstract - A brief discussion of the natural occurrence and biological action of 2-styrylchromones is considered in this review; for these compounds and their 3-isoanalogues a thorough description of the successful synthetic strategies is presented. Structural characterization (nmr and mass spectra) and reactivity in Diels-Alder and photooxidation reactions are other important features of 2-styrylchromones to be considered.

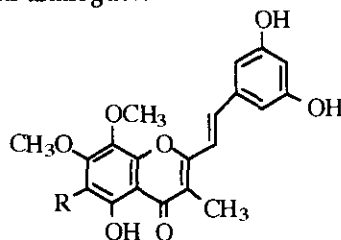
INTRODUCTION

Chromones (4*H*-1-benzopyran-4-ones) and their 2-phenyl derivatives (flavones) are abundantly distributed throughout the plant kingdom^{1,2} and are known to exhibit a wide variety of biological activity.^{3,4} In 1925, Robinson⁵ reasoned through the association of benzoyl and cinnamoyl natural products, that the abundance of flavones in nature makes it probable that representative 2-styrylchromones are naturally occurring as well. Although Venkataraman suggested the opposite, ("the occurrence of 2-styrylchromone derivatives in nature is doubtful"⁶) there was little debate over their potential pharmacological activity. Thus the synthesis of 2-styrylchromones was underway some six decades prior to the isolation of the first natural product.



ISOLATION AND BIOLOGICAL ACTIVITY

Although one of the rarest classes of natural chromones,^{7,8} both natural and synthetic 2-styrylchromones have shown a remarkable variety of biological activities.⁷⁻¹⁰ Only two naturally occurring 2-styrylchromones are known: Hormothamnione (**1a**, characterized in 1986⁷) and 6-desmethoxy-hormothamnione (**1b**, characterized in 1991⁸); both were found in extracts from blue-green algae, *Chrysophaeum taylori* in 1984 off the northern coast of Puerto Rico.⁸ Originally identified as *Hormothamnion enteromorphoides*, the taxonomy of these natural styrylchromones has since been revised. Specifically, **1a** has shown cytotoxicity toward P388 leukemia and HL-60 human promyelocytic cells *in vitro* and appears to operate by inhibiting the synthesis of RNA.⁷ This potent biological activity has stimulated interest in practical synthetic strategies toward these compounds and has resulted in three syntheses of **1a** as well as preparations of dozens of unnatural analogues.



1a, R=OCH₃ Hormothamnione
1b, R=H 6-Desmethoxyhormothamnione

Prior to the isolation of hormothamnione (**1a**), studies were carried out on numerous synthetic 2-styrylchromones as allergy inhibitors. Several compounds, all substituted at C-6 with a carboxylic acid group, have exhibited significant levels of anti-allergic activity when taken orally.⁹

More recently, synthetic 2-styrylchromone derivatives have shown anti-tumor activity against colon 38 tumors.¹⁰ Carboxylate substitution at C-6 again appears to be crucial for activity. 2-Styryl-chromone-8-acetic acid derivatives have also shown anticancer activity.¹⁰

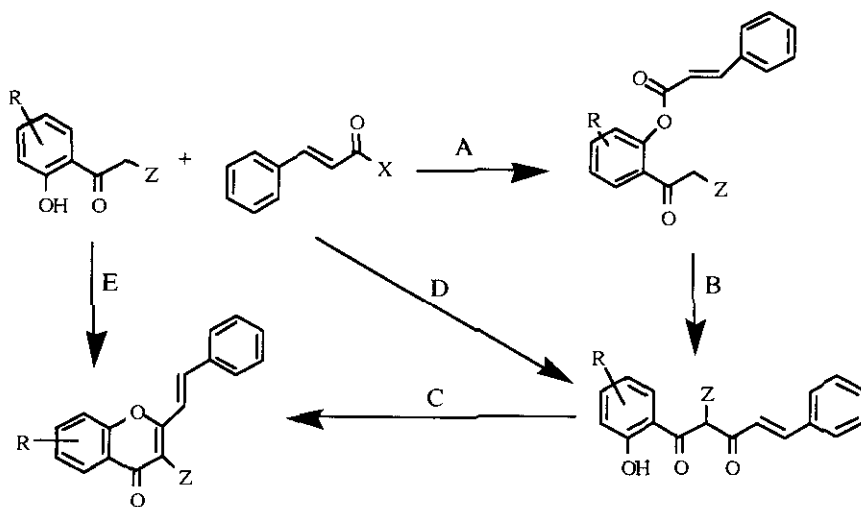
SYNTHESIS

The syntheses of 2-styrylchromones fall into several categories, all having a key carbon-carbon bond forming step. All of the strategies rely on classic, high-yielding convergent reactions. The approaches used are: 1) Baker-Venkataraman rearrangement, 2) Allan-Robinson condensation,

3) aldol condensation / oxidative ring closure, 4) intramolecular Wittig reaction and 5) 2-methylchromone / benzaldehyde condensation. A sixth approach, although not generally used, utilizes an acid catalyzed ring closure of an acetylenic ketone in the preparation of unsubstituted 2-styrylchromone. The preparation of 3-styrylchromones, although not naturally occurring and rarely cited in the literature, will be addressed in this section as well. In the schemes that follow, the different substituents on the A and B rings are generally identified by R and R'.

1) Baker-Venkataraman Rearrangement Approach:

The most common method for the construction of the 2-styrylchromone ring system relies on the *O*-acylation of a substituted *o*-hydroxyacetophenone with any of a number of cinnamic acid derivatives. Base-induced Baker-Venkataraman rearrangement^{11,12} (or a modification of this method) to the 2-cinnamoyl-*o*-hydroxyacetophenone preceeds an oxidative ring closure to the 2-styrylchromone.¹³⁻¹⁷ Depending on the conditions used, the *o*-cinnamoyloxyacetophenone and/or the 2-cinnamoyl-*o*-hydroxyacetophenone may not be isolated. Scheme I summarizes the variations on this approach.

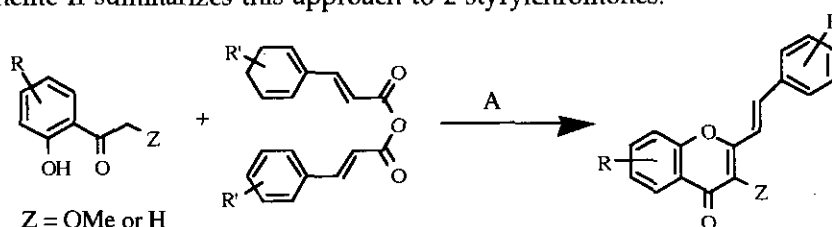


A: Z = H, X = OH; POCl₃, pyridine. **B:** KOH, pyridine, room temperature or NaH, DMSO, room temperature. **C:** 2% H₂SO₄ in AcOH, reflux, 1 h or 2% HCl in AcOH, reflux 1 h. **D:** Z = H, X = -O₂CAr, (n-Bu)₄N⁺HSO₄⁻, C₆H₆, K₂CO₃(aq.), 70-80°C. **E:** Z = CH₃ or Ph, X = Cl, K₂CO₃, acetone, reflux, 12 h.

Scheme I

2) Allan-Robinson Approach:

One of the earlier synthetic approaches to 2-styrylchromones involves the condensation of a cinnamoyl anhydride with a polyoxygenated (hydroxy and/or methoxy) *o*-hydroxyacetophenone in the presence of the corresponding sodium or potassium cinnamate.^{5,6} In this reaction, *O*-acylation of the *o*-hydroxyacetophenone, subsequent rearrangement to the 2-cinnamoyl-*o*-hydroxyacetophenone, and cyclization occur in one experimental step. Base-induced hydrolysis of any formed cinnamate esters results in the formation of polyhydroxylated 2-styrylchromones.⁵ The harsh reaction conditions (180°C, no solvent) place limits on the general applicability of this method. Scheme II summarizes this approach to 2-styrylchromones.

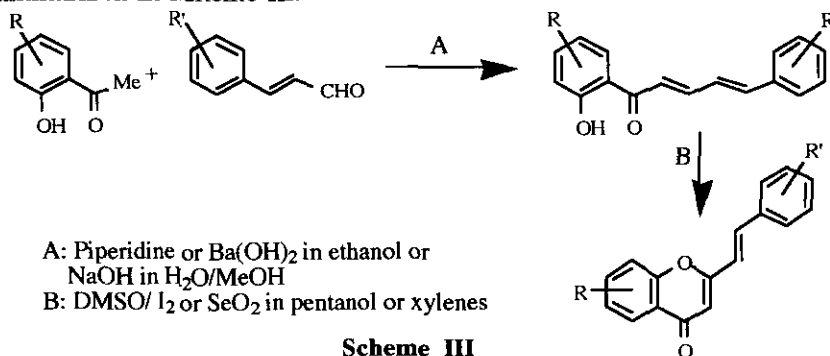


A: ArCH=CHCO₂Na, fusion, 3-8 h

Scheme II

3) Aldol Condensation/Oxidative Cyclization Approach:

The base-catalyzed condensation of cinnamaldehydes with *o*-hydroxyacetophenones in alcohol solutions affords *o*-hydroxy-2-cinnamylideneacetophenones. These can then be smoothly converted to the 2-styrylchromones using either DMSO with a catalytic amount of iodine,^{18,19} or SeO₂.²⁰ Interestingly, in 1932, Venkataraman⁶ successfully condensed cinnamaldehyde with *o*-hydroxyacetophenone but was unable to facilitate the closure to the pyranone ring. This method is summarized in Scheme III.

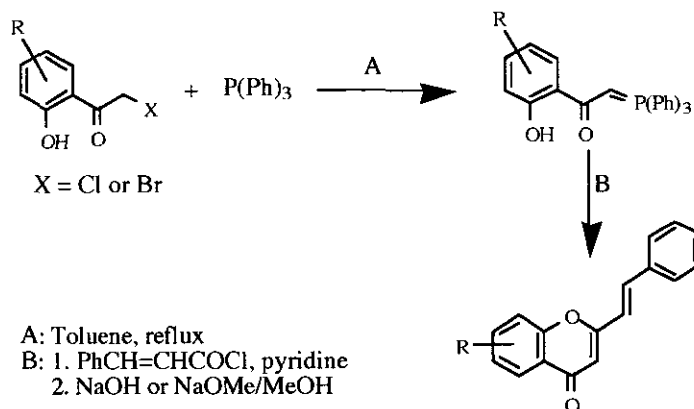


A: Piperidine or Ba(OH)₂ in ethanol or NaOH in H₂O/MeOH
B: DMSO/ I₂ or SeO₂ in pentanol or xylenes

Scheme III

4) Intramolecular Wittig Approach:

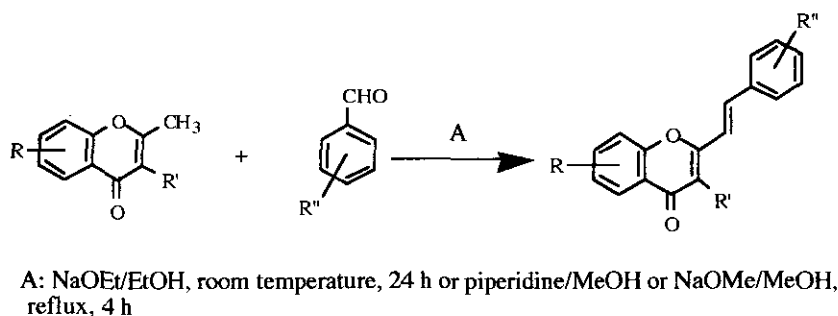
A novel approach to 2-styrylchromones utilizes a condensation between [1-(2-hydroxy-benzoyl)alkylidene]triphenylphosphoranes and cinnamoyl chloride.^{21,22} An intramolecular Wittig reaction of the presumed *o*-cinnamyl ester intermediate provides good yields of the target compounds (Scheme IV).



Scheme IV

5) 2-Methylchromone/Benzaldehyde Condensation Approach. Synthesis of hormothamnione:

There are several practical preparations of 2-styrylchromones that rely on the base-induced condensation of a 2-methylchromone with a substituted benzaldehyde (Scheme V).

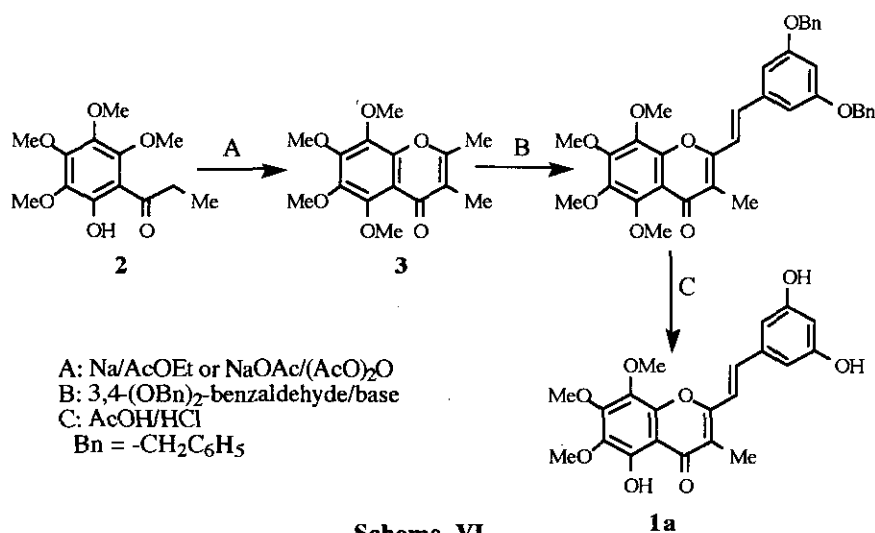


Scheme V

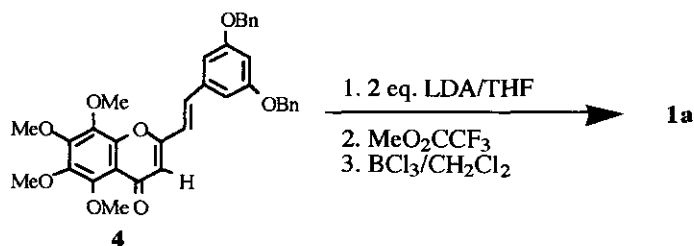
Heilbron²³ and Venkataraman^{6,24} synthesized several styrylchromones using this approach in the 1920's and 30's and it is through the use of this method that the three syntheses of hormothamnione (**1a**) were achieved.²⁵⁻²⁷ Several 3-nitro-2-styrylchromones were also prepared

using this technique and used as precursors to fused pyrrole-benzopyran ring systems.²⁸ Brion²⁹ used this method as well in the preparation of several (2-styrylchromon-8-yl)acetic acids.

In two syntheses of **1a**, the key intermediate propiophenone (**2**) was cyclized to the corresponding 2,3-dimethylchromone (**3**) as shown in Scheme VI.^{25,26} Condensation of this **3** with 3,5-di-benzyloxybenzaldehyde using sodium methoxide and sodium ethoxide respectively, followed by hydrolysis and selective demethylation at C-5 gave **1a** (Scheme VI).

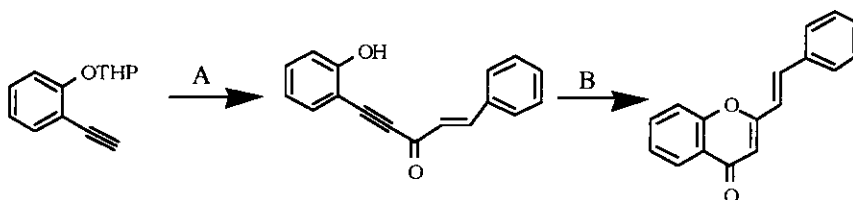


McGarry and Detty,²⁷ in their studies toward the synthesis of **1a**, used this approach for the preparation of 2-styrylchromone (**4**). The selective lithiation of **4** at C-3, using two equivalents of LDA in THF at -78°C, allows for the introduction of C-3 methyl substituents at later stages (Scheme VII). Selective demethylation at C-5 together with debenzylation of the 3' and 5'-benzyloxy groups occurs smoothly in the presence of boron trichloride.



6) Cyclization of Acetylenic Ketones:

Obrecht has modified an acid-catalyzed cyclization of conjugated acetylenic ketones in a synthesis of 2-styrylchromone³⁰ (Scheme VIII).



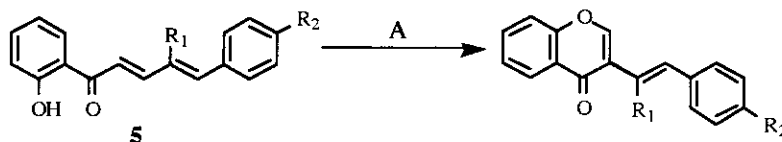
A: 1. *n*-BuLi, THF 2. PhCH=CHCHO 3. MnO₂ 4. Pyridinium *p*-toluenesulfonate/EtOH
 B: HBr (aq.), dioxane
 THP = tetrahydropyranyl

Scheme VIII

7) Synthesis of 3-Styrylchromones :

There are three methods used for the preparation of 3-styrylchromones. The activation of 3-bromochromones has been effectively demonstrated *via* a Pd⁰ insertion into the C-Br bond. Styrylation with styrene gave 3-styrylchromone in high yield.³¹ Alonso and Brossi, in their work on the synthesis of **1a**, selectively brominated 2,3-dimethylchromone at the C-3 methyl group. Wittig reaction of the derived phosphonium salt with a MOM-protected 3,5-dihydroxybenzaldehyde, followed by acidification, gave the desired 3-styrylchromone.²⁵

The oxidative rearrangement of 2'-hydroxychalcones to isoflavones using thallium (III) nitrate followed by treatment with acid is a well-documented procedure.³² An analogous reaction involving the rearrangement of 2'-hydroxycinnamylideneacetophenones **5**, gives access to 3-styrylchromones (Scheme IX).³³



A: 1. Tl(NO₃)₃·3H₂O / MeOH / TMOF 2. H₃O⁺
 a) R₁ = Me; R₂ = H b) R₁ = Me; R₂ = Cl c) R₁ = Et; R₂ = Cl
 TMOF = Trimethyl orthoformate

Scheme IX

STRUCTURE AND REACTIVITY OF 2-STYRYLCHROMONES

Characterization and Stereochemistry:

The value of the vicinal H_α - H_β coupling constant ($^3J = 15$ - 17 Hz) clearly shows a *trans* stereochemistry in every 1H nmr spectrum reported for 2-styrylchromones. Due to the high degree of conjugation in the dienone portion of 2-styrylchromones, there appears to be a considerable barrier to rotation about the C_2 - C_α bond. The X-ray crystal structure of **1a**⁷ as well as detailed nmr experiments using NOE,^{18,33} (Figure 1), and NOESY²⁹ techniques with 2-styrylchromone indicate that these compounds exist in the *s-trans* conformation as crystalline materials as well as in solution.

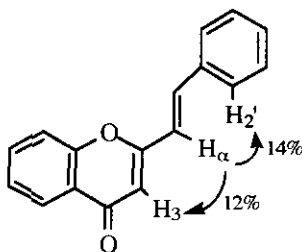


Figure 1 NOE Experiment: Irradiation of H_α of (*E*)-2-styrylchromone

Electron impact (EI) mass spectrometry is also helpful in the characterization of (*E*)-2-styrylchromones. These mass spectra show the following typical fragmentations: $(M-H)^+$, $(M-OH)^+$, $(M-CO)^+$, $(A_1+H)^+$, B_1^+ , B_2^+ , $(B_3-H)^+$.^{34,35} The capital letters A and B indicate fragments containing intact A- and B-rings (as shown in Figure 2); this is in accord with the terminology generally used in the description of EI mass spectra of chromones.³⁶ The molecular ion (M^+) has a typically high intensity and is often the base peak. Those fragments that are most important for structural elucidation are derived from the retro Diels-Alder reaction [$(A_1+H)^+$ and B_1^+], B_2^+ , and $(B_3-H)^+$.

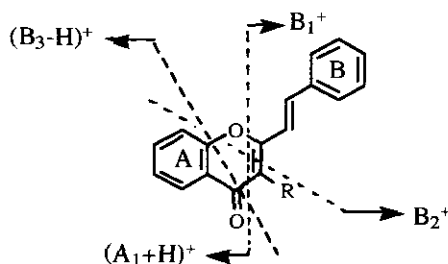


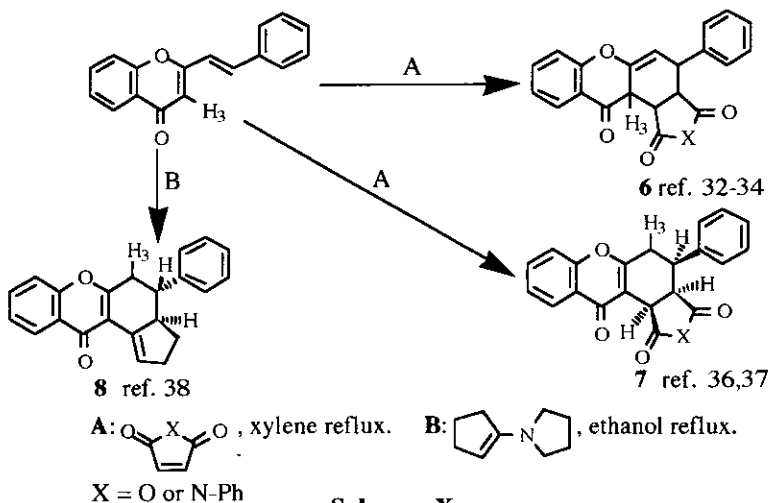
Figure 2 - Mass spectra of (*E*)-2-styrylchromones

Diels-Alder Reactions of 2-Styrylchromones:

Reactions involving the C₂-C₃ double bond in flavones and 2-styrylchromones are exceedingly rare. This is presumably due to the aromatic resonance contribution in the pyranone ring. Under extreme conditions, however, [4+2] cycloaddition reactions between 2-styrylchromones and electron-deficient dienophiles can be carried out. This suggests that the former can adopt an *s-cis* conformation, yet there is some dispute over the actual structure of the adducts. The earliest studies involved Diels-Alder reactions between 2-styrylchromones and maleic anhydride or N-phenylmaleimide in boiling xylene.³⁷⁻³⁹ Structural characterization was never carried out on these adducts although elemental analyses clearly showed 1:1 adduct formation. Thus, these products were assumed to have the expected 1,2,3,9a-tetrahydroxanthene (6) structure.

Elkashef⁴⁰ reacted *o*-, *m*-, and *p*-chlorostyryl-4-chromone with maleic anhydride and suggested the same general structure for the adducts. The proton nmr data provided for the *m*-chlorostyryl adduct (the only one characterized thusly), although not thoroughly interpreted, show a doublet signal at δ 7.78, assigned to H-4.

Letcher has suggested that the xanthene structures derived from these Diels-Alder reactions be revised to 1,2,3,4-tetrahydroxanthenes⁴¹⁻⁴³ (7) (Scheme X). Specifically, studies were carried out on reactions of (*E*)-2-styrylchromones with both electron deficient (path A) and electron rich (path B) dienophiles. All adducts were thoroughly characterized by extensive nmr studies, uv and ir spectroscopies.

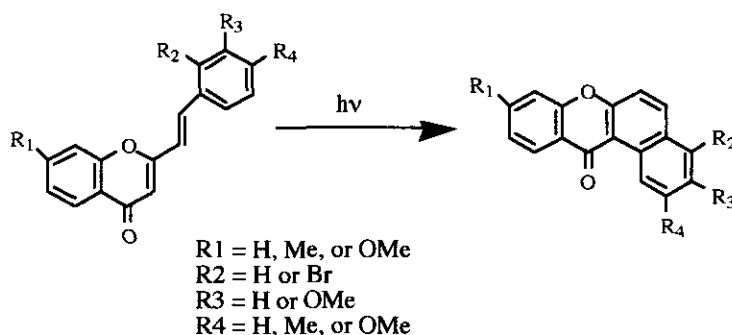


Scheme X

The 1,3-hydrogen shift that must accompany these reactions presumably is facilitated by the stabilized chromone product. In order for 3-methyl-2-styrylchromones to undergo Diels-Alder reactions in this manner, a 1,3-methyl migration is necessary; thus it is not surprising that these reactions have been unsuccessful to date.

Photo-oxidation of 2-Styrylchromones:

Irradiation of 2-styrylchromones facilitates a photo-oxidative cyclization to 12*H*-benzo[*a*]xanthen-12-ones. Although a facile entry into these fused ring systems, yields are typically between 10 and 20%^{44,45} (Scheme XI).



Scheme XI

CONCLUSION

A review of the literature reveals seven unique methods for the construction of 2-styrylchromones. Spectroscopic and X-ray analysis of these compounds clearly shows (*E*) stereochemistry as well as *s-trans* conformation about the vinyl portion of the molecule. Extensive work in the characterization of Diels-Alder adducts using (*E*)-2-styrylchromones as dienes, has shown convincing evidence that suggests a reevaluation of previously documented xanthene adducts.

ACKNOWLEDGEMENTS

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