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Arylxanthones and arylacridones: a synthetic overview

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Abstract: Arylxanthones and arylacridones although not yet found in nature are becoming an important group of heterocyclic compounds due to their promising biological activities. Their central cores, xanthone and acridone, are recognized as interesting motifs for drug development mainly to be used in antitumour chemotherapy. The synthesis of this type of compounds is still scarce but several successful examples were recently published and a large variety of arylated xanthone and acridone derivatives were prepared. A systematic survey of the literature dedicated to their synthesis will be presented and discussed in this review.

Keywords: 4-quinolones; acridones; Diels–Alder reactions; styrylchromones; TRAMECH VIII; xanthones.

Introduction

Xanthone (9*H*-xanthen-9-one) derivatives (Fig. 1), natural or synthetic, comprise a group of structurally diverse biologically active oxygen heterocyclic compounds. Many derivatives exhibited noticeable biological properties, from which antitumor effects can be highlighted [1, 2]. This family has been studied for over a century and several reviews, covering their natural sources [3–5], biological activities [6], chemical synthesis [7, 8] and even biosynthesis [1, 9], were published. Nonetheless, the field of xanthone chemistry is growing rapidly, due to several update publications, it is noteworthy that arylxanthones are not the focus of these articles. There are no evidences that arylxanthones occur in nature but some synthetic derivatives already proved their importance in medicinal chemistry research [10–12].

Acridone (acridin-9(10*H*)-one) derivatives (Fig. 1), the xanthones aza-analogues, are also an important group of natural bioactive compounds [13]. Both natural and synthetic derivatives are recognized as possible chemotherapeutic agents [14, 15]. These derivatives are less studied but some synthetic methodologies were developed and recently reviewed [13, 14]. Likewise for the above mentioned xanthones, arylacridones are not found in nature and only a few papers reporting their synthesis can be found in literature.

This review pinpoints the latest progress in the synthesis of arylxanthones and arylacridones, mainly mono- and diaryl derivatives. Developments for the synthesis of more intricate examples will be also disclosed. Through this review the structural numbering will follow the monomeric parent xanthone and acridone cores depicted in Fig. 1.

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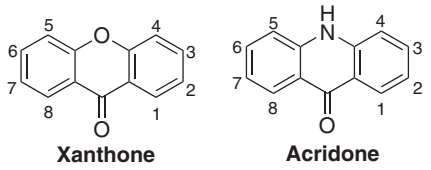


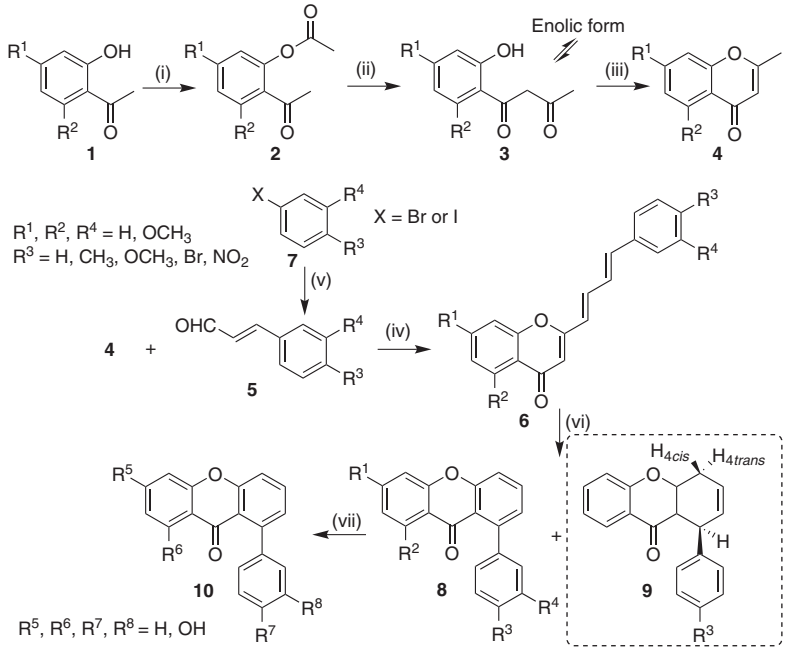
Fig. 1: Xanthone and acridone monomer cores with numbering.

Synthesis of arylxanthones

The ubiquitous 9*H*-xanthen-9-one core occurs in a large number of naturally occurring and synthetic compounds and several studies highlight their biological and pharmacological importance [1, 2, 16]. As far as we know, 9*H*-xanthen-9-ones linked to an aryl group are scarce and only a few synthetic derivatives have been reported. Herein, we will review the synthesis of monoarylated structures at positions 1, 2 or 3 of the 9*H*-xanthen-9-one scaffold, 2,3-diaryl-9*H*-xanthen-9-ones and other complex related analogues.

Synthesis of monoaryl-9*H*-xanthen-9-ones

A series of 1-aryl-9*H*-xanthen-9-ones have been prepared starting from 2′-hydroxy acetophenones **1**, in a multistep sequence [17, 18] (Scheme 1). It involves acetylation of 2′-hydroxyacetophenones **1**, base-catalyzed Baker–Venkataraman rearrangement to afford 1,3-diketones **3** and cyclodehydration using a catalytic amount of *p*-toluenesulfonic acid (*p*-TSA) to give the corresponding 2-methyl-4*H*-chromen-4-ones **4**. The condensation of 2-methyl-4*H*-chromen-4-ones **4** with cinnamaldehydes **5** carried out in the presence of sodium ethoxide (generated in situ) at room temperature provides 2-[(1*E*,3*E*)-4-arylbuta-1,3-dien-1-yl]-4*H*-chromen-4-ones **6** in good yields (62–80 %). The parent cinnamaldehyde was available while the 4-substituted cinnamaldehydes



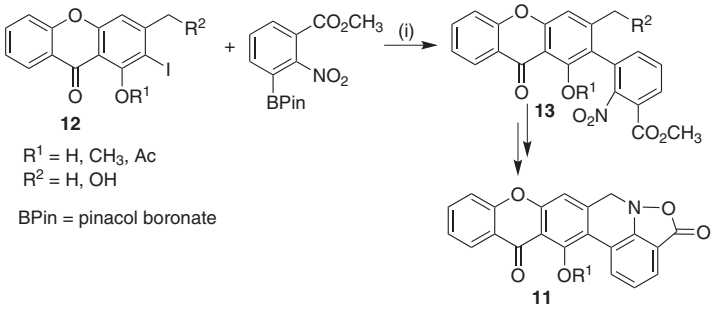
Scheme 1: Reagents and conditions: (i) MeCOCl, pyridine, r.t., 2 h; (ii) NaH, THF, reflux, 2 h; (iii) *p*-TSA, DMSO, 100 °C, 2 h; (iv) Na, EtOH, r.t., 12 h; (v) acrolein diethylacetal, Bu_4NOAc, K_2CO_3, $Pd(OAc)_2$, DMF, 90 °C, 4 h; (vi) I_2, 1,2,4-TCB, reflux, 48 h; (vii) BBr_3, dry CH_2Cl_2, −78 °C to r.t., 3–4 h.

5 were prepared from the reaction of the appropriate halobenzenes **7** with acrolein diacetal using palladium acetate as catalyst in DMF at 90 °C [17]. The synthesis of (*E*)-3-(3,4-dimethoxyphenyl)acrylaldehyde involved a two-step strategy starting with an acid-catalyzed iodination of 1,2-dimethoxybenzene to prepare the corresponding iodobenzene **7** followed by the palladium(II)-catalyzed reaction described before for the synthesis of cinnamaldehydes **5** [18]. 2-[(1*E*,3*E*)-4-Arylbuta-1,3-dien-1-yl]-4*H*-chromen-4-ones **6** undergo subsequent electrocyclization and oxidation reactions in the presence of a catalytic amount of iodine in refluxing 1,2,4-trichlorobenzene (1,2,4-TCB) to obtain the target 1-aryl-9*H*-xanthen-9-ones **8** (35–70 %). From this reaction it was also possible to isolate some semi-oxidized intermediates of the final xanthones, 1-aryl-1,4-dihydro-9*H*-xanthen-9-ones **9**. In order to prepare hydroxylated derivatives, demethylation of methoxyxanthones **8** was attained by their treatment with boron tribromide in anhydrous dichloromethane. Unfortunately, deprotection of 6-OMe xanthone did not occur and to overcome this drawback methoxyethoxymethyl (MEM) was used instead of methyl protecting group, in a similar procedure described in Scheme 1 [18]. Hydroxylated 1-aryl-9*H*-xanthen-9-ones **10** were shown to be remarkable scavengers of reactive oxygen species (ROS) and reactive nitrogen species (RNS), in non-cellular systems [18].

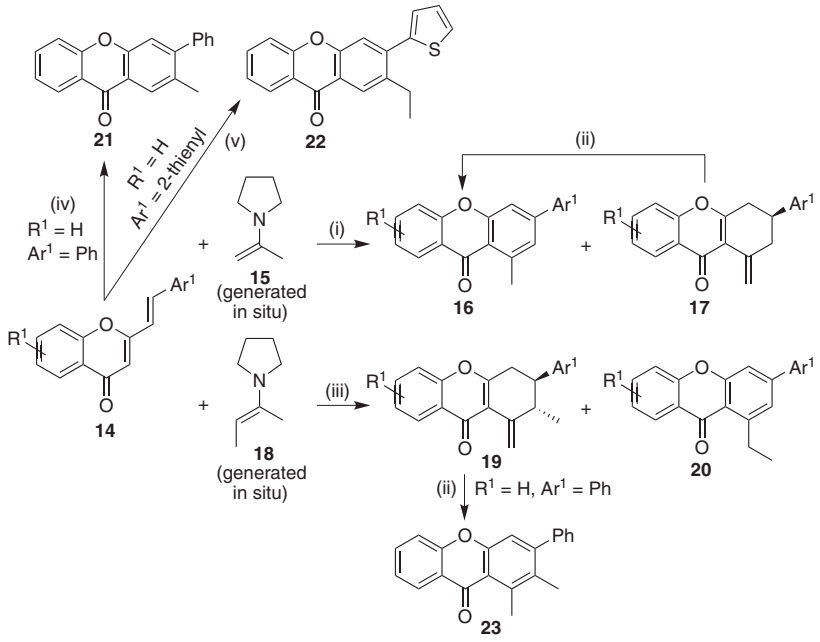
A reference to 2-phenylxanthone appeared in a European Patent and later also as US Patent [19] describing a novel crystalline aromatic polyketone copolymer and the process for producing the same. In this invention, aromatic ketones such as xanthone and 2-phenylxanthone were used as polymerization solvents, although no reference to their synthesis was presented.

The synthesis of parnafungin A and C **11**, hexacyclic antifungal agents bearing a xanthone unit, involved Suzuki–Miyaura coupling reaction of substituted 2-iodo-9*H*-xanthen-9-ones **12** with an excess of 3-carbomethoxy-2-nitrophenyl pinacol boronate as the first key step. The resulting 2-(3-carbomethoxy-2-nitrophenyl)-9*H*-xanthen-9-ones **13** were obtained in good yields (53–60 %) using the system $Pd(OAc)_2$/Sphos in a 3:1 mixture of THF/H_2O (Scheme 2) [20].

[4 + 2] Cycloaddition reaction of 2-styrylchromone derivatives **14** with 2-pyrrolidinoprop-1-ene **15**, generated in situ from acetone and a catalytic amount of pyrrolidine, provided a wide variety of 3-aryl-1-methyl-9*H*-xanthen-9-ones **16** (56–76 % yield, Scheme 3) [21]. It was also possible to isolate a couple of 3-aryl-1-methylidene-1,2,3,4-tetrahydro-9*H*-xanthen-9-ones **17** as minor products, which after treatment with a mixture of acetic acid/sulfuric acid yielded the corresponding 3-aryl-1-methyl-9*H*-xanthen-9-ones **16**. The mechanism proposed for this [4 + 2] inverse electron demand cycloaddition reaction involves the formation of tetrahydroxanthones **17** and subsequent migration of the exocyclic double bond and dehydrogenation of the C-ring to afford the fully aromatized 1-methyl-9*H*-xanthen-9-ones **16**. Meanwhile, cycloaddition reaction with the pyrrolidine enamine of butan-2-one **18** led to 3-aryl-2-methyl-1-methylidene-1,2,3,4-tetrahydro-9*H*-xanthen-9-ones **19** as major products (36–55 %) with a small amount of 3-aryl-1-ethyl-9*H*-xanthen-9-ones **20** (13–16 % yield, Scheme 3). These results indicate that two isomers were produced during enamine formation with butan-2-one, 2-pyrrolidinobut-2-ene as major product and 2-pyrrolidinobut-1-ene as minor component. Moreover, the synthesis of 2-methyl-3-aryl- **21** and 2-ethyl-3-heteraryl- **22** -9*H*-xanthen-9-ones was only possible when the pyrrolidine group is at the end of the alkyl chain as in aldehydes (propanal and butanal, respectively) rather than ketones (Scheme 3). Treating 2-methyl-1-methylidene-3-phenyl-1,2,3,4-tetrahydro-9*H*-xanthen-9-one with



Scheme 2: Reagents and conditions: (i) $Pd(OAc)_2$/Sphos, K_3PO_4, THF/H_2O (3:1), 80 °C, 1–2 h.



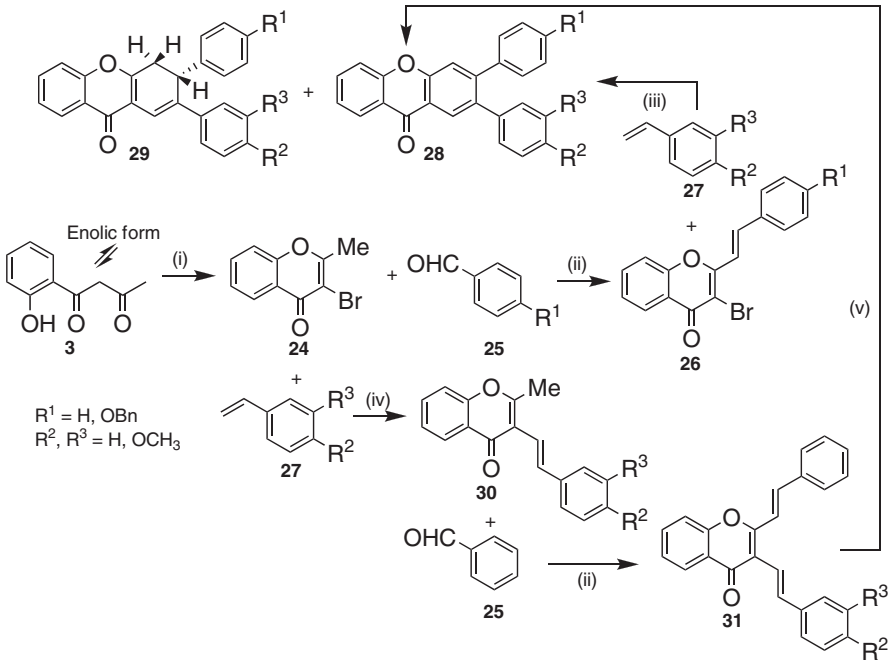
Scheme 3: Reagents and conditions: (i) refluxing acetone, 2–28 h; (ii) AcOH/H_2SO_4, 100 °C, 3 h; (iii) refluxing butan-2-one, 70 min-3 days; (iv) refluxing propanal, drop of pyrrolidine, 4 days; (v) refluxing butanal, drop of pyrrolidine, 4 days.

strong acid led to the corresponding 1,2-dimethyl-3-phenyl-9*H*-xanthen-9-one **23** in almost quantitative yield (Scheme 3) [21].

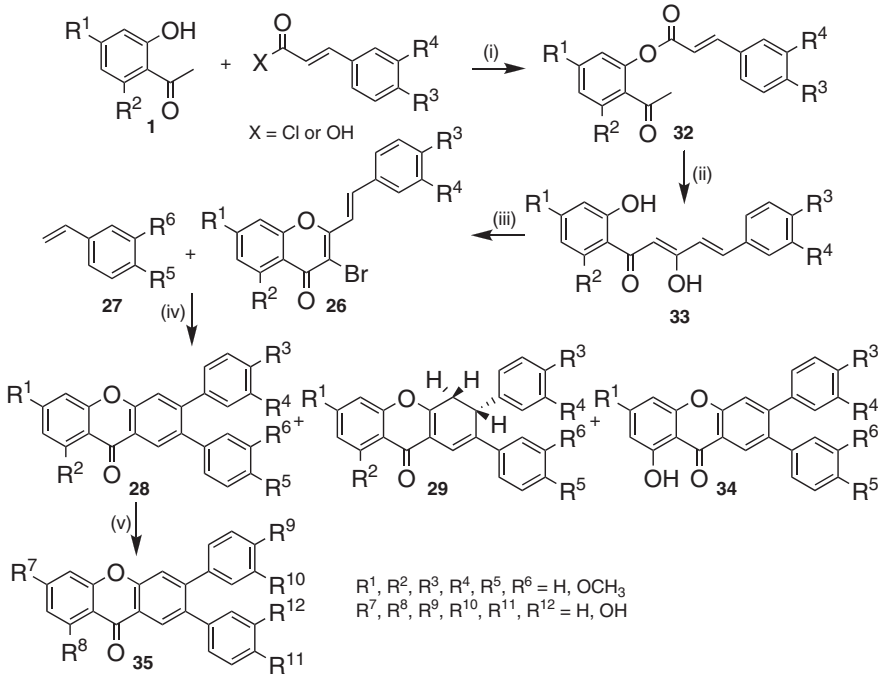
Synthesis of 2,3-diaryl-9*H*-xanthen-9-ones

Two different approaches were reported for the synthesis of 2,3-diaryl-9*H*-xanthen-9-ones. The first one uses 3-bromo-2-methyl-4*H*-chromen-4-one **24** as starting material, obtained through bromination, with bromine in ethanol, and acidic cyclization of 1,3-diketones **3**, in a one-pot process (Scheme 4) [22]. Aldol condensation of 3-bromo-2-methyl-4*H*-chromen-4-one **24** with benzaldehydes **25** (the reaction only occurred using parent benzaldehyde and 4-benzyloxybenzaldehyde) in the presence of sodium in methanol at room temperature afforded 3-bromo-2-styryl-4*H*-chromen-4-ones **26**, which undergo Heck reaction with styrenes **27** to produce 2,3-diaryl-9*H*-xanthen-9-ones **28** as major products (25–66 %) and the semi-oxidized xanthones **29** as minor products (6–27 %). The mechanism proposed involves Heck reaction of brominated chromones with styrenes to form 2,3-distyrylchromones followed by in situ electrocyclization, [1,5]-sigmatropic hydrogen migration to give 3,4-dihydroxanthones and oxidation reactions to achieve the corresponding 2,3-diaryl-9*H*-xanthen-9-ones [22]. On the other hand, Heck reaction of 3-bromo-2-methyl-4*H*-chromen-4-one **24** with styrenes **27** led to 2-methyl-3-styryl-4*H*-chromen-4-ones **30** (48–52 %). Subsequent aldol condensation was only possible with parent benzaldehyde **25** to form 2,3-distyryl-4*H*-chromen-4-ones **31** (53–69 %), which in refluxing 1,2,4-TCB gave the desired 2,3-diaryl-9*H*-xanthen-9-ones **28** (80–85 %) [23].

Due to the lack of reactivity of certain derivatives, a second and more general approach was developed to the synthesis of 2,3-diaryl-9*H*-xanthen-9-ones, starting from 2′-hydroxy acetophenones **1** and cinnamic acid derivatives (Scheme 5) [24]. The resulting 2-acetylphenyl cinnamates **32** (50–97 %) in the presence of potassium hydroxide in DMSO via Baker–Venkataraman rearrangement afforded 5-aryl-3-hydroxy-1-(2-hydroxyaryl)penta-2,4-dien-1-ones **33** in good yields (54–95 %). Phenyltrimethylammonium tribromide (PTT) in THF at room temperature promoted bromination and cyclization of these ketones to attain 3-bromo-2-styryl-4*H*-chromen-4-ones **26** (30–97 %) [24]. A great number of derivatives were obtained from the Heck reaction of several 3-bromo-2-styryl-4*H*-chromen-4-ones **26** with styrenes **27** carried out in the presence of



Scheme 4: Reagents and conditions: (i) 1. Br_2, EtOH, r.t., 2 h; 2. HCl, reflux, 2 h; (ii) Na, MeOH, r.t., 48 h; (iii) $Pd(PPh_3)_4$, PPh_3, Et_3N, NMP, 160 °C to reflux; (iv) $PdCl_2$, PPh_3, Et_3N, NMP, 160 °C, 9 h; (v) 1,2,4-TCB, reflux, 18 h.



Scheme 5: Reagents and conditions: (i) X = Cl, pyridine, r.t., 2 h; X = OH, $POCl_3$, pyridine, 60 °C, 2 h; (ii) KOH, DMSO, r.t., 2 h; (iii) PTT, THF, r.t., 12 h; (iv) $Pd(PPh_3)_4$, PPh_3, Et_3N, NMP, 160 °C to reflux; (v) BBr_3, dry CH_2Cl_2, –78 °C to r.t..

tetrakis(triphenylphosphine)palladium(0), triphenylphosphine, triethylamine and 1-methyl-2-pyrrolidin-1-one (NMP) as solvent: the desired 2,3-diaryl-9*H*-xanthen-9-ones **28** as major products (13–80 %), 2,3-diaryl-3,4-dihydro-9*H*-xanthen-9-one intermediates **29** (3–32 %) and also 6,7-diaryl-1-hydroxy-9*H*-xanthen-9-ones **34** (1–37 %) when 3-bromo-5-methoxy-2-styrylchromones were used as brominated derivatives (Scheme 5) [23].

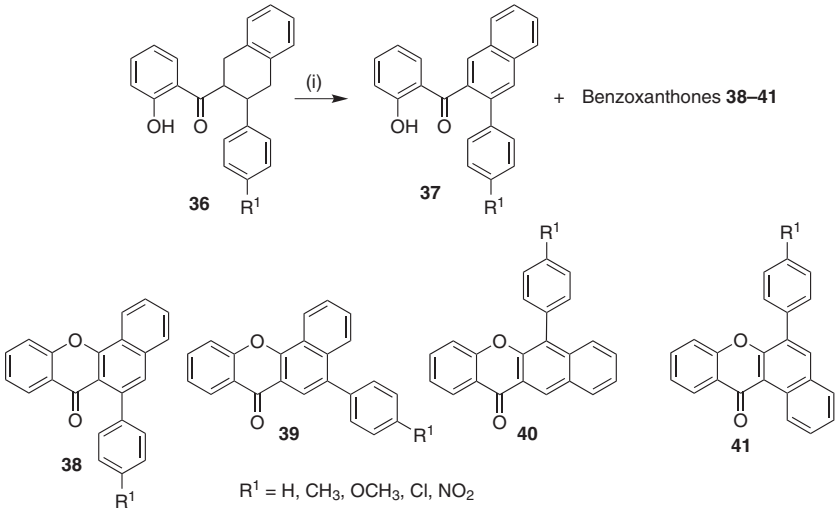
A series of hydroxylated 2,3-diaryl-9*H*-xanthen-9-ones **35** were prepared in moderated to good yields (37–94 %) after demethylation of 2,3-diaryl-9*H*-xanthen-9-ones **28** with boron tribromide in anhydrous dichloromethane [23, 24]. Some of these hydroxylated 2,3-diaryl-9*H*-xanthen-9-ones were tested for their ROS and RNS scavenging properties and were considered promising antioxidant agents taking into account the nanomolar to micromolar range of the IC_{50} values found [23].

Synthesis of arylbenzoxanthones

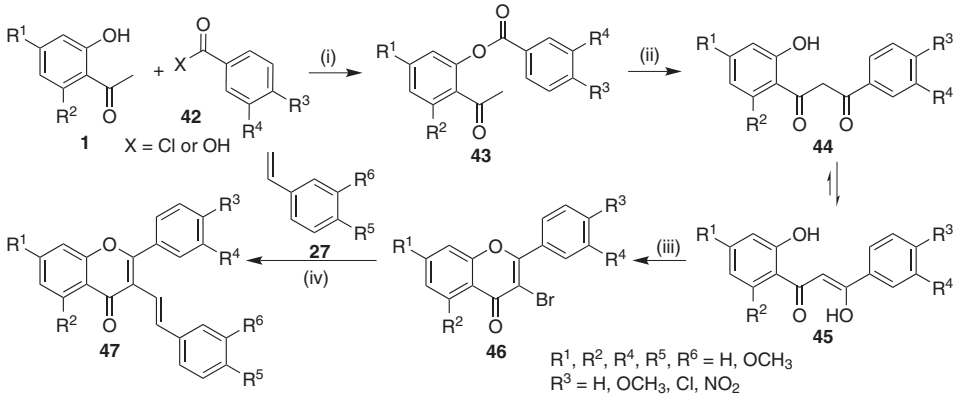
Benzoxanthones are a small class of xanthones with no significant representation in nature and only a few publications on their synthesis and/or biological activities have been reported in the last two decades. Nevertheless the most recent publications indicate that these tetracyclic ring systems can be potential lead compounds in the development of new antitumour agents [25, 26]. To the best of our knowledge arylbenzoxanthones are not found in natural sources and their synthesis is restricted [27, 28].

Four types of arylbenzoxanthones, 6-arylbenzo[*c*]xanthones **38**, 5-arylbenzo[*c*]xanthones **39**, 6-arylbenzo[*b*]xanthones **40** and 6-arylbenzo[*a*]xanthones **41**, were obtained as minor products in the oxidation of 3-aryl-1,2,3,4-tetrahydro-2-naphthyl 2-hydroxyphenyl ketones **36** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) under microwave irradiation (MW) conditions (Scheme 6) [27]. In addition to the low yields obtained in this reaction (1–17 %), selectivity is also very low being the nitro substituent selective towards the 6-arylbenzo[*c*]xanthones **38** whereas the methoxy group was selective towards the 6-arylbenzo[*b*] xanthones **40**. The reaction mechanism [27] seems to indicate that the methoxy group favors a 1,2-aryl shift, which is consistent with its electron-releasing effect.

Later our research group has also developed a new approach to obtain 5-arylbenzo[*c*]xanthones involving the photoinduced electrocyclization and oxidation of (*E*)-3-styrylflavones **47** (see below Scheme 9) [28]. Two strategies to synthesize the required (*E*)-3-styrylflavones **47** were established. The first one uses the Heck reaction of 3-bromoflavones **46**, obtained through previous established procedures, with styrenes **27** (Scheme 7) [28]. 2′-Hydroxyacetophenones **1**, benzoic acids or benzoyl chlorides **42**, were used to prepare 2-acetylaryl benzoates **43**. When using benzoic acids the catalytic system *N*,*N*′-dicyclohexylcarbodiimide (DCC) and 4-pyrrolidinopyridine (4-ppy) was used. In both conditions the benzoates **43** were obtained in very good yields (above 70 %). These esters were afterwards treated with base, potassium hydroxide or sodium hydride, to perform the Baker–Venkataraman rearrangement and obtain a tautomeric mixture of 3-aryl-1-(2-hydroxyphenyl)propane-1,3-diones **44**/(*Z*)-3-aryl-3-hydroxy-1-(2-hydroxyphenyl)prop-2-en-1-ones **45** in



Scheme 6: Reagents and conditions: (i) DDQ, 1,2,4-TCB, MW (800 W).

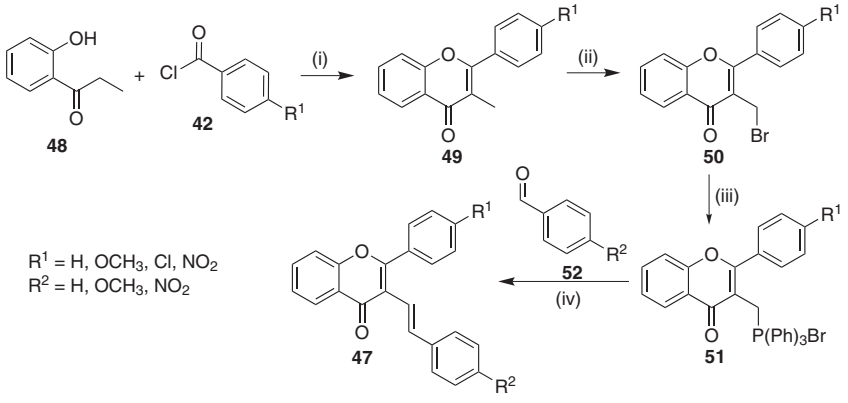


Scheme 7: Reagents and conditions: (i) X = Cl, dry pyridine, r.t., 24 h; X = OH, DCC, 4-ppy, CH_2Cl_2, r.t., 5 days; (ii) KOH, DMSO, r.t., 4 h or NaH, dry THF, reflux, 4 h; (iii) PTT, dry THF, r.t., 24–48 h; (iv) $Pd(OAc)_2$, K_2CO_3, Bu_4NBr, DMF, MW (300 W), 5–10 min.

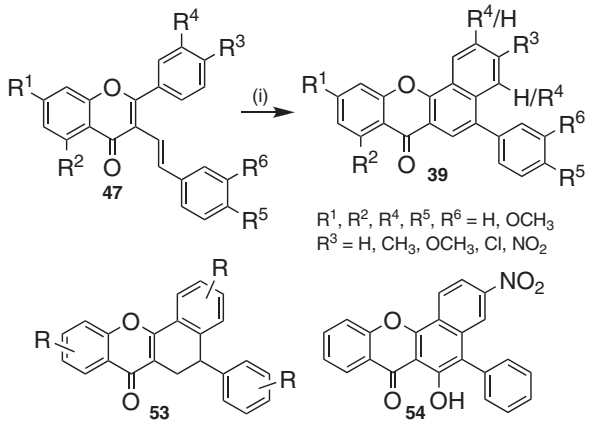
moderate to good yields (above 40 %). The use of sodium hydride was essential to perform the rearrangement in good yields for the polymethoxylated derivatives. Treating these ketones with PTT in THF at room temperature promotes bromination at their carbon C-2 and cyclization into 3-bromoflavones **46**. The yields were generally moderate although the presence of several methoxy substituents lowers the yields to values around 30 %.

Diastereoselective synthesis of (*E*)-3-styrylflavones **47** were obtained by the Heck/Jeffery reaction conditions of 3-bromoflavones **46** with styrenes **27** under MW irradiation, using palladium acetate, potassium carbonate, tetrabutylammonium bromide (TBAB) and DMF as solvent [28]. Although the (*E*)-3-styrylflavones **47** were the major products in several cases the yields were poor due to the formation of by-products such as the corresponding flavone derivatives. This was most evident in the case of polymethoxylated derivatives.

The second approach involves the synthesis of 3-methylflavones **49** and their transformation into 3-(bromotriphenylphosphoranyl)methylflavones **51** which were afterwards used in the diastereoselective synthesis of (*E*)-3-styrylflavones **47** through Wittig reactions (Scheme 8) [29]. The key intermediates in this procedure 3-methylflavones **49** were prepared, in very good yields (above 74 %) or moderate for the polymethoxylated derivatives (around 30 %), through a one-pot tandem reaction of 1-(2-hydroxyphenyl)propan-1-ones **48** with benzoyl chlorides **42**, using lithium bis(trimethylsilyl)amide (LiHMDS) as base [29, 30]. The selective bromination of 3-methylflavones **49** occurred with *N*-bromosuccinimide (NBS), benzoyl peroxide and using CCl_4 as solvent. The presence of other methyl groups or several methoxy substituents can interfere and lower the yield of the desired 3-bromomethylflavones **50**. The subsequent transformation of **50** into



Scheme 8: Reagents and conditions: (i) LiHMDS, dry toluene, r.t., 37 h; (ii) NBS, benzoyl peroxide, CCl_4, reflux, 7 h; (iii) PPh_3, dry toluene, reflux, 24–43 h; (iv) NaH, dry THF, r.t., 2.5 h.



Scheme 9: Reagents and conditions: (i) 1,2,4-TCB, I_2 (cat.), hυ (high pressure mercury lamp), 3–7 days.

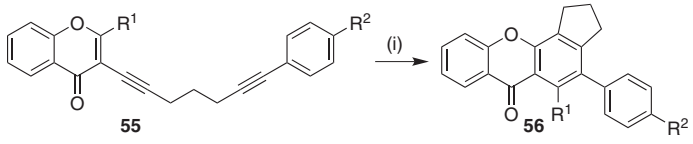
3-(bromotriphenylphosphoranyl)methylflavones **51** was accomplished by their reaction with triphenylphosphine in toluene. Finally, Wittig reaction was successfully employed in the synthesis of (*E*)-3-styrylflavones **47** using 3-(bromotriphenylphosphoranyl)methylflavones **51** and benzaldehydes **52** (Scheme 8).

The one-pot photoinduced electrocyclization and oxidation of (*E*)-3-styrylflavones **47** gave 5-aryl-7*H*-benzo[*c*]xanthen-7-ones **39** (Scheme 9) [28]. The procedure presents few drawbacks such as long reaction times and, when several methoxy substituents are present, yields are lower than 30 %. Long reaction times are essential to obtain the xanthone derivatives, otherwise the oxidation step into 5-aryl-7*H*-benzo[*c*]xanthen-7-ones **39** did not occur and 5-aryl-5,6-dihydro-7*H*-benzo[*c*]xanthen-7-ones **53** were obtained (Scheme 9). Furthermore the presence of the nitro electron-withdrawing group leads to the formation of the 6-hydroxy-3-nitro-5-phenyl-7*H*-benzo[*c*]xanthen-7-one **54**, as the main product (Scheme 9). Considering the proposed reaction mechanism [28], the presence of the nitro group should improve the acidic character of the α-protons allowing the formation of a diene which undergoes cycloaddition reaction with singlet oxygen. This cycloadduct can successively, rearrange, dehydrate and, through a keto-enol tautomerism, aromatize to give 6-hydroxy-3-nitro-5-phenyl-7*H*-benzo[*c*]xanthen-7-one **54**.

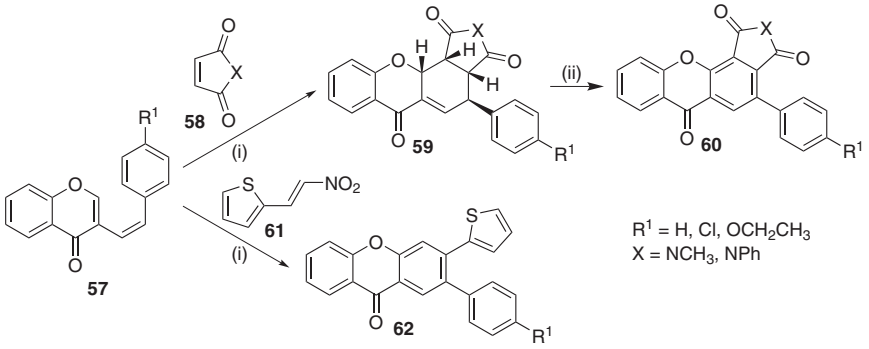
Synthesis of miscellaneous arylxanthones

3-(1,6-Diynyl)-4*H*-chromen-4-ones **55** underwent microwave-assisted tandem reaction using potassium *tert*-butoxide, tetrabutylammonium chloride and phenylacetonitrile as anion reagent transfer in DMSO to deliver tetracyclic 2-aryl-9*H*-xanthen-9-ones **56** (68–80 % yield, Scheme 10) [31]. This transformation involves ring-opening and ring-closing tandem process, [4 + 2] cyclization and aromatization reactions. A single example of 1,2-diphenyl-9*H*-xanthen-9-one derivative was obtained in 28 % yield when chromone possesses a 2-phenyl substituent.

Although 2-styrylchromones **14** were first used as dienes in Diels–Alder (DA) reactions, the reactivity in [4 + 2] cycloaddition reactions of their isomers (*Z*)-3-styrylchromones **57** was also studied. Dienophiles such as *N*-methylmaleimide (**58**, X = NCH_3), *N*-phenylmaleimide (**58**, X = NPh) and 2-(2-nitrovinyl)thiophene **61** were used and their DA reaction with (*Z*)-3-styrylchromones **57** gave several xanthone type compounds (Scheme 11)



Scheme 10: Reagents and conditions: (i) Bu_4NCl, *t*-BuOK, phenylacetonitrile, DMSO, MW, 110 °C, 20 min.

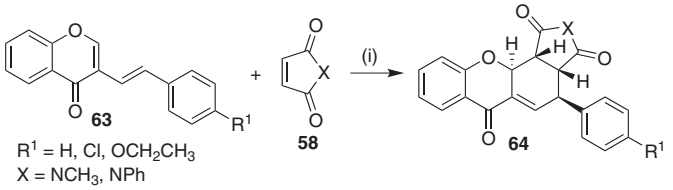


Scheme 11: Reagents and conditions: (i) MW (270 W), 30 min; (ii) DDQ, 1,2,4-TCB, MW (300 W), 45 min.

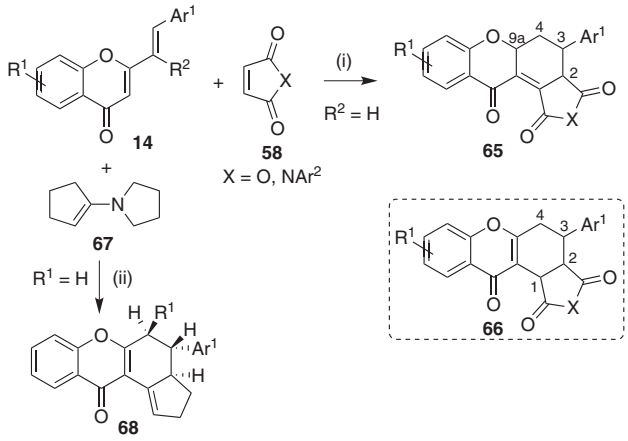
[32, 33]. The (*Z*)-3-styrylchromone derivatives **57** attained in previous works [34] undergo MW-assisted solvent-free DA reaction with maleimides **58** affording the respective cycloadducts, rel-(3a*R*,4*S*,11a*R*,11b*R*)-4-aryl-2-(methyl or phenyl)-3a,4,11a,11b-tetrahydrochromeno[2,3-*e*]isoindole-1,3,6(2*H*)-triones **59** in very good yields (>75 %, Scheme 11). The authors tried the same transformation using classic heating conditions, but the results were not improved (**59** X = NCH_3, up to 51 %) and other by-products such as 4-aryl-2-methylchromeno[2,3-*e*] isoindole-1,3,6(2*H*)-triones **60** (40–47 %), were formed [32, 33]. These xanthone derivatives **60** were also attained in very good yields using DDQ as oxidant in 1,2,4-TCB under MW irradiation. The use of 2-(2-nitrovinyl)thiophene **61** as dienophile allowed the direct synthesis of 2-aryl-3-(thiophen-2-yl)-9*H*-xanthen-9-one **62**, which results from the DA reaction followed by in situ oxidation due to the favoured HNO_2 elimination (Scheme 11) [32]. Moreover, the reaction is regioselective as only 2-aryl-3-(thiophen-2-yl)-9*H*-xanthen-9-ones **62** were obtained in very good yields (68–75 %). This regioselectivity is explained by orbital coefficients calculation that revealed the partially positively charged carbon atom in the dienophile and the most negatively charged carbon in the diene.

The stereochemistry observed in the obtained cycloadducts **59** confirms the DA reaction stereoselectivity towards the *endo* isomer. Theoretical calculations regarding the regio- and stereoselectivity of the reaction explain the experimental results [32]. The extension of the cycloaddition reaction using *N*-methylmaleimide (**58**, X = NCH_3) and *N*-phenylmaleimide (**58**, X = NPh) as dienophiles with (*E*)-3-styrylchromone derivatives **63** afforded in a stereoselective manner, the *exo* cycloadducts rel-(3a*R*,4*S*,11a*S*,11b*R*)-4-aryl-2-(methyl/phenyl)-3a,4,11a,11b-tetrahydrochromeno[2,3-*e*]isoindole-1,3,6(2*H*)-triones **64** (Scheme 12) [32, 33].

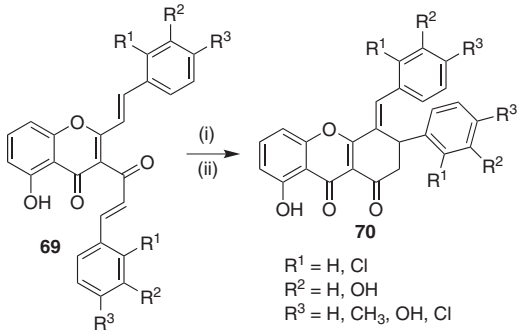
Various examples of 3-aryl-1,2,3,9a-tetrahydro-9*H*-xanthen-9-ones are known since 1954 when 2-styrylchromone derivatives **14** undergo DA reaction with maleic anhydride (**58**, X = O) in boiling xylene (Scheme 13) [35]. More derivatives arise when 2 years later the same group tested in the same reaction conditions the reactivity with *N*-arylmaleimides (**58**, X = NAr^2) as dienophiles [36]. Cycloaddition reaction of 2-styrylchromones with dibenzoylethylenes [37] and 1,4-benzoquinones [38, 39] to give 1,2,3,9a-tetrahydro-9*H*-xanthen-9-ones were also reported. In 1992, Letcher and Yue revised the cycloadduct structures **65** to the isomeric 1,2,3,4-tetrahydro-9*H*-xanthen-9-ones **66** [40, 41]. They also studied the reactivity of 2-styrylchromone derivatives **14** with electron rich dienophile enamine 1-pyrrolidinylcyclopentene **67**, in equimolar amounts, in refluxing 95 % ethanol (Scheme 13) [42]. The *trans*-stereochemistry of the cycloadducts obtained indicated that the DA



Scheme 12: Reagents and conditions: (i) MW (270 W), 30 min.



Scheme 13: Reagents and conditions: (i) boiling xylene; (ii) refluxing 95 % EtOH.



Scheme 14: Reagents and conditions: (i) BBr_3, dry CH_2Cl_2, r.t.; (ii) H_2O, r.t..

reaction occurred via an *exo*-addition and the corresponding 1,2,3,4-tetrahydro-9*H*-xanthen-9-one derivatives **68** were obtained in 50–60 % yield.

During a study of methyl groups cleavage of 3-cinnamoyl-2-styrylchromones **69** with boron tribromide very interesting (*E*)-3-aryl-4-arylidene-8-hydroxy-3,4-dihydro-1*H*-xanthene-1,9(2*H*)-dione derivatives **70** were obtained in moderate to very good yields (37–89 %, Scheme 14) [43]. The attempts to oxidize xanthenediones **70** were not fruitful due to the formation of several xanthone and tetracyclic xanthone derivatives, the yields were not improved and the reaction was not reproducible [44]. From this work one can also highlight the high antioxidant and the potent acetylcholinesterase inhibition demonstrated for (*E*)-3-aryl-4-arylidene-8-hydroxy-3,4-dihydro-1*H*-xanthene-1,9(2*H*)-dione (**70**, $R^1 = H$, $R^2 = R^3 = OH$) [44].

Synthesis of arylacridones

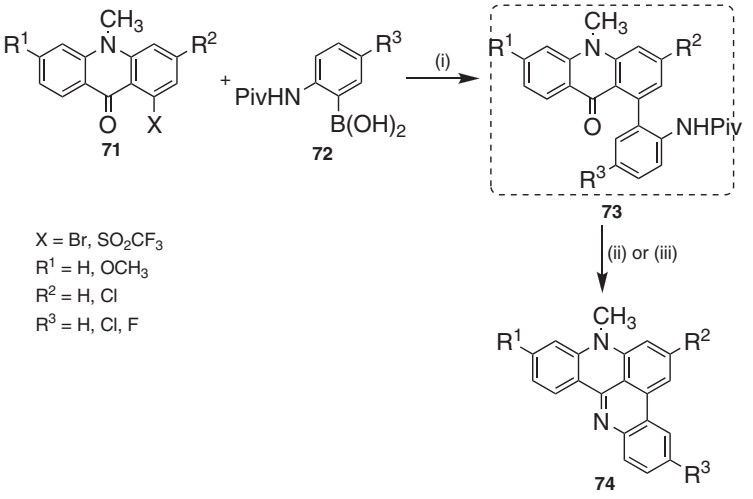
Acridin-9(10*H*)-ones, also called dibenzo-γ-pyridones, are tricyclic compounds presenting a γ-pyridone with two *ortho*-fused benzene rings and are the aza-analogues of 9*H*-xanthen-9-ones. Several naturally occurring and synthetic acridin-9(10*H*)-ones are known, the natural ones are found predominantly in plants of *Rutaceae* family [45], and their importance is recognized due to their biomedical potential mainly as antiviral [46], antimalarial [47], antitumoral and anticancer agents [13]. Moreover acridin-9(10*H*)-ones have important applications in host-guest interactions, as fluorescence probes in chemical, biochemical and environmental analysis and as analytical tools in biomimetic chemistry [48–50]. To the best of our knowledge, synthetic acridin-9(10*H*)-ones linked to one or more aryl rings are scarce and natural derivatives were not yet reported. However, there are synthetic acridin-9(10*H*)-ones unrelated to the natural products now emerging

as promising bioactive compounds. Herein we report the recent studies on the synthesis of 1-arylacridin-9(10*H*)-ones and 2,3-diarylacridin-9(10*H*)-ones and other related analogues.

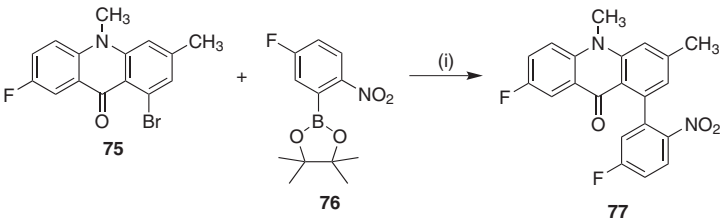
Synthesis of 1-arylacridones

Palladium(0)-mediated Suzuki–Miyaura cross-coupling reaction of 3,6-disubstituted-10-methylacridin-9(10*H*)-ones **71**, bearing a 1-bromo or 1-trifluoromethylsulfonyloxy substituent, with 2-(pivaloylamino)benzeneboronic acids **72** afforded 1-arylacridin-9(10*H*)-ones **73** in very good yields (Scheme 15) [51]. The reaction conditions depend on the acridin-9(10*H*)-one used as coupling partner. Thus, the reaction of bromoacridin-9(10*H*)-one **71** (X = Br) with 2-(pivaloylamino)benzeneboronic acid **72** (R^3 = H), using $Pd(PPh_3)_4$ as catalyst in aqueous DME with sodium bicarbonate (3 equiv) as base gave 1-arylacridin-9(10*H*)-one **73** ($R^1 = R^2 = R^3$ = H) in very good yield (88 %). Treating **73** with HCl (6 mol·dm^{-3}) in THF, or hot $POCl_3$, led to pentacycle **74** in yields higher than 90 %. The coupling of triflates **71** (X = SO_2CF_3) with boronic acids is more challenging to avoid triflate hydrolysis. In the best conditions involving $Pd(PPh_3)_4$, $NaHCO_3$ in DME with minimal water, 1-arylacridin-9(10*H*)-ones **73** (R^1 = OCH_3, $R^2 = R^3$ = H, Cl) were obtained but cyclize directly to pentacyclic quinoacridines **74**. Other conditions such as $Pd_2(dba)_3$–P(*t*-Bu)$_3$–KF or $Pd(OAc)_2$–PCy_3–KF, either gave no coupling, very limited conversions, or hydrolysis. To facilitate purification, a resin bound catalyst (Deloxan resin) under aqueous conditions was used but once again the hydrolysis of triflate groups occurred [51].

Later, it was reported the Suzuki–Miyaura cross-coupling reaction of bromoacridin-9(10*H*)-one **75** with the dioxaborolane **76** as an alternative coupling partner giving the 1-arylacridin-9(10*H*)-one **77** in 47 % yield with dichloro[1,1-bis(diphenylphosphino)ferrocene]palladium(II) and Na_2CO_3 in 1,4-dioxane (Scheme 16) [52].



Scheme 15: Reagents and conditions: (i) $Pd(PPh_3)_4$, $NaHCO_3$, DME, H_2O, 100 °C, 5 h; (ii) 6 mol·dm^{-3} HCl in THF (1:1 or 1:1.5), reflux, 18 h to 5 days; (iii) $POCl_3$, 100 °C, 20 min.

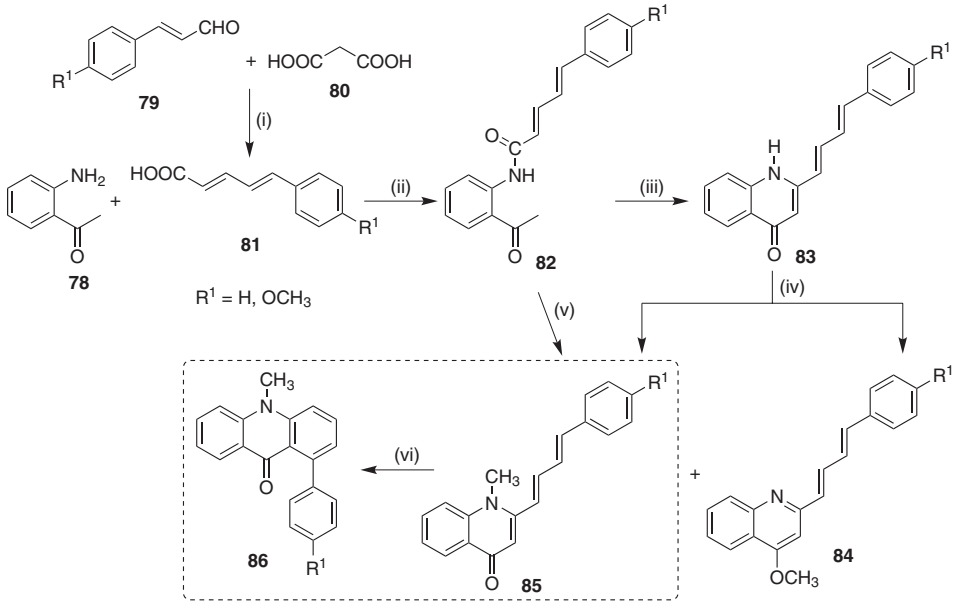


Scheme 16: Reagents and conditions: (i) $PdCl_2$(dppf), Na_2CO_3, 1,4-dioxane, 80 °C, 24 h.

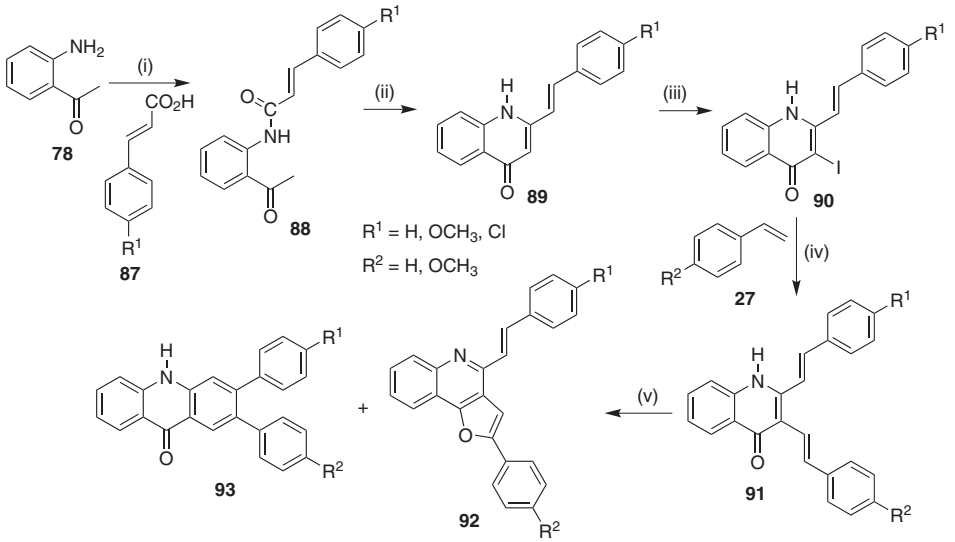
Another synthetic approach towards new 1-arylacridin-9(10*H*)-ones is being developed in our research group and until now two new derivatives were synthesized (Scheme 17). This approach involves the condensation of 2′-aminoacetophenone **78** with (2*E*,4*E*)-5-arylpenta-2,4-dienoic acids **81**, which were obtained from the reaction of cinnamaldehydes **79** with malonic acid **80** in dry pyridine at 120 °C, affording the (2*E*,4*E*)-*N*-(2-acetylphenyl)-5-arylpenta-2,4-dienamides **82**. Then, the base-induced cyclodehydration of **82** gave new 2-[(1*E*,3*E*)-4-arylbuta-1,3-dienyl]quinolin-4(1*H*)-ones **83** in good yields (80–91 %). Attempts to cyclize compound **83** (R = H) into the desired 1-phenylacridin-9(10*H*)-one were unsuccessful, so an alternative approach involved methylation of the NH group prior to cyclization. Thus, direct methylation of compound **83** (R = H) with methyl iodide and sodium hydride in dry THF gave a mixture of 1-methy-2-[(1*E*,3*E*)-4-phenylbuta-1,3-dienyl]quinolin-4(1*H*)-ones **85** as main compound (59 %), and the isomeric 4-methoxy-2-[(1*E*,3*E*)-4-phenylbuta-1,3-dienyl]quinoline **84** (10 %), due to the non-regioselective nature of this reaction [53]. A significant amount of starting material was also recovered (30 %) (Scheme 17). In a modification of this synthetic route, the methylation and in situ base-induced cyclodehydration of the (2*E*,4*E*)-*N*-(2-acetylphenyl)-5-arylpenta-2,4-dienamides **82** was carried out affording 2-[(1*E*,3*E*)-4-arylbuta-1,3-dienyl]-1-methylquinolin-4(1*H*)-ones **85** as the sole reaction product. Finally, electrocyclization of 2-[(1*E*,3*E*)-4-arylbuta-1,3-dienyl]-1-methylquinolin-4(1*H*)-ones **85** in the presence of a catalytic amount of iodine in refluxing 1,2,4-TCB afforded the desired 1-aryl-10-methylacridin-9(10*H*)-ones **86** in good yields (53–65 %) (Scheme 17). The main limitation of this synthetic approach is the lack of commercially available substituted cinnamaldehydes to allow the preparation of diversely substituted cinnamic acids **81** and the low yields obtained in their synthesis.

Synthesis of 2,3-diarylacridones

As far as we know, no natural 2,3-diarylacridin-9(10*H*)-ones have been described to date. Recently, our group reported two different approaches for the synthesis of 2,3-diarylacridin-9(10*H*)-ones **93** and **97** [54, 55]. The first one (Scheme 18) involves the condensation of 2′-amino acetophenone **78** with cinnamic acids **87** in the presence of DCC and 4-ppy to afford (*E*)-*N*-(2-acetylphenyl)-3-arylacrylamides **88** which after base-induced cyclodehydration into **89** followed by C-3 iodination, using iodine and sodium carbonate in dry THF, gave



Scheme 17: Reagents and conditions: (i) dry pyridine, 120 °C, overnight; (ii) DCC, 4-ppy, CH_2Cl_2, r.t., 6–8 days; (iii) *t*-BuOK, *t*-BuOH, 90 °C, 6 h; (iv) CH_3I (20 equiv), NaH (1.0 equiv), dry THF, r.t., 24 h; (v) CH_3I (1.5 equiv after 30 min.), NaH (1.5 equiv + 1.0 equiv after 18 h), dry THF, r.t., 24 h; (vi) I_2 (cat.), 1,2,4-TCB, reflux, 2 h.



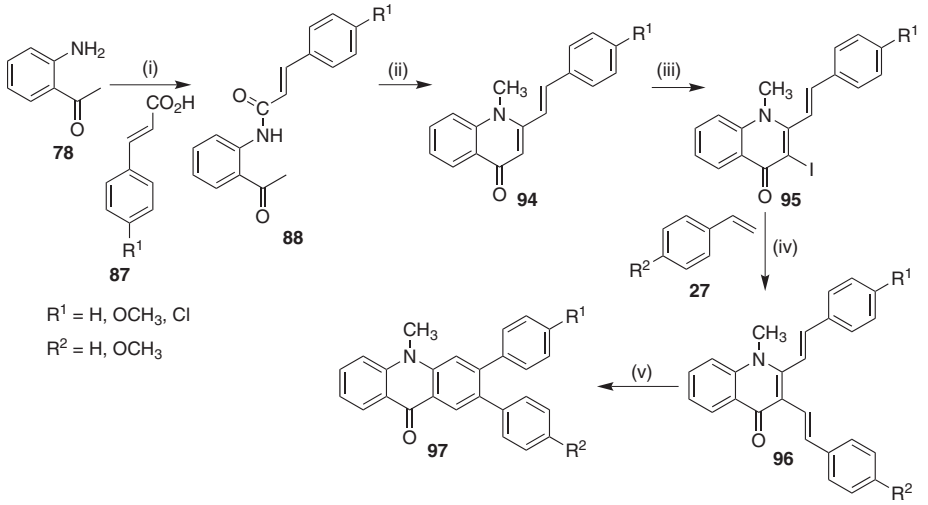
Scheme 18: Reagents and conditions: (i) DCC, 4-ppy, CH_2Cl_2, r.t., 6–8 days; (ii) *Classical heating*: *t*-BuOK, dry THF, 80 °C, 4 h. *Microwave*: *t*-BuOH, NaOH, 120 °C, 18 min.; (iii) I_2, Na_2CO_3, dry THF, r.t., 4–5 h; (iv) $Pd(PPh_3)_4$, Et_3N, with ligand [PPh_3, or tris(*o*-tolyl)phosphine] or without ligand, NMP or CH_3CN, 80–100 °C, 3–6.5 h; (v) 1,2,4-TCB, reflux, 24 h or 1,2,4-TCB, I_2 (10 %), *p*-TSA, reflux, 2–3 h.

(*E*)-3-iodo-2-styrylquinolin-4(1*H*)-ones **90** in very good yields (82–95 %). Heck reaction of these (*E*)-3-iodo-2-styrylquinolin-4(1*H*)-ones **90** with styrenes **27,** using $Pd(PPh_3)_4$ as catalyst, gave (*E,E*)-2,3-distyrylquinolin-4(1*H*)-ones **91** in moderate to good yields (36–81 %), which when heated at high temperatures cyclize in two different ways: i) electrocyclization and further in situ oxidation in the presence of a catalytic amount of iodine and *p*-TSA in refluxing 1,2,4-TCB leads to 2,3-diarylacridin-9(10*H*)-ones **93** (2–40 %), whereas ii) tautomerization, cyclization by nucleophilic addition followed by in situ oxidation produces (*E*)-2-aryl-4-styrylfuro[3,2-*c*]quinolines **92** as the main compounds (36–60 %) [54, 55]. When the electrocyclization and in situ oxidation reactions were performed in 1,2,4-TCB without addition of iodine and *p*-TSA, in general higher amounts of (*E*)-2-aryl-4-styrylfuro[3,2-*c*]quinolines **92** were obtained (35–66 %) together with 2,3-diarylacridin-9(10*H*)-ones **93** (16–37 %), after a longer reaction time [54].

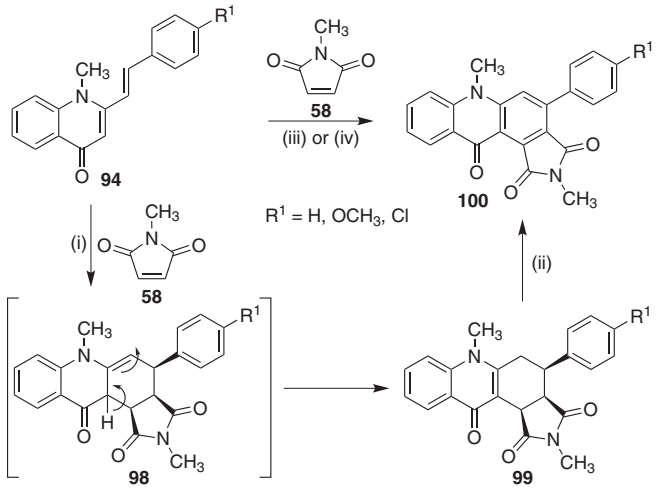
The second approach that gives only 2,3-diaryl-10-methylacridin-9(10*H*)-ones **97** (Scheme 19) [55], involves the methylation and in situ cyclodehydration of (*E*)-*N*-(2-acetylphenyl)-3-arylacrylamides **88** with methyl iodide and sodium hydride in dry THF to afford the (*E*)-1-methyl-2-styrylquinolin-4(1*H*)-ones **94** (66–86 %), which after C-3 iodination with iodine and cerium(IV) ammonium nitrate in acetonitrile at 80 °C were converted into the corresponding (*E*)-3-iodo-1-methyl-2-styrylquinolin-4(1*H*)-ones **95** in good yields (66–83 %). The Heck coupling reaction of (*E*)-3-iodo-1-methyl-2-styrylquinolin-4(1*H*)-ones **95** with styrenes **27** using $Pd(PPh_3)_4$ as catalyst, led to the expected (*E,E*)-1-methyl-2,3-distyrylquinolin-4(1*H*)-ones **96** in moderate to good yields (36–77 %), which when heated at high temperatures in refluxing 1,2,4-TCB in the presence of a catalytic amount of iodine and *p*-TSA underwent electrocyclization and oxidation processes affording only the expected 2,3-diaryl-10-methylacridin-9(10*H*)-ones **97** in good yields (60–79 %) [55].

Synthesis of miscellaneous acridones

Cycloaddition reaction of 1-methyl-2-styrylquinolin-4(1*H*)-ones **94** with *N*-methylmaleimide **58** in refluxing toluene afforded 4-aryl-2,6-dimethyl-4,5,6,11b-tetrahydro-1*H*-pyrrolo[3,4-*a*]acridine-1,3,11(2*H*,3a*H*)-triones **99** (34–52 %), unreacted starting material **94** (13–15 %) and traces of the oxidized cycloadducts **100** (Scheme 20) [56]. However, 4-aryl-2,6-dimethyl-1*H*-pyrrolo[3,4-*a*]acridine-1,3,11(2*H*,6*H*)-triones **100** were obtained directly carrying out the DA reaction in 1,2,4-TCB at 180 °C. Under these reaction conditions the



Scheme 19: Reagents and conditions: (i) DCC, 4-ppy, CH_2Cl_2, r.t., 6–8 days; (ii) CH_3I (1.5 equiv after 30 min.), NaH (1.5 equiv + 1.0 equiv after 18 h), dry THF, r.t., 24 h; (iii) I_2 (10 %), $(NH_4)_2Ce(NO_3)_6$, CH_3CN, 80 °C, 3–4 h; (iv) $Pd(PPh_3)_4$, Et_3N, with tris(*o*-tolyl)phosphine or without ligand, NMP or CH_3CN, 80–100 °C, 3–7 h; (v) 1,2,4-TCB, I_2 (10 %), *p*-TSA, reflux, 2–3 h.



Scheme 20: Reagents and conditions: (i) **58** (3 equiv + 3 equiv after 48 h), toluene, 120 °C, 72 h; (ii) chloranil, dry 1,4-dioxane, 80 °C, 3 h. (iii) *Classical heating*: 1,2,4-TCB, 180 °C, 42–48 h. *Microwave:* sealed vessels, 1,2,4-TCB, 150 °C, 1 h. (iv) **58** (3 equiv + 3 equiv after 7 h), 1,2,4-TCB, $Sc(OTf)_3$, 80 °C (for **4a** and **4b**) or reflux (for **4c**), 24–27 h.

in situ oxidation of cycloadducts **99** occurred leading to acridin-9(10*H*)-ones **100** in moderate yields (45–56 %) after 42–48 h [56]. When the reaction was performed in 1,2,4-TCB at 150 °C under MW heating under sealed vessels the cycloadducts **99** were obtained in a shorter reaction time (1 h of irradiation), however, the yields were disappointingly lower (13–34 %) and only traces of the oxidized cycloadducts **100** were obtained. Thus, the one-pot DA and oxidation reaction proved to be a valuable methodology to prepare acridin-9(10*H*)-ones **100** and led to the investigation of the oxidation of the cycloadducts **99** with chloranil in dry 1,4-dioxane at 80 °C. Under these conditions acridin-9(10*H*)-ones **100** were obtained in very good yields (87–90 %) (Scheme 20) [56].

The formation of the acridin-9(10*H*)-ones **100** from the reaction of 1-methyl-2-styrylquinolin-4(1*H*)-ones **94** with *N*-methylmaleimide **58** can be explained by a 1,3-hydrogen shift of cycloadducts **98** leading to the formation of the more stabilized quinolin-4(1*H*)-one nucleus (Scheme 20).

The Lewis acid catalyzed DA reaction of 1-methyl-2-styrylquinolin-4(1*H*)-ones **94** with *N*-methylmaleimide **58** also led to the acridin-9(10*H*)-ones **100** with moderate yields (42–51 %) in a shorter reaction time (24–27 h) and $Sc(OTf)_3$ (20 mol %) proved to be more efficient than $AlCl_3$ (Scheme 20) [56].

Conclusions

The most recent methodologies towards the synthesis of arylxanthone and arylacridone derivatives were covered in this review. The efficiency and scope of the described methods are largely corroborated by the wide range of structures prepared with classical and/or alternative heating conditions; however, efforts dedicated to reactions with higher performance and less environmental impact would be much appreciated. It should be highlighted that some chemical transformations were equally applied to both ring systems. Thus, it is expected that the already established chemistry, reactivity and biological properties for these compounds can boost the development of new methodologies and the search for novel decorated bioactive arylxanthone and arylacridone derivatives.

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