Alternative methodologies for the synthesis of substituted 3-arylcoumarins: Perkin reactions and Palladium-catalyzed synthesis

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"Abstract." With the aim to find out the best methodology to prepare different series of substituted coumarins, thinking on their pharmacological evaluation, in the present communication we report the synthesis of 3-phenylcoumarin with different number and position of substituent groups in both 3-phenyl and coumarin rings. The substituents in this new scaffold were introduced in the 6 and 8 positions of the coumarin moiety and in 3'and 4' positions of the 3-phenyl ring. The synthesized compounds **1-7**, **8** and **9-11** were prepared and characterized by different methodologies. Perkin modified reaction (method **A** and **B**) and Palladium-catalyzed synthesis (method **C**) were the methodologies described in this communication.

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Introduction

Coumarins (or benzopyrones) are a large family of compounds, of natural and synthetic origin, that show numerous biological activities.[1] Recent studies pay special attention to their antioxidant,[2,3] anticancer,[4,5] vasorelaxant,[6] and enzymatic inhibition properties.[7,8,9]

Phenylcoumarins are synthetic compounds in which an additional phenyl ring is attached in any position of the pyrone or the benzenic ring of the coumarin nucleus. The variety of biological activities of the 3-arylcoumarins makes their preparation an interesting topic in synthetic organic chemistry. For the last years, we have been studying deeply the 3-phenylcoumarin's scaffold. Our recent works demonstrated that some 3-phenylcoumarins play an important role in the monoamino oxidase (MAO) enzymatic inhibition.[6,7,8] Different methods can be used to obtain the described compounds. Wittig reaction,[10] photochemical reactions,[11] different cyclocondensations[12,13] (specifically the Perkin reaction),[14,15] phase transfer-catalyzed reactions,[16] titanium (III)-mediated reactions,[17] Knoevenagel reaction,[18,19,20] and lithiation reactions[21] are some of the synthetic routes to prepare 3-arylcoumarins. The classical Perkin condensation is perhaps the most direct and simple method known for the preparation of 3-arylcoumarins.[22] While this procedure is a suitable method, the variety of substrates is, however, limited.

Palladium synthesis of different arylcoumarins has been reported in the literature.[23] Because of its versatility, palladium catalyzed carbon-carbon and carbon-heteroatom coupling reactions are extensively used in the synthesis of complex organic molecules.[24,25] However, the use of coumarins themselves as starting compounds for the preparation of the 3-arylcoumarins is much rarer.[26] Although significant advances have been occurring in the metal-catalyzed synthesis starting from aryl halides during the last years, application of this coupling reaction to various heterocyclic structures is still a relatively unexplored process. This encourages us to explore this synthetic field. The palladium-catalyzed cross-coupling between different types of arylboronic acids and the 3-chlorocoumarin, to afford 3-arylcoumarins, is the new procedure that we described. This is a direct, rapid and effective method to prepare different substituted 3-arylcoumarins.

Results and discussion

In the present work we designed and synthesized a series of 3-phenylcoumarin derivatives with different number of substituent in both coumarinic and 3-phenyl rings. The compounds were synthesized according to **Scheme 1** and details are given in the **Experimental section** and **table 1**.

The traditional methodology, using a Perkin reaction, was carried out with good yields and the main obtained mixtures were relatively easy to purify. The principal problem, in these conditions, is the substituent groups present in the reagents. Both hydroxyl and nitro derivatives can´t be prepared by this methodology. To prepare the nitro derivatives, a different reaction using sodium hydride in acetic anhydride is the best solution. Under the traditional Perkin conditions, the resulting mixture of products is difficult to purify. With the new conditions, the products are easy to purify and the reaction conditions are moderated. Regarding to the hydroxyl derivatives, the best solution for the synthesis is the palladium-catalyzed reaction with different substituted boronic acids. In spite of having similar yields, this reaction is the best option. Under these conditions, all the derivatives were easily prepared.

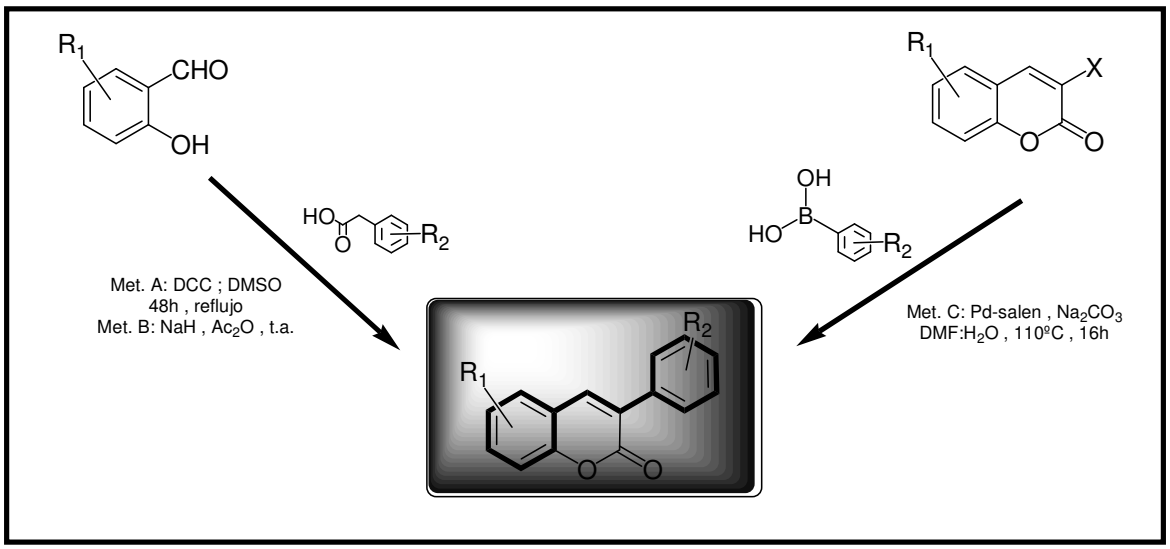
Chemistry. The coumarin derivatives **1-11** were efficiently synthesized according to the synthetic protocol outlined in **Scheme 1**.

The preparation of 3-phenylcoumarins **1-7** was performed via the classical Perkin reaction (method A).[7,8,9] This reaction occurs by condensation of the substituted salicylaldehyde and the conveniently substituted phenylacetic acids, with *N,N'*-dicyclohexylcarbodiimide (DCC) as dehydrating agent, in reflux of DMSO, during 24 hours. The reaction to obtain **1-7** is very clean and the yields are between 57-73 %. The obtained products are easy to purify by flash chromatography, using a mixture of hexane/ethyl acetate in a proportion 9:1 as eluent.

The synthesis of 3-phenylcoumarin **8** was performed via method B, using sodium hydride and acetic anhydride, at room temperature. The obtained compound was easy to purify by flash chromatography,

using a mixture of hexane/ethyl acetate in a proportion 85:15 as eluent.

Compounds **9-11** were synthesized via palladium-catalyzed synthesis, starting from the 3-chlorocoumarin and the conveniently substituted phenyl boronic acid, with Na_2CO_3 and a Pd-salen complex method C). The reaction was carried out in DMF:H_2O (1:1). The resulting products are purified by flash chromatography, using a mixture of hexane/ethyl acetate in a proportion 9:1 as eluent.



Scheme 1. Synthetic strategy for the prepared compounds

Table 1. Compounds **1-11**

Comp.	R1	R2	Yield %	Method	M.p. ºC
1	6-Me	4'-Me	72	A	139-140
2	6-OMe	4'-Me	62	A	130-131
3	8-Me	H	64	A	111-112
4	8-OEt	H	57	A	117-118
5	6-Me	4´-OMe	71	A	144-145
6	6-OMe	4'-Br	61	A	174-175
7	8-Me	4´-OMe	54	A	100-101
8	6-Me	3'-NO_2	75	B	196-197
9	H	3'-NH_2	59	C	154-155
10	H	3'-NO_2	55	C	252-253
11	H	3'-OH	41	C	241-242

Conclusions

A series of hybrid compounds with resveratrol-coumarin skeleton were prepared by different methodologies: we describe alternative methods for the preparation of 3-arylcoumarins. In conclusion, we have shown that palladium cross-coupling is an efficient synthetic method for the preparation of hydroxyl, amino and nitro 3-phenyl substituted coumarins, compounds that can't be prepared by traditional Perkin reaction. The Perkin reaction allows us more diversity in the coumarin ring, and in general the yields are higher than in the other conditions. We described suitable methods for the synthesis of the different substituted 3-arylcoumarins and using both methodologies we can diversify different positions this scaffold, in order to increase our coumarin library.

Experimental section

General method to prepare 3-phenylcoumarins by Perkin reaction (method A)

A solution of substituted *ortho*-hydroxybenzalhehyde (1.16 mmol), substituted phenylacetic acid (1.45 mmol) and DCC (1.81 mmol), in DMSO (2.0 mL), was heated in an oil-bath at 100-110 ºC for 24 h. Triturate ice (20.0 mL) and acetic acid (3.0 mL) were added to the reaction mixture. After keeping it at room temperature for 2h, the mixture was extracted with ether (3 x 25.0 mL). The organic layer was extracted with sodium bicarbonate solution (5 %, 50.0 mL) and then water (20.0 mL). The solvent was evaporated under vacuum and the dry residue was purified by FC (hexane/ethyl acetate 9:1) to give compounds **1-7**.

General method to prepare 3-phenylcoumarins (method B)

A solution of substituted *ortho*-hydroxybenzalhehyde (3.67 mmol), substituted phenylacetic acid (3.67 mmol) and sodium hydride (3.67 mmol), in acetic anhydride (2.0 mL), was stirred in a Schlenk

reactor at room temperature, for 3 h. The resulting solid was filtered and washed with diethylic ether. The resulting compound **8** was dry in vacuum.

General method to prepare 3-phenylcoumarins by Palladium-catalyzed reaction (method C)

To a 20 mL two neck round-bottom flash were added a solution of 3-chlorocoumarin (0.83 mmol), phenyl boronic acid (1.04 mmol), Na_2CO_3 (1.66 mmol) and Pd-salen complex (0.5 mol %) in DMF:H_2O (1:1). The reaction mixture was heated at 110 ºC for 120 minutes. The reaction was monitored by chromatography. After the completion of the reaction, the mixture was extracted with ethyl acetate (3 x 20 mL). The organic extracts were dried over anhydrous sodium sulphate, filtrated, and the solvent was evaporated under vacuum. The obtained residuum was purified by FC (hexane/ethyl acetate 9:1) to give compounds (**9-11**).

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