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Synthesis of 6-aryl/heteroaryl-4-oxo-4*H*-chromene-2-carboxylic ethyl ester derivatives

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ABSTRACT

The development of new chemical entities represents an important challenge in pharmaceutical industry, being the use of privileged scaffolds for library design and drug discovery a valuable approach. Among the panoply of privileged structures, our research group has focused its attention on the chromone (4*H*-benzopyran-4-one) scaffold due to its chemical versatility and ability to bind to multiple targets. With this endeavour we report an expedite two-step procedure for the synthesis of novel 6-aryl/heteroaryl-4-oxo-4*H*-chromene-2-carboxylic ethyl ester. The new chromones were synthesized by a C–C Suzuki cross-coupling microwave-assisted reaction, using $Pd(OAc)_2$ as a catalyst, and a classic Claisen condensation followed by an intramolecular cyclization process.

Drug research and development processes have undergone a dramatic transformation over the past decades. Nevertheless, the key premise remains the same: to discover innovative drugs new chemical entities are needed to be found.[1] Uncovering drug-like new chemical entities is a gigantic challenge and to overcome such hurdles several medicinal chemistry programmes have been resorted on the so-called privileged structures as they can result in drug-like libraries.[2] Moreover, natural products remain one of the best sources of drugs and drug lead compounds. The inherent diversity of natural-product structures have long been an inspiration for the development of 'natural product-like' libraries being natural scaffolds attractive starting points for R&D projects.

Among the panoply of privileged structures,[2] our research group has focused its attention on the chromone (4*H*-benzopyran-4-one) scaffold. The convincing results obtained for the development of monoamine oxidase B inhibitors (IMAO-B)[3–5] and adenosine receptors ligands[6,7] based on chromone scaffold stimulate to continue the project with the design and synthesis of a new series of 6-phenylchromone derivatives. The rationale for the design of the new chromone based library is presented in Figure 1.

The new biaryl compounds were inspired on the backbone of flavonoids (natural secondary metabolites), and involve a change of the position of the exocyclic aromatic nucleus **C**, which is attached to the chromone ring **A** instead of **B**. The new biarylchromone derivatives will contribute for extending chromone chemical space and biological applications.

To obtain the novel chromone based compounds a simple synthetic two-step strategy was planned (see Scheme 1). This strategy encompassed the use of the following reactions: a Claisen condensation followed by an intramolecular cyclization, and a Suzuki cross coupling reaction. In fact, Suzuki C–C cross-coupling reactions are by now considered robust chemical methodologies used to synthesize compounds on an industrial scale by the pharmaceutical industry. Moreover, Suzuki reaction is considered a valuable tool for R&D programmes, namely to attain chemical diversity of chemical libraries.[8] Recent catalyst and methodological developments have broadened its application enabling to perform simpler, faster and cheaper approaches, when compared to some well-known chemical transformations.[9,10] Within this context, the synthesis of the biaryl chromone derivative 6-phenyl-2-chromone carboxylic acid (Scheme 1, compound **2**) was done using the commercial 6-bromo-2-chromone carboxylic acid (**1**) as starting material via a Suzuki C–C cross-coupling reaction following the procedure of Miyaura et al. with minor modifications (Scheme 1).[11]

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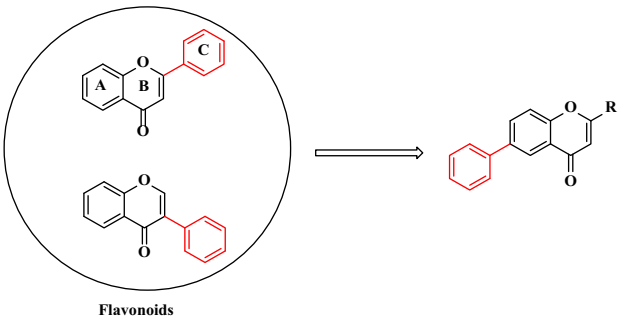


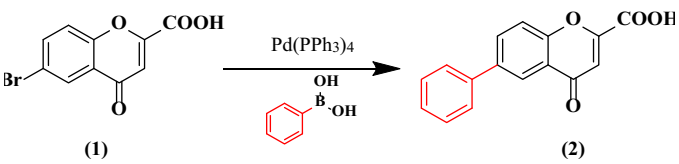
Figure 1. Rational followed for the development of new 6-phenyl-4*H*-chromen-4-one based library.

Briefly, 6-bromochromone carboxylic acid (**1**) was suspended in THF/K_2CO_3 (2 M) (10:1) and tetrakis(triphenylphosphonium) palladium(0) ($Pd(PPh_3)_4$, 4 mol %) was added. After stirring 30 min at room temperature, an equimolar amount of phenyl boronic acid was added. The reaction mixture was heated in reflux and stirred for 12 h. The crude material was purified by gradient flash chromatography. After a laborious purification process, two main fractions were isolated and characterized by ^{1}H NMR. The first fraction was identified as the phenyl boronic acid self-coupling product and the second was the desired, but still impure, chromone (**2**). Thus, due to the 6-bromochromone carboxylic acid (**1**) insolubility constraints and reaction purification drawbacks, the same reaction was performed using another starting material, the ester derivative ethyl 6-bromo-2-chromone carboxylate (Scheme 2, compound **3**). The ester derivative (**3**) was obtained in a 60% yield from 5′-bromo-2′-hydroxyacetophenone (**4**), via a Claisen condensation and subsequent intramolecular cyclisation process, following the procedure of Hadjeri et al. with minor modifications (Scheme 2, step **A**).[12,13] Then, a C–C cross coupling reaction was performed, in the same experimental conditions as described previously, using $Pd(PPh_3)_4$ as catalyst (Scheme 2, step $\mathbf{B_1}$).[11] After purification, compound (**5**) was obtained in 35% yield.

Since the $Pd(PPh_3)_4$ catalyst has been reported as having air/-moisture drawbacks it was decided to perform the C–C cross coupling reaction with $Pd(OAc)_2$ (Scheme 2, step $\mathbf{B_2}$).[14] However, compound (**5**) was obtained in a lower yield (10%). So, in order to try to improve reaction yield it was decided to use microwave (MW) irradiation as heating source, once MW heating has been described as a suitable tool to enhance the performance of C–C cross coupling reactions.[15–17]

The reaction was performed following the procedure Arvela et al. (Scheme 2, step $\mathbf{B_3}$),[18,19] by which tetrabutylammonium bromide (TBAB), K_2CO_3 and phenyl boronic acid were added to an aqueous suspension of the ester (**3**). After addition of $Pd(OAc)_2$ (0.4 mol %) the system was heated to 150 °C for 15 min in a microwave apparatus. After work-up, purification and ^{1}H NMR analysis, it was concluded that the intended compound was not obtained. Along the reaction, the chromone ring opened giving rise to an acetophenone derivative (data not shown).

In fact, the stability of the benzopyrone ring on basic medium[5] can be pointed out as a drawback of the synthetic strategy. So, one



Scheme 1. Synthetic strategy used to obtain the 6-phenyl-2-chromone carboxylic acid (**2**) by Suzuki cross-coupling reaction.

of the critical points of the approach is related to deciding the right step to perform the Suzuki coupling reaction (Scheme 2, compound **4**). As several works reported the synthesis of 6-hetero/aryl acetophenone derivatives,[20–22] a new synthetic route depicted in Scheme 3 was envisaged. Here, the first step corresponds to the introduction of the phenyl ring on 5′-bromo-2′-hydroxyacetophenone (**4**) by Suzuki cross-coupling reaction following the procedure of Arvela et al. with slight modifications.[18] The benzopyran backbone is then obtained by a Claisen condensation followed by a cyclisation process (Scheme 3).

Since the discovery of the Suzuki reaction, novel and more efficient air/moisture stable Pd catalysts have been described, such as those reported in the work of Alonso et al.[22] However, our main goal was the synthesis of a library of novel chromone derivatives, by a convergent and efficient protocol. The method must have the benefits of operational simplicity and provide good yields of the targeted molecules. The building of chemical libraries based on privileged scaffolds with several points of decoration diversity play a central role in drug discovery processes. The synthetic strategies defined to this end must encompass the use of confining and commercial available reagents.

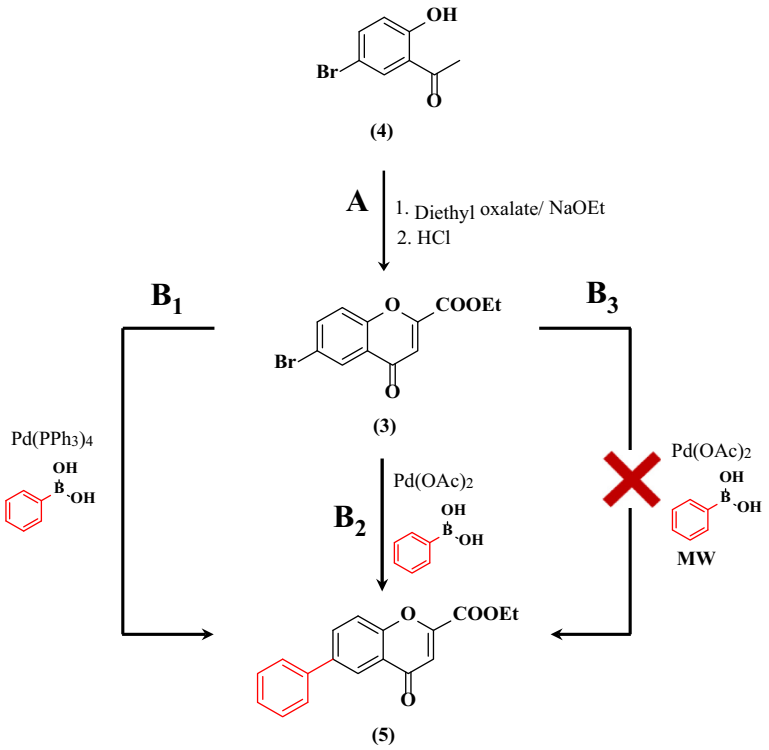
Therefore, the readily commercially available catalyst $Pd(OAc)_2$ was employed in a MW assisted reaction.[15] The pretended biaryl compound (**4′**) intermediate was obtained in good yield (see Table 1, entry 1) and used as starting material to obtain ethyl-6-phenyl-4-oxo-4*H*-chromene-2-carboxylate (Scheme 3, compound **5**) following the methodology previously described.[12]

After reaction optimization, the versatility of the new synthetic route was checked using diverse aryl/heteroaryl boronic acid reagents (Table 1).

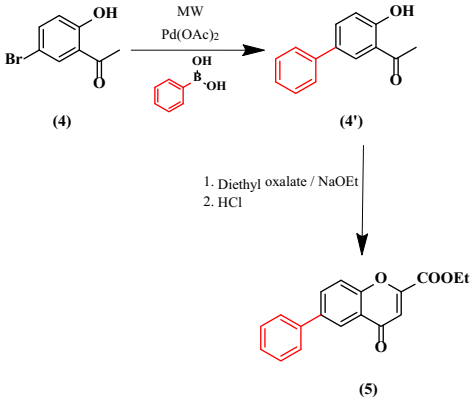
All aryl/heteroaryl derivatives were obtained in good yields (70–82%). It was found that neither the electronic donor/acceptor properties nor the number of the substituents in the aryl ring of the boronic acid (Table 1, entries 2–8) affect the course of the C–C cross coupling reaction. The same conclusion applies for the presence of a heterocyclic ring, instead of an aryl moiety (Table 1, entries 9 and 10), In contrast, and as regarding the intramolecular Claisen condensation and cyclization, it is important to stress that the presence of particular aryl substituents or heterocyclic rings on the boronic acids affects the performance of the second step. The presence of electron donating groups (Table 2, entries 2–4) and halogens (entries 5–7) lead to an improvement of the reaction yield, when compared with the aryl unsubstituted counterpart (Table 2, entry 1). Contrariwise, the presence of strong withdrawing groups (Table 2, entry 8) lead to a decrease of the reaction yield. The same tendency was observed with the of heteroaryl derivatives (Table 2, entries 9 and 10).

It is important to highlight that ethyl-6-phenyl-4-oxo-4*H*-chromene-2-carboxylate (Scheme 2, compound **5**) has already been obtained by Witiak et al.[23] Yet, the synthetic strategy was quite different from the one herein reported. Witiak et al.[23] used *p*-phenylphenol as starting material to attain 5-phenylsalicylic acid, by a Marasse modified Kolbe–Schmidt reaction, which was then converted into the desired 2-hydroxy-5-phenylacetophenone by a direct methylation reaction with MeLi in 1,2-dimethoxethane. Subsequently, the chromone ester (**5**) was obtained (63% overall yield) by a two-step process involving the obtention of a diketo ester intermediate by a condensation reaction with ethyl oxalate. The isolated intermediate was subjected to an intramolecular cyclization by refluxing it in acetic acid containing a catalytic amount of HCl. Thus, the synthetic strategy here described (Scheme 2, step **A** and $\mathbf{B_1}$) is less laborious, resourcing to a two-step methodology and using less harsh conditions.

All the chromones were fully characterized by ^{1}H and ^{13}C NMR and by MS mass spectrometry and several of them structurally characterized by single crystal X-ray diffractometry[24] but however,



Scheme 2. Synthetic strategies used to obtain ethyl-6-phenyl-4-oxo-4*H*-chromene-2-carboxylate (**5**).

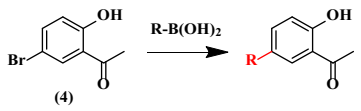


Scheme 3. Synthetic strategy used for the obtention of ethyl-6-phenyl-4-oxo-4*H*-chromene-2-carboxylate (**5**).

only the molecular and supramolecular structures of ethyl 6-(benzofuran-2-yl)-4-oxo-4*H*-chromene-2-carboxylate (Table 2, entry 10) is presented and discussed in this Letter. The ellipsoid diagram and adopted numbering scheme of this compound is shown in Figure 2.

The X-ray data confirm that the compound has two heteroaromatic moieties viz benzofuran and benzopyran rings, and an ethyl ester substituent linked to the position 2 of the chromone ring. The oxygen atom of the pyran ring is –*cis* related to the carbonyl oxygen atom O21 of the ester substituent. The aromatic rings are virtually planar and the dihedral angle between the mean planes of the benzofuran moiety and the 10-membered chromone moiety is 3.54 (3)°. The value for the C62—C6 bond distance (1.464 Å) is slightly shorter than the expected value for Csp3—Csp3 bond,[25] indicating a spread of the electronic cloud within the heteroaromatic rings similar to what happens with *p*-phenylenes. The planarity of the molecule is broken by a small twist around the

Table 1
Effect of aryl/heteroaryl boronic acids on the Suzuki cross-coupling reactions



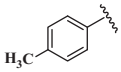
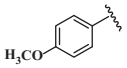
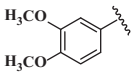
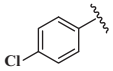
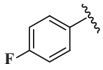
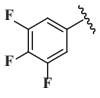
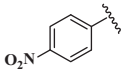
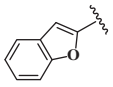
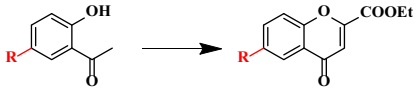
Entry	R =	Yield (%)
1		74
2		78
3		73
4		79
5		70
6		81
7		82
8		73
9		75
10		79

Table 2
Effect of aryl/heteroaryl acetophenones on the synthesis of chromone ethyl esters



Entry	R =	Yield (%)
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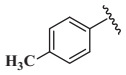
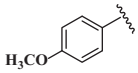
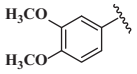
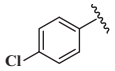
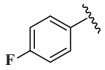
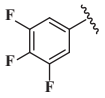
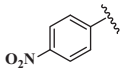
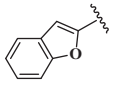
2		65
3		64
4		70
5		60
6		69
7		64
8		44
9		52
10		55

C2—C21 bond, the best plane formed by the non-hydrogen atoms of the ethoxy residue makes a dihedral angle of 12.85 (6)° with the best plane of the 10 membered chromone residue.

The supramolecular structure (Fig. 3) is built by weak C–H···O intramolecular interactions. Specifically, the molecules are linked by the C22—H22···O21 ($-x+3/2$, $y+1/2$, $-z+3/2$) and C63—H63···O21 hydrogen bonds, which link the asymmetric unit into a 3-dimensional network made up of centrosymmetric interconnected R24 (28) rings. There is also a π furan···π furan ($1-x$, $1-y$, $1-z$) contact with a distance of 3.7279 (7) Å [perpendicular distance of 3.2844 (5) Å and slippage of 1.763 Å].

In conclusion, an expeditious two-step procedure for the synthesis 6-aryl/heteroaryl-4-oxo-4*H*-chromene-2-carboxylic

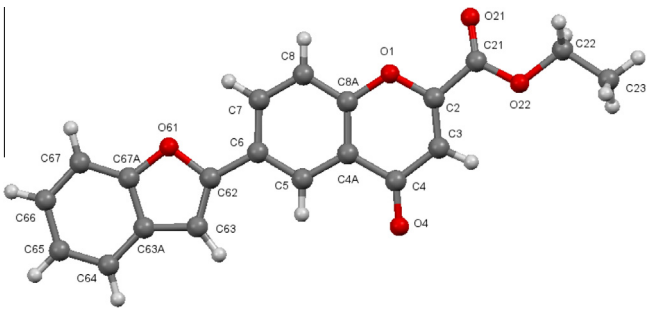


Figure 2. X-ray ellipsoid diagram and numbering scheme for ethyl 6-(benzofuran-2-yl)-4-oxo-4*H*-chromene-2-carboxylate.

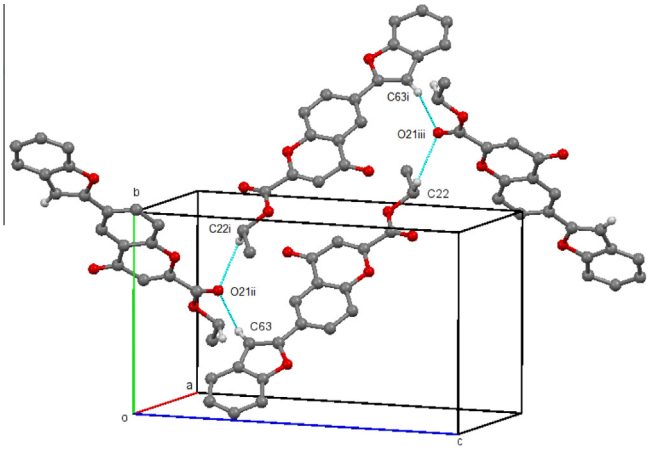


Figure 3. Supramolecular structure of 6-(benzofuran-2-yl)-4-oxo-4*H*-chromene-2-carboxylate.

ethyl ester derivatives was successfully developed. Moreover, the reduction of the reaction time, less formation of by-products, and easier work-up makes this new synthetic strategy suitable for obtaining analogue-based chemical libraries for medicinal chemistry programmes. The methodology herein described proved to be versatile and a stimulating starting point for the development of an automated process suitable for the synthesis of a larger library of new functionalized chromones with drug-like properties.

In addition, X-ray data allow to validate the planarity of this type of systems a property that can be of utmost importance for understanding their biological properties as antilipidemic agents.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.05.096.

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12. *General procedure:* A solution of 5′-bromo-2′-hydroxyacetophenone (4.7 mmol) in diethyl oxalate (18 mmol) was added to a ethanolic solution of EtONa (10 mL, 21 wt %). The mixture was stirred at reflux for 12 h, after which the mixture was cooled to room temperature. The ethanol was evaporated, and

water was added. The solution was acidified with HCl (2 M) and extracted with EtOAc (3 × 15 mL). The organic layer was separated, washed with brine, dried (Na_2SO_4) and evaporated. The product was then recrystallized from EtOAc.
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19. *General procedure:* To a suspension of 5′-bromo-2′-hidroxyacetophenone (2.3 mmol) in water (7–10 mL), TBAB (2.3 mmol), K_2CO_3 (6.9 mmol), the appropriate boronic acid (2.3 mmol) and $Pd(OAc)_2$ (0.4 mol %) were added. The system was heated to 150 °C for 15 min in a microwave apparatus. After cooling, the reaction mixture was filtered through a celite pad and washed with dichloromethane. The filtrated was collected dried (Na_2SO_4) and evaporated. The crude product was purified by flash chromatography using gradient elution (hexane/EtOAc).
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