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Synthesis of 3-arylcoumarins via Suzuki-cross-coupling reactions of 3-chlorocoumarin

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ABSTRACT

A convenient, new, and effective protocol for a rapid synthesis of different substituted 3-arylcoumarins is reported. The developed synthetic route involves Pd-catalyzed cross-coupling reaction, using a catalytic complex Pd-salen. Under these conditions, a series of different substituted boronic acids have been successfully reacted with a coumarin halide to afford the coupling products in good yields.

Coumarins are an important class of benzopyrones that are found in the vegetable kingdom, either in free or combined state.[1] They occupy an important place in the realm of natural products and synthetic organic chemistry. The diverse biological and pharmaceutical properties of natural and synthetic coumarins as antioxidants,[2] anti-HIV,[3] anticancer,[4] vasorelaxants[5] or enzymatic inhibitors[6] are well-known.[1] In the last few years our research group has been engaged in the synthesis of new biologically active coumarins. In particular, the 3-phenylcoumarin's scaffold has been the focal point of our most recent studies. In fact we have demonstrated that some 3-phenylcoumarins play an important role in the monoamino oxidase (MAO) enzymatic inhibition.[7–9] Accordingly, the interesting application potential of the 3-arylcoumarins in the Health Sciences promotes their preparation as an interesting topic in synthetic organic chemistry.

Two different strategies can be used to obtain the phenylcoumarins. One is the construction of the coumarin nucleus by condensation–cyclization-type reactions. Wittig,[10] Pechmann,[5,7,11,12] Perkin[8,9,13–17] or Knoevenagel[18,19] reactions are some of the synthetic routes frequently described to prepare 3-arylcoumarins, starting from phenols or aromatic carbonyl compounds. The classical Perkin condensation is perhaps the most direct and simple method known for the preparation of 3-arylcoumarins.[16] Although this method is often used, it has some drawbacks such as the application of strong acids and high temperatures and sometimes the request of multi-step reactions.

An alternative strategy consists in the direct 3-arylation of the coumarin scaffold by metal cross-coupling reactions. In recent years, palladium-catalyzed coupling reactions have been developing into a versatile and efficient method for the C–C bond formation. Suzuki[20,21] and Stille have described simple synthetic routes to obtain C–C liaisons throughout the coupling arylboronic or organotin compounds with organic halides catalyzed by a palladium-complex. In these reactions, Pd complexes are used as catalysts in which the ligands are P and/or N lone pairs donors or active Pd complexes are generated in situ.[22] In the first case, some of these ligands are expensive, toxic, and sensitive to air and a major challenge lies in the separation of product from the expensive catalyst, much to the dismay of large-scale producers.[22] Ionic liquids,[23] free of organic solvent systems or phase-transfer catalysts[24] have been used to provide a green alternative chemistry to the conventional organic methodologies, but they are not devoid of toxicity. In turn, phosphine ligands[25] had played an important role in C–C bond formation, in homogeneous reaction medium. Several efforts have been made in order to discover air and moisture-stable palladium ligands.[25] However, these ligands are air- and moisture-sensitive and the P–C bond degradation frequently occurs at elevated temperature.[26] The degradation of the catalyst strongly affects conversion and selectivity of the derivatives.[27] So, different methods using phosphine-free ligands have been explored for application in this kind of reactions.[28]

Because of its versatility, palladium catalyzed coupling reactions were widely used to synthesize different arylcoumarins. The arylation in 4-position of the coumarin nucleus is usually achieved by arylation of 4-hydroxycoumarins with arylboronic

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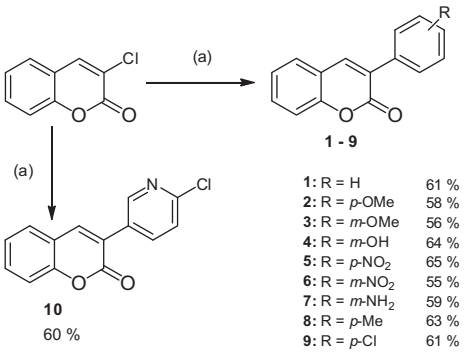

Scheme 1. Synthesis of 3-arylcoumarin derivatives. Reagents and conditions: (a) 3-chlorocoumarin (1.0 equiv), phenylboronic acid/2-chloro-5-pyridineboronic acid (1.25 equiv), sodium carbonate (2.0 equiv), palladium complex (0.5 mol %), DMF/H_2O (1:1), 110 °C, 120–180 min.

acids via C–OH bond activation.[29] Accordingly, the 4-hydroxy group is converted in *pseudo*halides, such as triflates or tosylates which are used instead of halides in a coupling reaction with arylboronic acids (via a Suzuki type reaction). In other cases, the aryl substituents have been successfully incorporated in 4-position of the hydroxycoumarin using organostannanes[30] or organozinc compounds[31] under Stille or Negishi conditions, respectively.

However, the formation of the aryl C–C bond using coumarin as starting material is till now an uncommon subject.[32,33] To our knowledge, few papers have been published so far concerning the 3-arylation of coumarin nucleus by direct coupling under Suzuki conditions: in all these cases, the halide was 3-bromocoumarin. And the catalysts were the classic palladium acetate ($Pd(OAc)_2$), tetrakis(triphenylphosphine)palladium (0) $Pd(PPh3)_4$[34,35], and [1,1′-bis(diphenylphosphino)ferrocene]palladium(II) dichloride.[36,37] Salen ligand has been found to be a highly active catalyst for the Suzuki reaction performed with aryl iodides, bromides, and chlorides, giving excellent yields, in a short reaction time.[38,39] Salen ligand is a bright yellow solid, soluble in polar organic solvents, and effective in C–C bond forming reactions with high selectivity. This symmetrical palladium(II) complex was a product of the reaction of the Salen ligand with palladium acetate (for 20 h at room temperature) in a good yield. This complex promotes a catalytic activity in a low concentration (0.5 mol %).[40] Noteworthy to mention that Salen is a chelating ligand generally used in coordination chemistry and homogeneous catalysis.[41]

Although significant advances have been performed in the metal-catalyzed synthesis, the palladium-catalyzed cross-coupling reaction using 3-chlorocoumarin to afford 3-arylcoumarins has never been described. This constraint encourages us to explore this synthetic strategy. Accordingly, preliminary experiments were done to examine the effect of various ligands for Pd-based coupling.[42,43] The most promising one was *N,N′*-bis(salicylidene)-ethylenediamino-palladium (salen-Pd). In fact, $Pd(OAc)_2$-salen couple in presence of a Na_2CO_3 in DMF/H_2O (1:1) was found to be an efficient catalytic system to obtain a variety of 3-arylcoumarin derivatives (Scheme 1).[40] As coumarins are sensitive substrates to alkaline conditions, and may result in the cleavage of the lactone ring, the solvent, and base for the coupling reaction were carefully studied. To optimize the reaction the influence of the palladium source in the catalytic activity was also performed. $Pd(OAc)_2$ was found to be the best option.[40] After reaction optimization, the influence of the Pd-salen complex in the Suzuki reaction involving cross-coupling of a coumarin halide and different arylboronic acids was investigated. The Suzuki reaction developed herein was found to be effective when using arylboronic acids with a variety of functional groups. Furthermore the reaction works with iodo-, bromo- or chloro-coumarin substrates. Different reaction times are required for each coumarin halide type. Although it is well-known that in Suzuki reaction the chloride derivatives are less reactive than the bromide or the iodide ones, the use of the 3-chlorocoumarin as starting material in the reaction is related with its commercial availability. The synthesis of 3-iodocoumarin and 3-bromocoumarin involves the introduction of other synthetic steps in the overall reaction.

Comparing the synthetic route herein proposed with the classic one, previously reported by us,[7,8] one can verify that both are easy and not too expensive methodologies. The main advantage of this new synthetic approach is that it can afford 3-arylcoumarins with different substitution patterns. By means of the traditional methodology, hydroxyl and nitro derivatives could not be obtained and/or purified. The reaction was not clean and the obtained crude product was a complex mixture with several sub-products and the purification process was worthless. The reaction versatility is the main advantage of this synthetic strategy comparing to the classic Perkin reaction. Compounds **4**–**7**[44–46] and **10**[47] are exclusively prepared by the Suzuki methodology while compounds **1**–**3**, **8**, and **9** can be prepared by both methods (Table 1).[48–50] The proposed synthetic strategy operates from micro- to macro-scale and avoids the formation of undesired sub-products. The palladium complex can be easily and almost totally recuperated at the end of the process. The catalyst is recovered from the reaction mixture when the product is purified by flash chromatography and it is ready to be reused. This subject has great interest because of the toxicity and the cost of palladium complexes.

In conclusion, a novel and versatile route for the synthesis of 3-arylcoumarins is proposed. The palladium cross-coupling reaction can be applied to obtain a series of different functionalized derivatives. In addition, we have shown that *N,N′*-bis(salicylidene)-ethylenediamino-palladium proved to be a good catalyst for the Suzuki reaction of heterocyclic activated chlorides with arylboronic acids, under aerobic conditions. This methodology is an efficient synthetic route for obtaining different 3-arylcoumarins.

Table 1
Synthesis of 3-arylcoumarins (**1**–**10**) by Perkin reaction and/or via Suzuki-cross-coupling reaction

Compounds	Perkin reaction[a]		Suzuki reaction[b]	
	Time (min)	Yield (%)	Time (min)	Yield (%)
1	1440	60	120	61
2	1440	65	120	58
3	1440	68	120	56
4	*	*	180	64
5	*	*	160	65
6	*	*	160	55
7	*	*	160	59
8	1440	70	120	63
9	2160	63	140	61
10	*	*	140	60

* Compounds **4**–**7** and **10** are exclusively prepared by the Suzuki methodology.
[a] Conditions: phenylacetic acids, DCC, DMSO, 110 °C, 24–36 h.
[b] Reactions with 3-chlorocoumarin. Compound **1** was synthesized using 3-bromocoumarin—reaction time: 100 min; yield: 70%.

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46. *General method to prepare 3-arylcoumarins*: To a 20 mL two neck round-bottomed flask was added a solution of 3-chlorocoumarin (0.83 mmol), aryl 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 °C for 120–180 min. The reaction was monitored by chromatography. After the completion of the reaction, the mixture was extracted with ethyl acetate (3 × 20 mL). The organic extracts were dried over anhydrous sodium sulphate, filtrated, and the solvent was evaporated under vacuum. The obtained crude product was purified by column chromatography (hexane/ethyl acetate 9:1) to give the coumarins (**1**–**9**). *3-(3′-Nitrophenyl)coumarin* (**6**): yellow solid, yield 55%; mp 252–3 °C. ^{1}H NMR ($CDCl_3$): δ = 7.17–7.22 (m, 2H, H-7, H-8), 7.39–7.48 (m, 3H, H-5, H-6, H-5′), 7.52–7.54 (m, 1H, H-6′), 7.60–7.71 (m, 2H, H-4, H-4′), 8.44 (s, 1H, H-2′). ^{13}C NMR ($CDCl_3$): δ = 110.0, 114.2, 116.7, 117.6, 119.3, 122.8, 125.5, 128.5, 131.1, 132.6, 132.7, 141.4, 149.1, 152.8, 158.6. MS: *m/z* (%) = 268 (26), 267 (M^+, 100), 239 (24), 221 (38), 193 (17) 165 (52), 164 (16), 163 (19), 139 (12), 82 (11). Anal. calcd. for $C_{15}H_9NO_4$ (267.24): C, 67.42; H, 3.39. Found: C, 67.38; H, 3.36. *3-(3′-aminophenyl)coumarin* (**7**): white solid, yield 59%; mp 154–5 °C. ^{1}H NMR ($CDCl_3$): δ = 4.12 (s, 2H, $-NH_2$), 7.27–7.38 (m, 4H, H-2′, H-4′, H-6′, H-8), 7.47 (dd, 2H, H-6, H-7, *J* = 7.74, *J* = 1.31), 7.53–7.58 (m, 2H, H-5, H-5′), 7.88 (s, 1H, H-4). ^{13}C NMR ($CDCl_3$): δ = 116.8, 118.8, 122.4, 125.0, 125.2, 127.2, 127.8, 128.7, 131.9, 133.3, 140.1, 152.6, 155.2, 157.3, 158.8. MS: *m/z* (%) = 239 (10), 238 (19), 237 (M^+, 100), 182 (36), 181 (12), 152 (50), 124 (18), 89 (45), 63 (28), 62 (18). Anal. calcd. for $C_{15}H_{11}NO_2$ (237.25): C, 75.94; H, 4.67. Found: C, 76.00; H, 4.72.
47. *3-(4′-Chloropyridin-3′-yl)coumarin* (**10**): white solid, yield 60%; mp 234–5 °C. ^{1}H NMR ($CDCl_3$): δ = 7.32–7.37 (m, 2H, H-5′, H-8), 7.46 (d, 2H, H-6, H-7, *J* = 7.51), 7.52–7.58 (m, 2H, H-5, H-6′), 7.88 (s, 1H, H-4), 8.58 (s, 1H, H-2′). ^{13}C NMR ($CDCl_3$): δ = 116.8, 118.8, 122.3, 124.7, 125.0, 125.2, 127.2, 131.8, 137.0, 140.0, 147.7, 149.6, 152.7, 157.3. MS: *m/z* (%) = 260 (5), 259 (32), 258 (15), 257 (M^+, 100), 223 (18), 182 (34), 152 (44) 123 (13), 89 (40), 85 (23), 71 (30), 63 (18), 57 (35). Anal. calcd. for $C_{14}H_8ClNO_2$ (257.57): C, 65.26; H, 3.13. Found: C, 65.24; H, 3.10.
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