Organic & Supramolecular Chemistry

One-Pot Synthesis of Xanthone by Carbonylative Suzuki Coupling Reaction

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Xanthone derivatives have a dibenzo-y-pyrone scaffold which has gained great interest in Medicinal Chemistry due to their diverse biological activities. Usually, its synthesis requires multi-step synthetic routes using harsh conditions and high catalyst loadings. In this communication, we report for the first time a one-pot synthesis of the xanthone scaffold based on a carbonylative Suzuki coupling. Iodophenol and (2-methoxyphenyl) boronic acid were coupled under carbon monoxide, generated from a carbon monoxide surrogate. An experimental data-based model was built to guide the reaction optimization. The optimized conditions were 1 mol% of a pincer complex as palladium catalyst, 5 equivalents of K_2CO_3 as base, and DMF: water (7:3) as solvent. The robustness of the synthetic method, namely in terms of the reactants scope, was also evaluated. This approach provided the xanthone scaffold in high yields and provided a deep insight into the carbonylative Suzuki couplings.

Xanthones are a class of *O*-heterocycles compounds with the dibenzo-γ-pyrone scaffold, that show a wide range of biological activities, such as, anti-inflammatory, antibacterial, and antitumor.[1] Bioactive xanthones can be of natural or synthetic origin.[2] The most common synthetic route for xanthones is a two-step approach, where a benzophenone intermediate is firstly formed, by a Friedel-Crafts acylation or 1,2-addition of an organolithium intermediate, which is then cyclized into xanthone.[3] The bottleneck of this route is the benzophenone formation as it requires harsh experimental conditions and generates significant waste.[3] Recently, palladium-catalyzed carbonylative Suzuki (CS) coupling emerged as a suitable alternative for the synthesis of benzophenones, which are synthetized by the cross coupling of aryl halides with aryl boronic acids in carbon monoxide (CO) atmosphere.[4] When compared to the classical methods, CS coupling reactions use mild conditions, are efficient processes with high atom economy, and have a good functional group tolerance.[5] CS reaction involves a considerable number of parameters (discrete parameters, *e.g.* the catalyst type, and continuous parameters, *e.g.* the catalyst concentration).[6] Design of experiments (DoE), a set of statistical/mathematical tools that only has been scarcely used for optimization of organic reactions, helps to accelerate and to improve the optimization process.[7]

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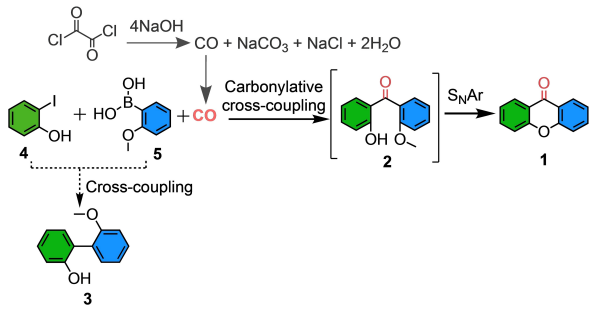
In this work, we report for the first time a carbonylative Suzuki based one-pot method for xanthone **1** (Scheme 1). In addition, we describe the reaction optimization using a DoE based methodology.

The proposed one-pot method consists in the benzophenone formation and its subsequent cyclization to xanthone by an *in situ* intramolecular nucleophilic aromatic substitution (S_NAr) (Scheme 1). Benzophenone **2** is formed by the carbonylative coupling of iodophenol **4** with (2-methoxyphenyl) boronic acid **5**, in the presence of a CO atmosphere. CO, which is the source of the carbonyl group, was generated *ex situ* from a surrogate and supplied with a balloon.[8] If the CO insertion do not occur during the CS catalytic cycle, the biaryl side product **3** is formed by direct coupling of **4** with **5**. The formation of this kind of side products is very common in CS couplings.[9]

A systematic reaction optimization was performed by considering both the discrete and the continuous parameters. The discrete parameters, namely the catalyst, the solvent and the base were optimized by an OVAT (one variable at the time)



Scheme 1. Synthesis of xanthone **1** and isolable intermediate **2** and side product **3**.

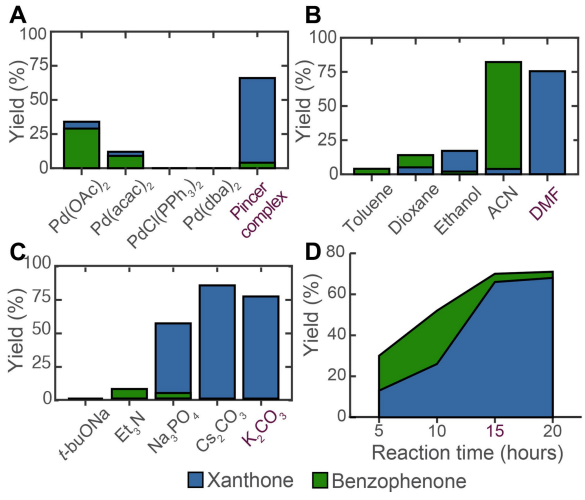


Figure 1. Optimization of the reaction (discrete parameters): palladium catalyst (A), solvent (B), and base (C). The best condition are highlighted in purple. Evolution of the reaction with the best discrete parameters (D). Reaction conditions are available in Table S1 in the Supporting Information.

method (Figure 1). Among the evaluated catalysts, the aminophosphine pincer complex [C_6H_3-2,6-(NHPpiperidinyl$_2$)$_2$]Pd(Cl)[5a] afforded the desired xanthone **1** with the highest yield (Figure 1A). The best solvent for this reaction is a mixture of organic solvent and H_2O. Xanthone **1** was synthesized in higher yields with DMF, while the isolable benzophenone intermediate was obtained in higher yields with ACN (Figure 1B). Carbonate bases provided xanthone **1** in higher yields than phosphate (Na_3PO_4) or organic bases (*t*-BuOK, Et_3N) (Figure 1C). K_2CO_3 and Cs_2CO_3 showed similar results, but K_2CO_3 is less moisture sensitive and inexpensive. With the previous selected parameters, the optimal reaction time for the synthesis of xanthone **1** was 15 hours at 100 °C (Figure 1D).

The continuous parameters, namely the Pd:iodophenol ratio, the amount of base (K_2CO_3:iodophenol ratio), and the percentage of water (% H_2O), were optimized by the DoE method. A central composite design (CCD) was used as the design model. CCD allows the evaluation of all parameters at five different levels[10] (Table S2 in the Supporting information) just using a set of 20 reactions (Table S3 in the Supporting information). These reactions were performed and the formed products were quantified by HPLC-DAD (detailed description in the Supporting information).

The yields of xanthone **1** were used to build a mathematical model for predicting the reaction outcome. The model was statistically significant (p-values ≤ 0.05) (statistical analysis conveyed in Table S4 in the Supporting information). Surface and contour plots displaying the relationship between the predicted yield and the reaction parameters are presented in Figure 2.

The yield of xanthone **1** increased significantly (p-values $<$ 0.05) with increasing Pd:iodophenol ratio, meaning that within the reaction time frame (15 h), the higher catalyst load provided a higher reaction rate (Figure 2A). Moreover, the yield also increased significantly (p-values < 0.05) with the % H_2O in the solvent, reaching a plateau around 30% (Figure 2A). This high amount of water is justifiable, as water is needed to activate the catalyst pincer complex[11] and it is also needed for the benzophenone cyclization into xanthone **1**. The best yield of xanthone **1** is obtained with ratios of K_2CO_3:iodophenol higher than four (Figure 2B). Therefore, five equivalents are optimal for the transmetalation step in CS reaction and for the deprotonation of iodophenol **4** in the intramolecular S_NAr. It was not observed any meaningful relationship between % H_2O and K_2CO_3:iodophenol ratio (Figure S5 in the Supporting information). Thus, merging the information of the two optimization procedures (OVAT and DoE), the best reaction conditions were: pincer catalyst with the Pd:iodophenol ratio of 1.0 x 10^{-2}, K_2CO_3:iodophenol ratio of 5, DMF:water (7:3) and 15 hours of reaction time. Using the optimized reaction conditions, xanthone **1** was synthetized in 95% yield. Regarding the biaryl side product **3**, no correlation was found between its formation and any of the reaction conditions (Figure S6 in the Supporting information). The side product formation was attributed to deficient CO saturation. Therefore, special caution should be taken with CO supply, mainly when assembling large scale reactions.

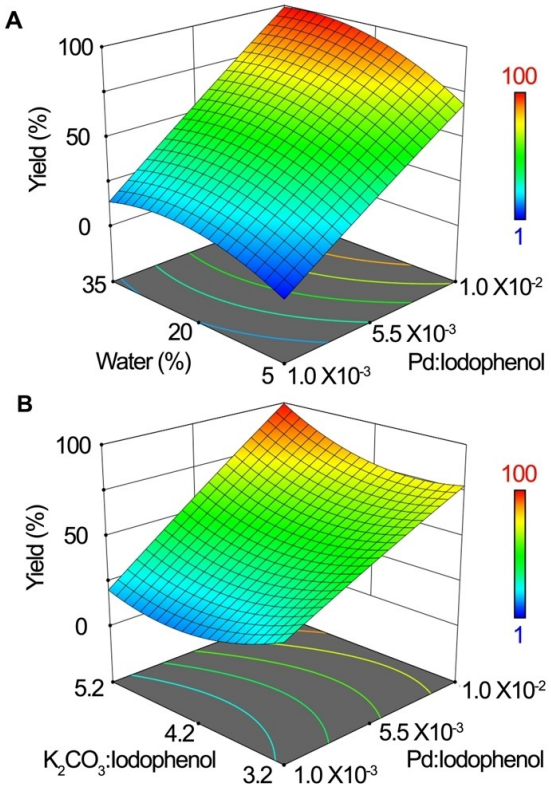
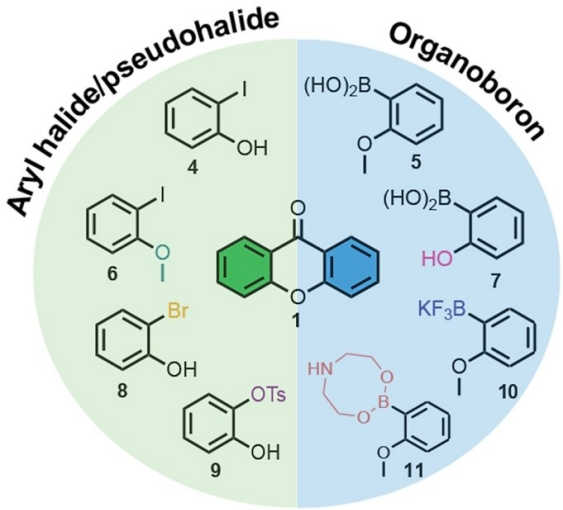


Figure 2. Surface and contour plots of the effect of reaction parameters on xanthone **1** yield.



Aryl halide	Organoboron	Yield (%) of 1[a]
6	7	20
8	5	7
9	5	0
4	10	12
4	11	3

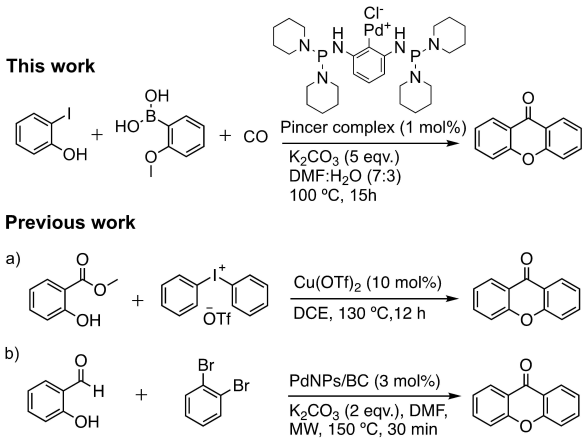
[a] Yield is calculated based on HPLC analysis. Quantification was based on UV detection at λ= 210 nm.
Reaction conditions: Aryl halide/pseudohalide (0.5 mmol, 1 eq.), organoboron (0.6 mmol, 1.2 eq.), CO (balloon), 0.01 eq. Pd, 5.2 eq. K_2CO_3, DMF: H_2O (7:3), 100 °C, 15h.

Figure 3. Aryl halides/pseudohalide and organoboron compounds studied for the synthesis of xanthone **1** and the corresponding yields (%).

Using the optimal conditions for the carbonylative coupling of **4** and **5**, we studied the reactivity of aryl halide and organoboron reactants in order to better understand the influence of other substituents groups (Figure 3 and Table S5 in the Supporting Information). Aryl iodide **6** and organoboron **7** were used to investigate the impact of the interchange of the hydroxyl and methoxyl groups. Aryl bromide **8**, a less expensive halide, was used to study the influence of a less reactive halide.[12] The aryl tosylate **9** was used to evaluate the potential of this alternative to iodide.[13] Potassium trifluoroborate salt **10** and DABO (2,8-dioxa-5-aza-1-bora-bicyclo[3:3:0]octanes) boronate **11** were used to access the reactivity with protected boronates.[14]

The coupling of **6** with **7** yielded xanthone **1** in a lower yield (20%) than the coupling of **4** and **5**. The presence of a second acidic group, a phenol, in the boronic acid counterpart shifts the boronic acid-borate equilibria and might affect the conversion of the boronic acid to the more reactive organoborate.[15] The low yield obtained using aryl bromide **8** was attributed to the lower reactivity of bromide when compared with iodide.[4c,16] Aryl tosylate **9** did not allow the obtention of xanthone **1** probably due to its great stability, which hampers the initial oxidative addition.[17] The low reactivity found for boronic derivatives **10** and **11** was attributed to the need for an additional step (hydrolysis) to form the activated boronic acid **5**.[14f,18]

When compared with previously classical xanthone synthesis (Scheme 2), the presented method: i) does not requires the presence of the carbonyl group in one of the building



Scheme 2. Comparison of the presented method with previously reported methods.[19]

blocks; ii) gives higher yields than most of the other methods (Table S6 in the Supporting information); iii) requires lower catalyst loading than the equally efficient methods (3–10 mol% vs. 1 mol%) (Scheme 2 and Table S6 in the Supporting information).

In conclusion, a novel one-pot methodology for the synthesis of xanthone was described. As far as we know, this is the first example of carbonylative Suzuki coupling reaction applied to the synthesis of a xanthone. The optimized of discrete and continuous parameters allowed the synthesis of xanthone **1** in high yield. Beyond the numerical optimization, the DoE approach also contributed to a better understanding of the reaction, which can be used to guide the planning of one-pot synthesis of xanthone derivatives.

Supporting Information Summary

The detailed experimental section including general procedures, characterizations of all synthesized compounds, copies of ^{1}H and ^{13}C NMR spectra of the products, quantifications performed by HPLC and design of experiments data can be found in the supporting information.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: xanthone · synthetic methods · optimization · carbonylation · design of experiments

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