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Tetrahedron Letters

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Green synthesis of novel chalcone and coumarin derivatives via Suzuki coupling reaction

Lucas C.C. Vieira, Márcio Weber Paixão, Arlene G. Corrêa*

Departamento de Química, Universidade Federal de São Carlos, 13565-905 São Carlos, SP, Brazil

ARTICLE INFO

Article history:

Received 17 February 2012

Revised 8 March 2012

Accepted 20 March 2012

Available online 29 March 2012

Keywords:

Suzuki reaction

Chalcone

Coumarin

Microwaves

Green technology

ABSTRACT

Chalcones and coumarins are important naturally occurring plant constituents and display a wide range of pharmacological and biological activities. In an environmentally benign approach, synthesis of biphenyl chalcone and coumarin derivatives was successfully accomplished via Suzuki coupling by using PEG-400 as a solvent under microwave irradiation. Salient feature of this methodology includes: short reaction time, good to excellent yields, and prominent tolerance of different functional groups.

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Chalcones and coumarins are important naturally occurring plant constituents and display a wide range of pharmacological and biological activities,¹ such as, anti-inflammatory,² antibacterial,³ antiviral,⁴ and antitumoral,⁵ among others.⁶ In synthetic perspective, chalcone and coumarin derivatives are gaining more prominence due to their pivotal role in the organic synthesis. However, only few methods have been already reported on derivatization of flavonoids, especially chalcones under Suzuki cross-coupling conditions.⁷

Substantial number of reports appeared in the literature for the synthesis of 3, 4, 6, and 7-substituted coumarins by Suzuki coupling,⁸ but none for the 8-substituted coumarins. Moreover, these methodologies usually employ conventional organic solvents, for example, toluene, acetonitrile, and dichloromethane,⁹ expensive, and unstable catalysts such as Pd(PPh₃)₄ and Pd(dppf)Cl₂,¹⁰ with an elevated temperature and reflux for several hours.¹¹ Besides, green Suzuki coupling reactions have been well accomplished for simple substrates but not for the densely functionalized substrates.¹² Thus, there is still considerable interest in the development of highly efficient methods for the synthesis of substituted chalcones and coumarins.

On account of these aspects, herein we report an eco-friendly, efficient, and versatile approach for the synthesis of Suzuki coupling reaction of chalcones and coumarins with arylboronic acids with low catalyst loading using non-toxic polyethyleneglycol

(PEG) as a solvent. Furthermore, the reaction conditions employed include an economically cheap and stable catalyst, Pd(OAc)₂, microwave irradiation as a source of energy, in short reaction time, contemplating the principles of green chemistry.

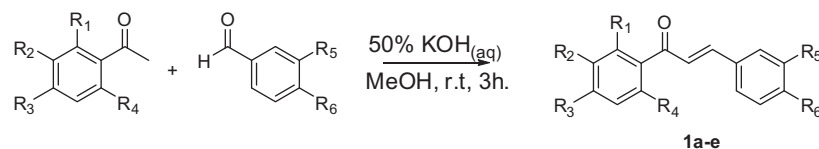
Chalcones **1a–e** (Scheme 1) were synthesized via Claisen–Smith condensation reaction with 3,4-substituted benzaldehyde and an aromatic acetophenone, aqueous KOH (50% w/v) in methanol, at room temperature for 3 h.¹³ After completion of the reaction, the mixture was filtered to collect the precipitates and purification by recrystallization affords the pure chalcones **1a–e** in 62–95% yield.

The coupling of compound **1a** and phenylboronic acid was chosen as the model reaction for the optimization. Initially, the reaction was carried out in a 3:1 mixture of PEG-400/H₂O in the presence of K₂CO₃ (3 equiv), Pd(OAc)₂ (10 mol%) at 110 °C for 30 min, under microwave irradiation (Table 1, entry 1). The reaction proceeds, however the desired product **2a** was delivered in only 34% yield. Different Pd sources were then examined, and Pd(OAc)₂ was found to be the most effective catalyst (Table 1, entry 3). Among the bases screened, K₂CO₃ and Cs₂CO₃, promote the reaction in moderate yields (Table 1, entries 1 and 5). Having KF as base the desired product could be obtained in good yield (Table 1, entry 6).

The influence of solvent system was further evaluated. To our delight, by using 3:1 mixture of PEG-400/EtOH as solvent, excellent yield was achieved (92%, Table 1, entry 8). While other solvents such as PEG-400 and PEG-400/H₂O furnished the desired arylated product in moderate yields. Regarding the influence of the solvent in this coupling reaction, optimal results were achieved using a mixture of

* Corresponding author. Tel.: +55 16 33518281; fax: +55 16 33518350.

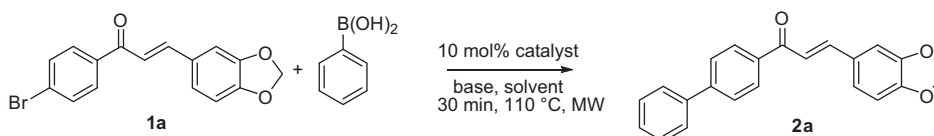
E-mail address: agcorrea@ufscar.br (A.G. Corrêa).



	Yield (%)
1a: R ₁ =H, R ₂ =H, R ₃ =Br, R ₄ =H, R ₅ =R ₆ =OCH ₂ O	95
1b: R ₁ =H, R ₂ =R ₃ =OCH ₂ O, R ₄ =H, R ₅ =H, R ₆ =Br	92
1c: R ₁ =H, R ₂ =H, R ₃ =Br, R ₄ =H, R ₅ =H, R ₆ =OCH ₃	90
1d: R ₁ =H, R ₂ =H, R ₃ =Br, R ₄ =H, R ₅ =H, R ₆ =H	83
1e: R ₁ =OH, R ₂ =I, R ₃ =OCH ₃ , R ₄ =OCH ₃ , R ₅ =H, R ₆ =OCH ₃	62

Scheme 1. Synthesis of chalcones.

Table 1
Suzuki reaction of chalcone **1a** with phenylboronic acid in different conditions^a



Entry	Catalyst	Base (3 equiv)	Solvent ^b	Yield ^c (%)
1	PdCl ₂	K ₂ CO ₃	PEG-400:H ₂ O	34
2	Pd ₂ (dba) ₃	K ₂ CO ₃	PEG-400:H ₂ O	41
3	Pd(OAc) ₂	K ₂ CO ₃	PEG-400:H ₂ O	54
4	Pd(PPh ₃) ₂ Cl ₂	K ₂ CO ₃	PEG-400:H ₂ O	46
5	Pd(OAc) ₂	Cs ₂ CO ₃	PEG-400:H ₂ O	48
6	Pd(OAc) ₂	KF	PEG-400:H ₂ O	65
7	Pd(OAc) ₂	K ₃ PO ₄	PEG-400:H ₂ O	11
8	Pd(OAc) ₂	KF	PEG-400:EtOH	92
9	Pd(OAc) ₂	KF	PEG-400	56
10	Pd(OAc) ₂	KF	PEG-400:EtOH	89 ^d
11	Pd(OAc) ₂	KF	PEG-400:EtOH	88 ^e
12	Pd(OAc) ₂	KF	PEG-400:EtOH	78 ^f

^a Reaction conditions: Chalcone (1.0 equiv), PhB(OH)₂ (1.5 equiv).

^b PEG-400 (3 mL) and water or EtOH (1 mL).

^c Isolated yields.

^d Reaction performed in 15 min.

^e Reaction performed in 45 min.

^f 5 mol % of catalyst.

PEG-400/EtOH (Table 1, entry 8). It can be easily rationalized, once the use of ethanol instead of water enhances the solubility of reagents and thus increased the product yield. It is important to note that when the amount of catalyst is reduced from 10 to 5 mol %, a decrease in the yield was observed (Table 1, entry 12).

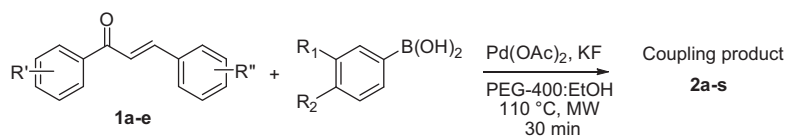
With the optimal reaction condition in hands, the scope of this greener catalytic system was then studied, with various chalcones and phenylboronic acids as reaction patterns (Table 2). We have observed that the catalytic system was tolerant to a broad range of functional groups, such as NO₂, OMe, OH, C=C, and C=O. Both electron-rich and electron-deficient chalcones gave the products with moderate to high yields, and the reaction was not affected by the standard reaction conditions. Furthermore, sterically hindered chalcones gave moderate yields (Table 2, entries 17–19).

Encouraged by the results of this eco-friendly catalytic system, we extended the substrate studies for the cross coupling reaction of 8-iodocoumarin **4** with various phenylboronic acids. Coumarin **4** was prepared via Knoevenagel condensation of 2-hydroxybenzaldehyde¹⁴ with diethyl malonate followed by the iodination reaction¹⁵ (Scheme 2).

Initially, we evaluated the Suzuki reaction with phenolic coumarin **4** and phenylboronic acid using the standard conditions applied for chalcones, like 10 mol % of Pd(OAc)₂ as catalyst, KF as base, and PEG-400/EtOH as solvent (Table 3). Gratifyingly, this reaction indeed proceeded to give compound **5a** in excellent yield (95%). Analyzing Table 3, the reaction proceeded very well both for electron donating and for electron withdrawing groups attached at boronic acids affording the corresponding products in good to excellent yields (**5b–f**).

In conclusion, a useful general synthetic strategy for biphenyl chalcones and coumarins was developed starting from substituted halochalcones and 8-iodocoumarin. A series of new chalcone and coumarin derivatives were able to be synthesized via Suzuki coupling. This approach allows the introduction of different phenyl substituents in natural products and analogs employing green conditions, using palladium acetate as catalyst, PEG as solvent under microwave irradiation. Furthermore, many functional groups withstanding our standard reaction conditions providing the desired product in good to excellent yield are one of the most important features of the present methodology.

Table 2
Suzuki reaction of chalcones with different phenylboronic acids^a

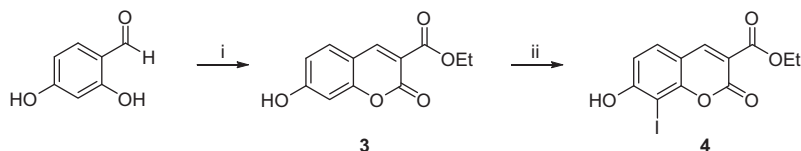


Entry	Chalc.	Prod.	R ₁	R ₂	Yield ^c (%)
1	1a	2a	H	H	92
2	1a	2b	H	OCH ₃	95
3	1a	2c	NO ₂	H	94
4	1a	2d	OCH ₃	H	90
5	1a	2e	F	OCH ₃	87
6	1a	2f	CH ₃	F	94
7	1a	2g		O-CH ₂ -O	91
8	1b	2h^b	H	H	91
9	1b	2i^b	H	OCH ₃	95
10	1b	2j^b	NO ₂	H	84
11	1b	2k^b	F	OCH ₃	90
12	1b	2l^b	CH ₃	F	91
13	1c	2m	H	OCH ₃	91
14	1c	2n		O-CH ₂ -O	90
15	1d	2o	H	OCH ₃	81
16	1d	2p	NO ₂	H	79
17	1e	2q	H	OCH ₃	53
18	1e	2r	OCH ₃	H	50
19	1e	2s	NO ₂	H	52

^a Reaction conditions: Chalcone (1.0 equiv), boronic acid (1.5 equiv), base (3 equiv), ethanol (1 mL) and PEG-400 (3 mL).

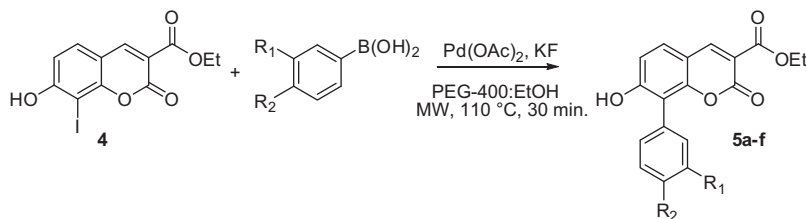
^b Reaction performed in 45 min.

^c Isolated yields.



Scheme 2. Synthesis of 8-iodine coumarin. Reagents and conditions: (i) Diethyl malonate, piperidine, rt, 2 h, 97%, (ii) KI, KIO₃, HCl, HAc, rt, 4 h, 88%.

Table 3
Suzuki reaction of coumarin 4 with different phenylboronic acids^a



Compound	R ₁	R ₂	Yield ^b (%)
5a	H	H	95
5b	H	OMe	85
5c	NO ₂	H	72
5d	OMe	H	87
5e	H	CH ₂ OH	78
5f	Cl	H	80

^a Reaction conditions: Coumarin (1.0 equiv), boronic acid (1.5 equiv), KF (3 equiv), ethanol (1 mL) and PEG-400 (3 mL).

^b Isolated yields.

Acknowledgments

The authors are grateful to FAPESP, CNPq and CAPES for their financial support and fellowships, and Dr. Senthil Narayanaperumal for suggestions in the manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2012.03.079>. These data include MOL files and InChIKeys of the most important compounds described in this article.

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