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Synthesis of arylated chalcone derivatives *via* palladium cross-coupling reactions

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ABSTRACT

A useful protocol for arylation of the olefin double bond of chalcones to afford tri- and tetra-substituted chalcone derivatives is reported. The protocol begins with the Heck reaction between chalcones and aryl iodides providing β -arylchalcones. This reaction tolerates various functional groups on both rings, as well as deactivated aryl iodides. The products are obtained in moderate to excellent yields and the (*E*)- β -arylchalcones (*E*:*Z* > 96:4) can be isolated *via* precipitation. Competitive Heck reactions pointed to a significant effect of ring one substituents on the reaction rate, while substituents on ring two have a much smaller effect. To access α , β -diarylchalcones, a sequential bromination-Suzuki cross coupling strategy was applied to the β -arylated compounds which afforded double arylated chalcone derivatives in 60–99% yield over two steps.

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Introduction

The chalcone backbone can be considered a privileged organic scaffold since its derivatives exhibit numerous biological activities^{1,2} and a wide range of other applications, for example in optical materials,^{3,4} and fluorescent probes for biomedical⁵ and analytical⁶ purposes. Two additional factors make these compounds even more attractive: (i) chalcones can be easily accessed by aldol condensation and, (ii) the α,β -unsaturated carbonyl system can act as a platform⁷ for further regioselective functionalization of the olefin moiety. Moreover, it has been reported that the β arylchalcone and α,β -diarylchalcone backbones are present in compounds that display important pharmacological effects, including activities in hyperlipidemia,⁸ arteriosclerosis⁸ and cancer treatment (Fig. 1).⁹⁻¹¹ Therefore, methods for the selective installation of aryl groups on the α - and β -positions of the alkenyl moiety of chalcones, providing tri- and tetra-substituted derivatives, are welcomed.

The regio- and stereo-controlled insertion of aryl groups into organic scaffolds remains a significant challenge in organic synthesis.^{7,12-14} Palladium-catalyzed coupling reactions are among the easiest strategies for the rational insertion of aryl groups into alkenyl substrates either *via* the Heck reaction¹⁵⁻¹⁸ or cross-coupling

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Fig. 1. Representative examples of bioactive β -arylchalcones and α , β -diarylchalcones.

using alkenyl halides (or pseudohalides).^{19–26} Regarding the Heck β -arylation of chalcones, only a few examples have been described in the literature and its scope remains under-explored; not only because most methodologies were applied solely to non-function-alized benzalacetophenone **1a** as the substrate, but also the isolation of β -arylchalcones as single stereoisomers from these reactions has not yet been reported.^{27–31} In addition, the only previously reported α -arylation of these derivatives *via* cross-coupling reactions, providing doubly arylated chalcones, involves a multisstep α -iodo- β -arylchalcone synthesis using an alkyne as starting material.³²

Herein, we report a useful protocol for double arylation of the olefin double bond of chalcones. The protocol begins with a Heck reaction between the enone and aryl iodides, providing β -arylchalcones. These compounds are obtained in moderate to excellent yields and can be isolated with *E*:*Z* ratios greater than 96:4 via

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Table 1

Optimization of the Heck reaction between benzalacetophenone **1a** and aryl halides.

Entry	Х	Base	Ligand	Time (h)	Yield (%) ^a	E:Z ratio
1	Ι	AcOK	P(o-Tol) ₃	8	5	nd
2	Ι	Ag ₂ CO ₃	P(o-Tol) ₃	8	6	nd
3	Ι	K ₃ PO ₄	P(o-Tol) ₃	8	94	72:28
4	Ι	NEt ₃	$P(o-Tol)_3$	8	73	60:40
5	Ι	K ₂ CO ₃	P(o-Tol) ₃	8	99 (99) ^b [78] ^c	81:19
6	Ι	K ₂ CO ₃	PPh ₃	8	90	75:25
7	Br	K ₂ CO ₃	P(o-Tol) ₃	24	80	62:38

Reagents and conditions: 1a (0.2 mmol), 4-haloanisole (0.3 mmol), Pd(OAc)₂, (2 mol%), PR₃ (4 mol%), base (0.4 mmol), 120 °C.

^a NMR yields.

^b Isolated yield for the *E*:*Z* mixture (1.0 mmol scale).

^c Isolated yield for (*E*)-**2a** (1.0 mmol scale).

Table 2

Heck Reactions between substituted chalcones and aryl iodides.





Reagents and conditions: chalcone (1.0 mmol), aryl iodide (1.5 mmol), Pd(OAc)₂, (2 mol%), P(o-Tol)₃ (4 mol%), base (2.0 mmol), 120 °C, 8 h.

^a Isolated yield as an E:Z mixture.

^b Values in parenthesis refer to stereo-enriched product yields (*E*:*Z* > 96:4) obtained after precipitation.

^c 24 h.

precipitation. Subsequently, the α -position can be easily arylated *via* a sequential bromination/Suzuki cross coupling, providing α , β -diarylchalcones.

Results and discussion

The chalcones used as substrates were prepared via classical base-catalyzed Claisen-Schmidt condensation (EtOH, KOH, r.t.).¹ For the Heck β -arylation, various parameters were screened in order to determine the optimal conditions, using the coupling between benzalacetophenone (1a) and 4-iodoanisole as a model reaction (Table 1). A catalytic system based on Pd(OAc)₂ and P(o-Tol)₃ was chosen due to the favourable results previously reported with this precursor and ligand in the Heck arylation of diarylethenes, in terms of both reactivity and stereoselectivity.^{23,33} Five bases were evaluated and the best results in terms of yield were achieved with K₃PO₄ (Entry 3) and K₂CO₃ (Entry 5), with the latter furnishing better stereoselectivity. Upon changing the ligand to PPh₃ a small decrease in both yield and E:Z ratio was observed. Concerning the arvl halide, the reaction with bromoanisole required an extended reaction time, which also resulted in a significant decrease in both yield and stereoselectivity.

After optimization, the conditions of entry 5 were employed in a 1.0 mmol scale reaction and the β -arylchalcone **2a** was isolated in 99% yield with an *E:Z* ratio of 81:19. To our delight, after the addition of EtOH to the isomeric mixture, (*E*)-**2a** precipitated as single stereoisomer in 78% yield. It is important to note that to the best of our knowledge, in the previously reported Heck arylations of chalcones, the obtention of β -arylchalcones as single stereoisomers has not yet been reported.

Subsequently, the reaction scope was evaluated by varying the aryl iodide and the groups attached to both rings of the chalcones (Table 2). When the reaction was performed using non-substituted chalcone or chalcones substituted with the electron-donating methoxy group on ring 1 (Entries 1–4), high to excellent results were achieved (**2a-d**, 80–99%), with total consumption of the starting material within eight hours. The presence of the electron-withdrawing cyano group on the same ring (Entry 5) considerably decreased the reactivity, and product **2e** was obtained in only 34% yield, even with an extended reaction time (24 h). Significant formation (13%) of the 1,4-addition product (reductive Heck product) was noted, which is a by-product often observed in Heck reactions with enones.^{15,34} Regarding ring 2, a small decrease in the yield was observed when the hydrogen was replaced by a flu-

orine (Entry 1 vs Entry 6). A slight decrease in the yield was also observed when the hydrogen was replaced by a methoxy group (entry 3 vs entry 4).

Concerning the stereoselectivity, *E*:*Z* ratios ranging from 71:29 to 81:19 were obtained. Moreover, there is not a clear relationship between the chalcone structure and the diasteroisomeric ratio. Fortunately, the strategy applied for obtaining (*E*)-**2a** could be successfully extended to the other β -arylchalcones. Thus, products **2e** and **2f** were obtained in a stereo-enriched form (*E*:*Z* ≥ 96:4) in 20% and 66% yield, respectively, after precipitation from EtOH. Analogously, the NH₂-substituted **2g** was obtained in 26% yield (*E*:*Z* ratio 97:3) after precipitation from Et₂O.

For additional insight regarding the Heck reactivity of chalcones, substrates with different substitution patterns were employed in competitive reactions, and the initial rates were compared using the product distribution and chalcone consumption at low conversions (<20%), as depicted in Scheme 1. As expected, a substantial effect of the substitution pattern on ring 1 was observed (Scheme 1a), since the presence of a 4-methoxy group enhanced the reaction rate, while a 4-nitro group led to an opposite and even more pronounced effect. These findings can be explained by a facilitated migratory insertion into the more electron-rich chalcones¹⁵ which is in agreement with the high yields obtained in the synthesis of **2c** and **2d** and the low yield observed



Fig. 2. Molecular structure of compound 2e, with 50% thermal ellipsoids (using ORTEP software).



Scheme 1. (a) Competitive reaction for evaluation of the ring 1 substituent effect on the reaction rate. (b) Competitive reaction for evaluation of the ring 2 substituent effect on the reaction rate. ^cReagents and conditions: chalcones (0.1 mmol), 4-iodobenzene (0.3 mmol), Pd(OAc)₂ (2 mol%), P(o-Tol)₃ (4 mol%), K₂CO₃ (0.4 mmol), DMF 120 °C, 30 min.

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Scheme 2. Sequential bromination/Suzuki cross-coupling of β-arylchalcones **2c** and **2a**, providing double arylated chalcone derivatives. Reagents and conditions: Bromination: β-arylchalcone (0.69 mmol), Br₂ (0.75 mmol), CHCl₃, reflux, 1 h. Suzuki coupling: crude **3c** or **3a**, arylboronic acid (0.74 mmol), K₂CO₃ (1.4 mmol), Pd(OAc)₂ (5 mol%), PPh₃ (10 mol%), PhMe, EtOH, 75 °C, 2 h.

for β -arylchalcone **2e** (Table 2). In relation to the substitution pattern on ring 2 of the chalcones (Scheme 1b), no substantial effect was observed, with methoxy, hydrogen and fluorine-substituted substrates leading to coupling products with similar yields.

In order to confirm the stereochemistry of the obtained (E)- β -arylchalcones, NOESY experiments were performed for selected compounds (see ESI). These experiments confirmed the expected inversion of the double bound configuration of the substrate and consequent formation of the (*E*)-isomer. In addition, an X-ray crystal structure of compound **2e** was obtained, unambiguously establishing the *E* configuration of the major β -arylated products (Fig. 2). The X-ray analysis also revealed a considerable twist between the planes of the C=C-C enone system and the β -aryl groups.

Aiming at the preparation of tetra-substituted chalcone derivatives, we first subjected compound **2c** to the bromination conditions previously described for the conversion of **2b** into the corresponding vinyl bromide without the need of an additional dehydrobromination step (Br₂, CHCl₃, reflux, 6 h).³⁵ Under these conditions, however, significant formation of by-products was observed. Fortunately, decreasing the reaction time to 1 h led to the desired alkenyl bromide **3c** in high purity.

Considering the low stability of vinyl bromide **3c**, for application to the Suzuki reaction, this compound was not isolated and



Fig. 3. Molecular structure of compounds 4a (left) and 4b (right), with 50% thermal ellipsoids.

was directly submitted to the cross-coupling conditions with different arylboronic acids using a simple catalytic system based on Pd(OAc)₂, PPh₃ and K₂CO₃ (Scheme 2). In this way, α , β -diarylchalcones **4a-d** were obtained in 60–72% yield over two steps. In order to evaluate the stereoselectivity of the reaction, (*E*)-**2a** was also subjected to a sequential bromination-Suzuki coupling and provided α , β -diarylchalcone **4e** in excellent yield (99%), although unfortunately, as an 1:1 stereoisomeric mixture.

Single crystal X-ray structures were also obtained for α , β diarylchalcones **4a** and **4b** (Fig. 3). For both compounds, the three aryl groups bounded to the olefin moiety are highly twisted in relation to the C=C-C enone plane. Moreover, in opposition to **2e**, the benzoyl group is not coplanar with the α , β -carbonyl system.

Conclusion

In summary, a simple and useful methodology to insert aryl groups into both the α - and β -positions of chalcones is described. The Heck β -functionalization tolerates several functional groups, and is accelerated by electron-donating aryl groups on ring one of the chalcones, affording the products with *E:Z* ratios greater than 96:4. The α -arylation of β -arylchalcone derivatives was achieved *via* sequential bromination/Suzuki cross-coupling, providing double arylated chalcones in 60–99% yield over two steps.

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A. Supplementary data

Experimental procedures, NMR data and spectra, NOESY of selected β -arylchalcones and crystal data for compounds **2e** (CCDC 1587998), **4a** (CCDC 1588000) and **4b** (CCDC 1588001) are pro-

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vided as supplementary material. Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.01.038.

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