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Expeditious synthesis of 3,4-dihydroisocoumarins and phthalides using the Heck–Matsuda reaction

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ABSTRACT

Several 3,4-dihydroisocoumarins and phthalides were synthesized by an effective Heck–Matsuda reaction involving an *ortho* carboxybenzenediazonium salt with a series of styrenes bearing electron donating and electron withdrawing groups, methylvinyl ketone, and methyl acrylate. The reaction was carried out in an open-flask with 1% mol of palladium acetate in aqueous ethanol at ~80 °C, giving the correspondent 3-aryl-3,4-dihydroisocoumarins and phthalides with good overall yields. The electronic nature of the group attached to the olefin is a key feature for the regioselectivity of the cyclization step.

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1. Introduction

The 3-aryl-3,4-dihydroisocoumarins¹ and phthalides² are families of natural products that stand out for displaying an extensive list of biological activities. For example, 3-aryl-3,4-dihydroisocoumarin 1,^{1b} isolated from *Haloxylon scoparium*, is an efficient GABA_A inductor and phthalide **2**,^{2b} isolated from *Ligusticum chuanxiong*, has remarkable vasorelaxation activity (Fig. 1).

Many synthetic methods are available in the literature for the preparation of these scaffolds.^{3–5} However, only a few of them are capable of producing the two basic cores in a divergent manner. Among the methods available, the *ortho* lithiation of arenes is the most used.⁶ Another common strategy is the acid- (or base-) mediated cyclization of alkenes and alkynes.⁷ However, these strategies have their drawbacks, such as the need for structurally complex starting materials. Less frequently used methods include condensation reactions such as the Horner–Witting reaction and/or the use of metal catalysis.^{8,9}

Regarding the methods using transition metal catalysts,⁹ palladium, and copper are by far the most common metals employed. Moreover, these methods often employ the protected *ortho* arene derivatives as the arylating agent.¹⁰ Recently, the Heck–Matsuda (HM) reaction reappeared as an effective alternative for attaching an aryl group to styrene double bonds.¹¹ Unlike the conventional Heck reactions, the HM reaction employs arenediazonium salts

* Corresponding author. *E-mail address:* roque@iqm.unicamp.br (C.R.D. Correia). as electrophiles and no σ -donor ligands (phosphines, for example) are needed for high catalytic activity.

The ortho carboxybenzenediazonium tetrafluoroborate salt **4** is a particularly interesting diazonium salt, which is extensively used in aryne chemistry.¹² Its use in Merweein coupling is also known,¹³ but application in the Heck–Matsuda reaction is somewhat rare.¹⁴ In this work we extend the applicability of this arenediazonium salt in the efficient synthesis of dihydroisocoumarins and phthalides in a concise manner.

2. Results and discussion

We chose styrene **3** as a model olefin for optimization studies. We began with 5 mol % of the $Pd(OAc)_2$, at 40 °C and ethanol as the solvent to obtain the desired stilbene **5** in a moderate 64% yield, after 30 min (entry 1, Table 1). Increasing the temperature to 60 °C provided **5** in 82% yield, and at 80 °C (oil bath temperature) we obtained almost quantitative yield of stilbene **5** in only 10 min (entries 2 and 3). We then set this temperature as the optimal one for this transformation. Next, we evaluated the influence of the catalyst loading. To



Figure 1. Examples of dihydroisocoumarins and phthalides.





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Table 1Method optimization



Entry	<i>T</i> ^a (°C)	t (min)	Solvent	Pd (mol %)	Yield ^b (%)
1	40	30	EtOH	5	64
2	60	30	EtOH	5	82
3	80	10	EtOH	5	99
4	80	10	EtOH	2.5	99
5	80	10	EtOH	1.0	99
6	80	10	EtOH	0.5	81
7	80	10	MeCN	5	-

^a Oil bath temperature.

^b Yields after purification.



Scheme 1. Regiocontrolled synthesis of a dihydroisocoumarin.

our delight, reducing the catalyst loading from 5 mol % down to 1 mol % did not cause any significant drop in yields (entries 4 and 5). Further decrease in the catalyst loading to 0.5 mol % provided a good 81% yield of stilbene **5** (entry 6). A slight excess of the arenediazonium salt (10% excess) is recommended for an efficient reaction, and the use of bases is detrimental for the reaction in EtOH leading to decomposition of the arenediazonium, possibly with the formation of the corresponding arynes.¹² Somewhat surprising, the reaction seems to be inhibited when using MeCN as a solvent.

Once optimal conditions were established, we moved forward to *p*-AcO-styrene **6**, since previous results suggested that the presence of the electron withdrawing acetyl group is advantageous in this type of HM reaction.¹⁵ As predicted, initial tests showed that besides formation of the expected primary Heck adduct **7**; we also obtained the phenolic derivative **8** due to the loss of the acetyl group in the acidic ethanolic medium. However, extending the



Figure 2. Rationale for the regioselective cyclization: (a) with EDG to dihydroisocoumarins (b) with EWG to phthalides.

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Synthesis of dihydroisocoumarins and phthalides



^a Yields after purification.

reaction time to 60 min, we obtained the corresponding dihydroisocoumarin **9** regioselectively in 63% yield (Scheme 1).

The formation of dihydroisocoumarin **9** is straightforward and can be explained by both the acidification of the medium and the electronic nature¹⁶ of the Heck adduct **8** (Fig. 2). The observation that the electronic nature of the aryl group on the starting styrene might be controlling the cyclization outcome prompted us to investigate the formation of phthalides from olefins bearing electron-withdrawing groups. Keeping this principle in mind, we carried out a



Scheme 2. 'One-pot' formation of isocoumarin 23.



Figure 3. Rationale for the synthesis of isocoumarin 23.

reaction of methyl vinyl ketone with arenediazonium **4**. Gratifyingly, the reaction went smoothly providing the anticipated phthalide **11** in 65% yield. Since two important frameworks can now be obtained from this type of Heck reaction, a more extensive investigation on the electronic nature of the starting olefin was carried out (Table 2).

In agreement with the mechanistic proposal (Fig. 2), we found that olefins bearing electron-withdrawing groups provide the phthalide core (Table 2, entries 6–8), whereas those bearing electron-donating groups generate the dihydroisocoumarin core (Table 2, entries 1–5).

The one-pot cyclization took place only in the synthesis of compounds **9**, **11**, and **14**. In the case of dihydroisocoumarins **12**, **16**, and **18**, the desired product was obtained after reaction with the acid. On the other hand, phthalides **20** and **22** were formed after reaction with the base. It is worth mentioning that yields can be improved if the cyclization step is preceded by chromatographic purification of the Heck product. For example, the overall yield for dihydroisocoumarins **12** goes up to 94% if the Heck product is isolated and then submitted to cyclization under acidic conditions. Nevertheless, we found the one-pot sequence advantageous on practical and economic grounds.

Another interesting feature of this protocol is the fact that the Pd catalyst used in the Heck reaction can be converted into a mild Lewis acid thus promoting the acid catalyzed cyclization of the Heck adduct into the isocoumarin system in a sequential manner. To achieve that, ethanol was simply evaporated, replaced by DMSO,¹⁷ and the reaction placed under O₂. This procedure provided the unsaturated isocoumarin **23** in 63% yield from styrene **3** in a one-pot procedure (Scheme 2). Attempts to oxidize dihydro-isocoumarin **12** into **23** using the same reaction conditions (Pd(OAc)₂, O₂, DMSO) failed, which indicates that compound **12** is not an intermediate in this process.

Formation of the isocoumarin **23** can be explained by the oxidation of the Pd(0), generated in the Heck step, to Pd(II) by oxygen, followed by the formation of the π -olefin palladium(II) complex **24**¹⁸ (Fig. 3). Next, the added base (sodium acetate) forms a carboxylate anion **25**, which attacks the double bond regioselectivity. Subsequent β -hydride elimination affords the isocoumarin **23** and Pd(0), which undergoes re-oxidation by O₂, closing the catalytic cycle. Further applications of this protocol and the reuse of the catalyst are currently under investigation.

3. Conclusion

Expeditious and concise syntheses of 3,4-dihydroisocoumarins and phthalides can be accomplished from the Heck–Matsuda reaction of styrenes, methylvinyl ketones, and acrylates. 6-Membered dihydroisocoumarins or the 5-membered phthalide can be assembled quickly using a one-pot procedure from some substrates. These preliminary results indicate that the type of skeleton generated depends upon the electronic nature of the group attached to the olefin. Electron rich styrenes provided the dihydroisocoumarin skeleton, whereas electron deficient olefins provided the phthalide skeleton. The protocol can also be used for the direct synthesis of isocoumarins by converting the Pd(0) generated during the Heck arylation into the mild Lewis acid Pd(II) in a sequential manner.

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