

Expeditious syntheses of 3,4-dihydroisocoumarins and phthalides via a Heck-Matsuda reaction.

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INTRODUCTION

The 3-aryl-3,4-dihydroisocoumarins and phthalides are families of natural products that exhibit an extensive list of biological activities.¹ For example, the sweetener phyllodulcin is more effective than sucrose^{1a}, and isochracinic acid, is a phthalide that causes the black spot disease on Japanese pears^{1b}.

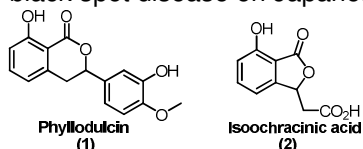
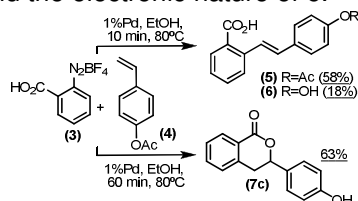


Figure 1. Examples of isocoumarins and phthalides.

Employing Heck-Matsuda (HM) conditions², we developed an efficient protocol for the synthesis of these cores structures using arenediazonium salt **3**.

RESULTS AND DISCUSSION

We started with *p*-AcO-styrene **4** since previous results suggested its advantageous use in HM reaction.³ Initial tests showed that besides formation of the Heck adduct **5**, we also observed compound **6**. After some experimentation, we obtained the cyclized product **7c** in 63% yield. Its formation is readily explained by both the acidification of the medium and the electronic nature of **6**.



Scheme 1. Regiocontrolled syntheses of isocoumarin.

In order to investigate the electronic influence of the substituent, we proceed with arylation of olefins bearing EWG. Thus, the reaction of **3** with methyl vinyl ketone gave the anticipated phthalide **8a** in 65% yield.

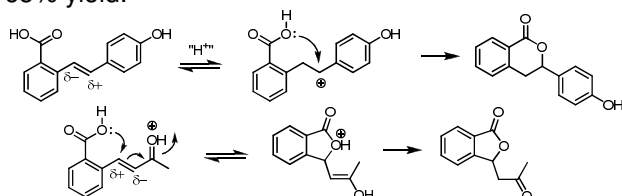
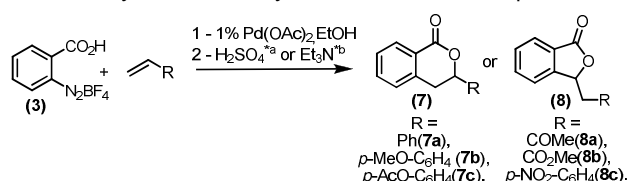


Figure 2. Rationale for the formation of products.

The scope of this reaction was explored and the results are summarized in table 1.

Table 1. Synthesis of dihydroisocoumarins and phthalides.



#	R	%	#	R	%
7a ^a	Ph	85	8a	COMe	65
7b	4-MeO-C ₆ H ₄	45	8b ^b	CO ₂ Me	82
7c	4-AcO-C ₆ H ₄	63	8c ^b	4-NO ₂ -C ₆ H ₄	68

In agreement with our mechanistic proposal (figure 2), we found that olefins bearing EWG provide the phthalide core (**8a,8b,8c**) whereas those bearing EDG generate the isocoumarin core (**7a,7b,7c**). The one-pot cyclization took place only in the cases of **7b,7c** and **8a**. In the others cases, the desired product was obtained by further addition of acid (**7a**) or base (**8b,8c**).

CONCLUSION

An expeditious synthesis of 3,4-dihydroisocoumarins and phthalides was developed. The choice of a 6 or 5 membered ring is made based upon the electronic nature of the group attached to the olefin. Therefore, EDG and EWG groups give the isocoumarin and phthalides, respectively.

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