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An efficient synthesis of 4-substituted coumarin derivatives via a palladium-catalyzed Suzuki cross-coupling reaction

Trideep Rajale, Shikha Sharma, Daniel A. Stroud [†], Daniel K. Unruh, Emily Miaou, Kimberly Lai, David M. Birney [*]

Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061, USA

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ABSTRACT

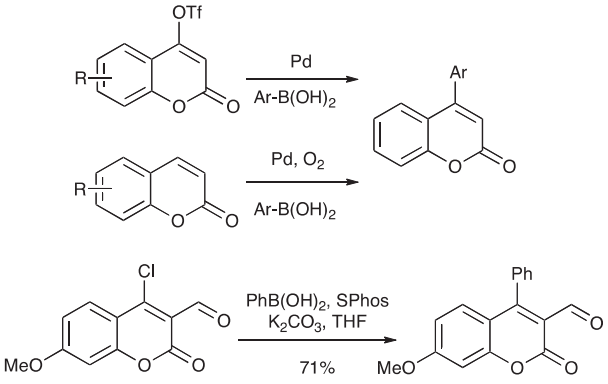
An efficient Pd-catalyzed Suzuki cross-coupling reaction of sterically crowded 4-chlorocoumarin derivatives with air- and moisture-stable potassium organotrifluoroborates is developed. This methodology has been used to generate a series of novel alkyl, aryl, and vinyl substituted coumarin derivatives in good to excellent yields. The twisted conformation of the vinyl groups in the X-ray crystal structures of (2-oxo-4-vinyl-2*H*-chromen-3-yl)methyl acetate (**2**) and (2-oxo-4-vinyl-2*H*-chromen-3-yl)methyl 2,2,2-trichloroacetimidate (**3**), along with the atropisomerism of 3-(hydroxymethyl)-4-(2-methoxyphenyl)-2*H*-chromen-2-one (**1d**), are evidence of the steric crowding in these adducts.

Introduction

The coumarin ring system is present in a variety of natural products and biologically active compounds.[1] These important heterocycles are known for their diverse physiological activities such as antibacterial, anticoagulant, antioxidant, and anti-inflammatory.[2] The 4-arylcoumarin skeleton forms the major structural component of neoflavones, a type of neoflavonoids.[3]

A number of methods are known in the literature to access coumarin scaffolds.[4] Among these, direct substitution at C-4 of the preformed coumarin ring is reported as an efficient strategy.[5] Finet and co-workers have reported the synthesis of polyoxygenated 4-heteroaryl substituted coumarins by the Suzuki–Miyaura cross-coupling utilizing heteroaryl boronic acids and 4-trifluoromethylsulfonyloxycoumarins.[6] Very recently Duan et al.[7a] reported Pd-catalyzed oxidative Heck coupling to access 4-arylcoumarins using coumarins and arylboronic acids. Glass and co-workers[7b] reported a fluorescent chemosensor for studying neurotransmitters for which a key synthetic step was a Suzuki coupling of phenylboronic acid to a chlorocoumarin (Scheme 1).

As part of our continuing interest in pseudopericyclic 3,5-sigmatropic rearrangements[8] we sought a convenient synthesis of 3,4-disubstituted coumarin **1a**. We expected that **1a** could be readily converted into acetate **2** and isoelectronic trichloroacetimidate **3** (Scheme 2). The acetate **2** contains a pentadienyl ester, a bonding pattern which we have previously shown can undergo a 3,5-sigmatropic rearrangement, in preference to a 3,3-rearrangement.[8]



Scheme 1. Prior examples of Suzuki and Heck couplings of coumarins.

In our effort to synthesize compound **1a**, we have developed an efficient protocol to access new analogs of 4-substituted coumarins that potentially have biological activity. Coumarin **5** was prepared in high yield in two steps starting from commercially available 4-hydroxycoumarin. Following a literature procedure,[9] 4-hydroxycoumarin underwent a Vilsmeier–Haack reaction using $POCl_3$/DMF to yield 4-chlorocoumarin aldehyde **4**. Selective reduction of the aldehyde **4** under typical $NaBH_4$ reduction condition led to

* Corresponding author. Tel.: +1 806 834 7167; fax: +1 806 742 1289.
E-mail address: david.birney@ttu.edu (D.M. Birney).
† Current address: University of Texas Southwestern Medical Center, Dallas, TX 75235, USA.

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