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

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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-2H-chromen-3-yl)methyl acetate (2) and (2-oxo-4-vinyl-2H-chromen-3-yl)methyl 2,2,2-trichloroacetimidate (3), along with the atropisomerism of 3-(hydroxymethyl)-4-(2-methoxyphenyl)-2H-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. These important heterocycles are known for their diverse physiological activities such as antibacterial, anticoagulant, antioxidant, and anti-inflammatory. The 4-arylcoumarin skeleton forms the major structural component of neoflavones, a type of neoflavonoids.

A number of methods are known in the literature to access coumarin scaffolds. Among these, direct substitution at C-4 of the preformed coumarin ring is reported as an efficient strategy. 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. Very recently Duan et al. reported Pd-catalyzed oxidative Heck coupling to access 4-arylcoumarins using coumarins and arylboronic acids. Glass and co-workers 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 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.

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, 4-hydroxycoumarin underwent a Vilsmeier–Haack reaction using POCl3/DMF to yield 4-chlorocoumarin aldehyde 4. Selective reduction of the aldehyde 4 under typical NaBH4 reduction condition led to...