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Palladium-catalyzed cross-coupling reactions of 4-tosylcoumarin and arylboronic acids: synthesis of 4-arylcoumarin compounds

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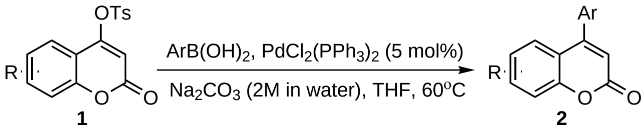
Abstract—The palladium-catalyzed reaction between 4-tosylatecoumarin and arylboronic acids was investigated. This reaction provides an efficient approach to synthesize diversified 4-arylcoumarins in good yields. © 2002 Elsevier Science Ltd. All rights reserved.

The prominence of coumarin in natural products and biologically active molecules[1] has promoted considerable efforts toward their synthesis.[2] As a 'privileged' scaffold, 4-substituted coumarin shows interesting biological properties, especially for their anti-HIV and antibiotic activities.[3] Our continued interest to build-up a coumarin based combinatorial library led us to devote our efforts to develop efficient methods for the synthesis of diversified coumarin molecules.

In our previous paper,[4] we discussed a chemistry of the palladium-catalyzed cross-coupling reactions of substituted 4-tosylcoumarins with acetylenes or zinc reagents under very mild conditions with satisfactory yields. We fortunately identified the 4-tosylcoumarin as an ideal synthon for synthesizing 4-substituted coumarin in terms of its stability, cost-effective issues and easy preparation comparing to its corresponding triflate. These advantages inspired us to look for other applications of 4-tosylcoumarins, such as the Suzuki-type cross-coupling reaction.[5]



1a: R = H; **1b**: R = 7-OMe;
1c: R = 6-Me; **1d**: R = 6-OMe.

Scheme 1.

From a synthetic point of view, the use of aryl sulfonates (in particular tosylates) as electrophiles for the Suzuki-type cross-coupling is a very attractive alternative due to their unique characteristics aforementioned. There are some interesting reports related to utilizing arene sulfonates as electrophiles in the Suzuki couplings, but most of them utilized organo-nickels as catalysts. High loading catalysts (up to 10%) and harsh reaction conditions (130°C for 10–60 h) had to be utilized in order to achieve the respective yields.[6]

We assumed that the 4-tosyl group attached to the electron-withdrawing α,β-unsaturated double bond in 4-tosylcoumarins would definitely increase its capability to oxidatively add to the transition metals, therefore, the rate limited step in this 4-tosylcoumarin based Suzuki reaction would be significantly improved as comparing with other aryl or vinyl sulfonates species.

Initially, we selected 4-tosylcoumarin as a substrate to react with 2-methoxyphenylboronic acids in the presence of nickel catalysts (NiCl$_2$(dppe), NiCl$_2$(dppf)), and a complicated mixture was generated, even though a variety of reaction conditions were tested. We thought that the nickel catalysts maybe so active to cause the substrates decomposition. We therefore focused our attention to the palladium-catalyzed cross-coupling reaction with the hope of finding a less reactive catalyst, which may give a better selectivity. Primarily, when

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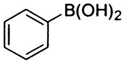
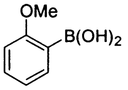
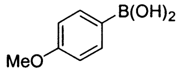
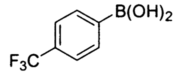
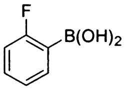
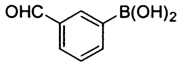
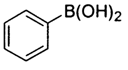
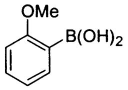
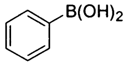
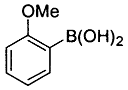
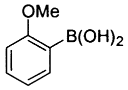
$Pd(PPh_3)_4$ was employed to mediate the cross-coupling reaction between 4-tosylcoumarin and 2-methoxyphenyl-boronic acid in the presence of potassium carbonate as the base, the reaction indeed proceeded albeit in 32% yield. After systematic investigation by studying a variety of combination, such as the amount of different catalysts ($PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, $Pd(PPh_3)_4$), the solvents (THF, DCM, CH_3CN, DMF, dioxane), and the bases (Na_2CO_3, Cs_2CO_3, K_2CO_3, K_3PO_4), an optimal condition for the coupling of 4-tosylcoumarin with 2-methoxyphenylboronic acid was selected. The best catalyzed reaction was employed by using $PdCl_2(PPh_3)_2$ in THF at 60°C in the presence of Na_2CO_3 and the results are depicted below in Scheme 1.

As is demonstrated in Table 1, all the reactions proceeded smoothly under the selected condition and afforded the corresponding products in good to excellent yields. Synthetically, all these cross-coupling reactions illustrated in Table 1 went to completion at 60°C in less than 12 h, regardless of different substitution patterns on these substrates. Therefore, diversified substitutions on both coumarin and boronic acids were tolerated under the reaction conditions, and indeed boronic acids with electron-donating group gave better yields.

In a typical experimental procedure, 4-tosylatecoumarin (0.25 mmol), arylboronic acid (0.50 mmol) and $PdCl_2(PPh_3)_2$ (9 mg, 5 mol%) was dissolved in THF (2.0 mL) under argon atmosphere, and then an aqueous sodium carbonate solution (2 M, 2.0 mL) was added. The reaction mixture was stirred at 60°C for 12 h (completion of a reaction was monitored by TLC). The reaction mixture was cooled, and extracted with ethyl acetate (2×20 mL). The organic phase was washed successively with water (5.0 mL), brine (5.0 mL), and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was purified by silica gel chromatography to give the corresponding product.

In summary, the cross-coupling reactions between 4-tosylcoumarins and boronic acids have been investigated. The chemistry described above illustrates 4-tosylcoumarin as an alternative for the palladium-catalyzed Suzuki reaction. The superiority of 4-tosylcoumarin versus its corresponding triflate in terms of its stability, the synthetic reagent cost, and easy preparation should make it an ideal synthon for combinatorial

Table 1.

Entry	Substrate	Boronic acid	Product	Yield (%)[a]
1	**1a**		**2a**	63
2	**1a**		**2b**	80
3	**1a**		**2c**	82
4	**1a**		**2d**	69
5	**1a**		**2e**	62
6	**1a**		**2f**	51
7	**1b**		**2g**	91
8	**1b**		**2h**	81
9	**1c**		**2i**	68
10	**1c**		**2j**	76
11	**1d**		**2k**	72

[a] *Isolated yield based on 4-tosylcoumarin.*

synthesis of coumarin on solid support. Application of this methodology on a silyl linker-based solid support to synthesize coumarin derivatives is currently under investigation in our laboratory.

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