Tetrahedron Letters 50 (2009) 2103–2105

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Palladium-catalyzed direct arylation of 4-hydroxycoumarins with arylboronic acids via C–OH bond activation

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ARTICLE INFO

Article history:
Received 18 December 2008
Revised 10 February 2009
Accepted 17 February 2009
Available online 21 February 2009

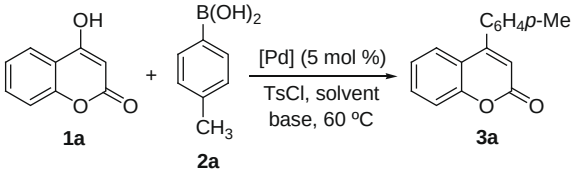
Keywords:
Arylboronic acid
4-Hydroxycoumarin
Palladium chloride
C–OH bond activation

ABSTRACT

Operationally simple $PdCl_2$-catalyzed direct arylation of 4-hydroxycoumarins with arylboronic acids via C–OH bond activation under mild conditions is described, which gave rise to the corresponding 4-arylcouamrins in good to excellent yields.

The transition metal-catalyzed cross-coupling reactions are known to be a powerful tool for C–C bond formations.[1] Traditionally, these cross-coupling reactions rely on the use of pre-activated substrates, such as organic (pseudo)halides. Recently, the first palladium-catalyzed cross-coupling reactions via C–OH bond activation of tautomerizable heterocycles with arylboronic acids utilizing phosphonium salts as activation reagent were reported. In this Letter, Kang disclosed that the presence of phosphonium salt enabled an in situ activation of tautomerizable heterocycle, which then underwent the subsequent palladium-catalyzed cross-coupling reactions with arylboronic acids.[2] Usually, this methodology required a separate pre-formation of the corresponding heterocycle-phosphonium salt electrophile in the absence of the palladium catalyst. In addition, high temperature was required in the reaction process. Very recently, Ackermann reported that phenols could be employed as proelectrophiles in ruthenium-catalyzed dehydrative direct arylations, proceeding through chemo- and regioselective functionalizations of C–H and C–OH bonds.[3] As part of a continuing effort in our laboratory toward the development of new methods for cross-coupling reactions and their application in the synthesis of natural product-like compounds,[4] we became interested in developing novel and efficient method to construct the diverse coumarins and related heterocycles.[5] It is well known that coumarins as a privileged scaffold show interesting biological properties.[6,7] Continuous efforts toward their synthesis have been reported due to the prominence of coumarins in natural products and biologically active molecules.[8–10] Recently, we also discovered that 4-substituted coumarins showed good anti-HCV (hepatitis C virus) activity.[11] With a hope for finding promising lead antivirus compounds by evaluations of analogous structures, we developed an efficient method for rapid syntheses of diverse coumarins. Herein, we would like to disclose our recent efforts for the synthesis of 4-arylcouamrins via palladium-catalyzed direct arylation of 4-hydroxycoumarins with arylboronic acids. This C–OH bond activation is highly effective under mild conditions.

At the outset, a set of experiments were carried out using 4-hydroxycoumarin **1a** and 4-methylphenylboronic acid **2a** as model substrates. We reasoned that the presence of arenesulfonyl chloride would enable an in situ activation of 4-hydroxycoumarin substrates. Based on these considerations, the reactions were performed in the presence of different palladium catalysts, base, and *p*-toluenesulfonyl chloride (Scheme 1). Only a trace amount of product **3a** was detected when the reaction was catalyzed by $PdCl_2(PPh_3)_2$ (5 mol %) in the presence of Na_2CO_3 as base in THF



Scheme 1.

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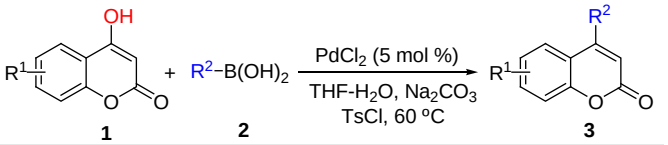
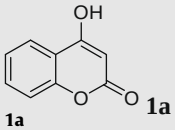
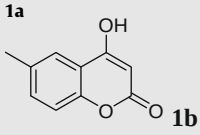
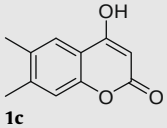
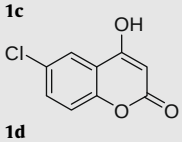
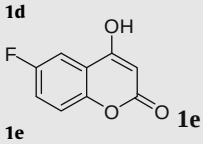
doi:10.1016/j.tetlet.2009.02.116

Table 1
Palladium-catalyzed direct arylation of 4-hydroxycoumarin **1** with arylboronic acid **2**[12]



Entry	Coumarin **1**	R^2	Yield (%)[a]
1	 **1a**	4-MeC_6H_4 (**2a**)	98 (**3a**)
2	**1a**	4-$MeOC_6H_4$ (**2b**)	98 (**3b**)
3	**1a**	C_6H_5 (**2c**)	91 (**3c**)
4	**1a**	2-ClC_6H_4 (**2d**)	88 (**3d**)
5	**1a**	3-$NO_2C_6H_4$ (**2e**)	68 (**3e**)
6	**1a**	3-NCC_6H_4 (**2f**)	90 (**3f**)
7	**1a**	4-$CF_3C_6H_4$ (**2g**)	52 (**3g**)
8	 **1b**	C_6H_5 (**2c**)	92 (**3h**)
9	 **1c**	4-$MeOC_6H_4$ (**2b**)	98 (**3i**)
10	**1c**	C_6H_5 (**2c**)	94 (**3j**)
11	**1c**	2-ClC_6H_4 (**2d**)	80 (**3k**)
12	 **1d**	4-$MeOC_6H_4$ (**2b**)	97 (**3l**)
13	**1d**	C_6H_5 (**2c**)	88 (**3m**)
14	**1d**	2-ClC_6H_4 (**2d**)	54 (**3n**)
15	 **1e**	4-$MeOC_6H_4$ (**2b**)	96 (**3o**)
16	**1e**	C_6H_5 (**2c**)	87 (**3p**)
17	**1e**	2-ClC_6H_4 (**2d**)	90 (**3q**)

[a] Isolated yield based on 4-hydroxycoumarin **1**.

at 60 °C. Same results were observed when the base was replaced by other inorganic or organic bases. To our delight, 40% yield of product **3a** was generated when water was used as co-solvent in the above reaction. With this promising lead in hand, we then sought to screen different palladium catalysts. Finally, we identified that $PdCl_2$ was the best choice. Under this condition, the desired 4-arylcoumarin **3a** was isolated in almost quantitative yield (98%). Decreasing the amount of catalyst or lowering the reaction temperature diminished the product yield with prolonged reaction time.

Having demonstrated the viability of this catalytic strategy, we next investigated the scope of the transformation under the preliminary optimized conditions [$PdCl_2$ (5 mol %), Na_2CO_3, TsCl, THF–H_2O, 60 °C]. The results are summarized in Table 1. To assess the impact of the structural and functional motifs on the reaction, we tested a range of linking units between 4-hydroxycoumarins and arylboronic acids. For all cases, 4-hydroxycoumarin **1** reacted with arylboronic acid **2** leading to the corresponding products **3** in good to excellent yields. For instance, reaction of 4-hydroxycoumarin **1a** with 4-methoxyphenylboronic acid **2b** under the standard conditions gave rise to the desired product **3b** in 98% yield (Table 1, entry 2). Similar yield was obtained when phenylboronic acid **2c** was utilized as coupling partner (Table 1, entry 3, 91% yield). Reaction of 4-hydroxycoumarin **1a** and arylboronic acid with electron-withdrawing group attached on the aromatic ring also proceeded well to afford the desired product in good yield (Table 1, entries 4–7). It seems that the group attached on the aromatic ring of arylboronic acid **2** does not effect the reaction markedly. Other 4-hydroxycoumarins were also examined. 4-Hydroxy-6-methylcouamrin **1b** reacted with phenylboronic acid **2c** leading to the desired product **3h** in 92% yield (Table 1, entry 8). 6,7-Dimethyl-4-hydroxycoumarin **1c** was also good substrate in the reaction of arylboronic acids, and the corresponding products were generated in good yields (Table 1, entries 9–11). Reactions of fluoro- or chloro-substituted 4-hydroxycoumarin with different arylboronic acids proceeded well to give rise to the desired products in good yields (Table 1, entries 12–17).

In conclusion, we have described an efficient route for the synthesis of 4-arylcouamrins via palladium-catalyzed direct arylation of 4-hydroxycoumarins with arylboronic acids. This C–OH bond activation is highly effective under mild conditions. The focused library generation and screening for biological activity of these small molecules are under investigation in our laboratory, and the results will be reported in due course.

Acknowledgments

Financial support from National Natural Science Foundation of China (20772018), Shanghai Pujiang Program, and Program for New Century Excellent Talents in University (NCET-07-0208) is gratefully acknowledged.

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12. *General experimental procedure for palladium-catalyzed direct arylation of 4-hydroxycoumarin* **1** *with arylboronic acid* **2**: A solution of 4-hydroxycoumarin **1** (0.3 mmol), *p*-toluenesulfonyl chloride (0.33 mmol, 1.1 equiv), $ArB(OH)_2$ **2** (0.36 mmol, 1.2 equiv), Na_2CO_3 (0.9 mmol, 3.0 equiv), and $PdCl_2$ (5 mol %) in H_2O/THF (1:20, 2.1 mL) was stirred at 60 °C for a period of time. After completion of the reaction as indicated by TLC, the solvent was diluted with EtOAc (10 mL), washed with saturated NaCl (10×2 mL), and dried by anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel provided the corresponding compound **3**. *Selected example: 4-phenylcoumarin* (**3c**): ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.41 (s, 1H), 7.20–7.30 (m, 2H), 7.40–7.60 (m, 7H). ^{13}C NMR (125.7 MHz) δ (ppm) 161.0, 155.9, 154.5, 135.5, 132.2, 129.9, 129.1, 128.7, 127.3, 124.4, 119.3, 117.6, 115.5. *m/z* (M^++1): 223.