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A Novel and Convenient Method to 4-Substituted Coumarins

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ABSTRACT: *The palladium-catalyzed cross-coupling reaction of aryl-; alkenyl-; and cyclopropylboronic acids with 4-trifluoromethanesulfonyloxycoumarin provides the corresponding 4-substituted coumarins in yields of 63–85%.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:380–382, 2000

INTRODUCTION

4-Substituted coumarins are known to possess antibacterial, antifungal, anthelmintic, insecticidal, hypnotic, and other biological properties [1]. In addition, 4-substituted coumarin subunits, especially the 4-aryl coumarin subunits, are prevalent in a variety of natural products [2] isolated from species of the *Leguminosae, Rubiaceae,* and *Guttiferae* families. A recent patent [3] demonstrated that various 4-substituted coumarins also could be used as light-emitting screen compositions.

Due to the involvement of a low-yielding cyclization step in a multistep route, the yields of the traditional approaches [4] to 4-substituted coumarins are generally unsatisfactory. From the point of view of retrosynthesis, the direct functionalization at C-4 of the preformed coumarin skeleton would be more efficient. Therefore, the direct arylation of 3-hydroxycoumarin using aryl-lead triacetates, followed by triflation and reduction to give 4-arylcoumarins, was reported [5]. However, the requirement of having a hydroxy function at C-3 debased its feasibility. Although the reaction [6] of organometallic reagents (Mg, Cu, Li) with 4-chlorocoumarin at low temperatures can give the desired product, the yields were unsatisfactory because of the coexistence of many side reactions. A transition metal-catalyzed coupling reaction, often used as a successful approach to C–C bond formation, is a powerful method for the preparation of 4-substituted coumarins. The Stille reaction [7] of 4-trifluoromethanesulfonyloxycoumarin **(1)** [8] has been reported, but it is not advantageous because of its troublesome preparation and the toxicity of organotin compounds [9]. Except for the moderately efficient reactions with $NaBAr_4$ [10] and 9-alkyl-9-BBN [11], the Suzuki reaction [12] in this area has not been utilized much. Herein we wish to report the coupling reaction of the triflate **(1)** with various boronic acids, which are readily available and environmentally friendly compounds.

To obtain an appropriate yield, several reaction conditions were examined using phenylboronic acid and the triflate **(1)** as the reactants (Scheme 1). The experiments showed that a satisfactory coupling yield of 83% could be achieved by carrying out the reaction in THF at 70°C using $Pd(MeCN)_2Cl_2/AsPh_3$ as the catalyst and Ag_2O as the base.

After we established the optimal reaction conditions, we evaluated the scope of the coupling reaction by investigating the reaction with various boronic acids (Table 1).

As shown in Table 1, the established conditions were applicable to various boronic acids, including the cyclopropylboronic acids [13]. The coupling reaction conditions were mild, and the yields were satisfactory. The ^{1}HNMR data of **3d–h** showed that the

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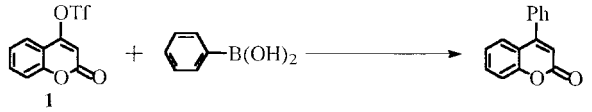
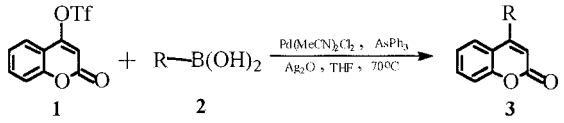
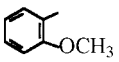
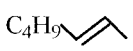
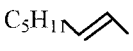
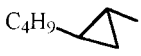
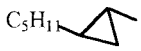
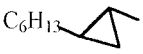


	isolated yield(%)
$K_3PO_4 \cdot 3H_2O$, Dioxane, $Pd(PPh_3)_4$, 85°C	56
K_3PO_4, Dioxane, $Pd(PPh_3)_4$, 85°C	67
Ag_2O, THF, $Pd(PPh_3)_4$, 70°C	74
Ag_2O, THF, $Pd(MeCN)_2Cl_2/AsPh_3$(4eq.), 70°C	83

SCHEME 1

TABLE 1. Suzuki-Type Coupling Reaction of Boronic Acids with the Triflate 1[a]



Boronic acid	R	Yield(%)
a		83
b		85
c		63
d		74
e		78
f		73
g		74
h		71

[a]See Experimental section.

configurations of both the alkenyl function in alkenylboronic acids and the cyclopropyl function in cyclopropylboronic acids were retained during the coupling reaction.

In conclusion, we have studied for the first time the coupling reactions of various boronic acids with 4-trifluoromethanesulfonyloxycoumarin and have developed an efficient and general method for the synthesis of various 4-substituted coumarins using the triflate of the commercially available 4-hydroxycoumarin as a starting material.

The biological activities of these compounds are being studied in our laboratory.

EXPERIMENTAL SECTION

All reactions were performed under an argon atmosphere. 4-Trifluoromethanesulfonyloxycoumarin was prepared according to the literature procedure [8]. Melting points were uncorrected. ^{1}HNMR spectra were recorded on a Brucker AMX-300(300 MHz) instrument, using $CDCl_3$ as the solvent with TMS as an internal standard. MS spectra were obtained on a HP5989A spectrometer. Elemental analyses were determined using a Foss-Heraeus Vario EL instrument. IR spectra were recorded on a Shimadzu IR-440 infrared spectrometer.

General procedure for the coupling reaction: 4-trifluoromethanesulfonyloxy-coumarin **1** (294 mg, 1.0 mmol), the boronic acid **2** (1.1 mmol), $Pd(MeCN)_2Cl_2$ (13 mg, 0.05 mmol), $AsPh_3$ (61 mg, 0.20 mmol), Ag_2O (696 mg, 3 mmol) were placed in a flask under an argon atmosphere, then the degassed and dried THF(4 mL) was added. The reaction mixture was stirred at 70°C and monitored by TLC. On completion of the reaction, the mixture was diluted with ether (50 mL), filtered through a short pad of silica gel, and evaporated. Purification of the residue by silica gel chromatography (ethyl acetate:petroleum ether = 1:2~8) gave the corresponding products **3a–3h.**

Product **3a**: m.p. 104–106°C (reported: 104°C [4c]); IR ν_{max}/cm^{-1}:1756; 1723; 1602; 1447; 1369; 1247; 746; 703. ^{1}HNMR δ_H(ppm): 7.21–7.56 (m, 9H); 6.38 (s, 1H). MS(EI) *m/z*: 165 (100); 82 (69.43); 194 (50.73), 63 (33.21); 222 (30.92); 139 (26.44); 51 (22.73); 62 (22.33). Anal. calcd. for $C_{15}H_{10}O_2$ C%, 81.07; H%, 4.54. Found: C%, 81.06; H%, 4.34.

Product **3b**: m.p. 137–139°C (reported: 138–139°C[14]); IR ν_{max}/cm^{-1}: 1754; 1724; 1603; 1452; 1357; 1253; 934; 782; 752. ^{1}HNMR δ_H(ppm): 7.94–8.02 (m, 2H); 7.44–7.62 (m, 7H); 7.02–7.08 (m, 2H); 6.51 (s, 1H). MS(EI) *m/z*: 252 (100); 221 (94.16); 210 (58.23); 152 (53.95); 165 (39.47); 181 (36.36); 223 (29.56); 253 (26.96). Anal. calcd. for $C_{19}H_{12}O_2$ C%, 83.81; H%, 4.40. Found: C%, 83.74; H%, 4.39.

Product **3c**: m.p. 83–85°C; IR ν_{max}/cm^{-1}: 1763; 1722; 1609; 1448; 1369; 1261; 1021; 752. ^{1}HNMR δ_H(ppm): 7.04–7.49 (m, 8H); 6.38 (s, 1H); 3.76 (s, 3H). MS(EI) *m/z*: 271 (100); 272 (63.37); 215 (46.28); 255 (40.20); 243 (36.12); 213 (26.70); 94 (26.56); 107 (23.10). Anal. calcd. for $C_{16}H_{12}O_3$ C%, 76.18; H%, 4.79. Found: C%, 76.15; H%, 4.80.

Product **3d**: m.p. 66–68°C (reported: 67°C[15]); IR ν_{max}/cm^{-1}: 2931; 1718; 1643; 1605; 1447; 1383; 1182; 938; 755. ^{1}HNMR δ_H(ppm): 7.29–7.72 (m, 4H);

6.67 (d, 1H, J = 15.6); 6.52 (dt, 1H, J = 6.8; 15.6 Hz); 6.42 (s, 1H); 2.32 (dt, 2H, j = 1.0; 6.8); 1.34–1.57 (m, 4H, 2 × CH_2); 0.96 (t, 3H, J = 7.2). MS(EI) *m/z*: 171 (100); 115 (15.17); 228 (14.88); 229 (8.75); 127 (8.23); 129 (5.90); 41 (5.33). Anal. calcd. for $C_{15}H_{16}O_2$ C%, 78.92; H%, 7.06. Found: C%, 78.98; H% 7.09.

Product **3e**: m.p. 67–69°C; IR ν_{max}/cm^{-1}: 2935; 1712; 1647; 1601; 1448; 1376; 1180; 968; 866. ^{1}HNMR-400 MHz δ_H(ppm): 7.29–7.72 (m, 4H); 6.67 (d, 1H, J = 15.6); 6.52 (dt, 1H, J = 6.7; 15.6 Hz); 6.43 (s, 1H); 2.33 (dt, 2H, J = 1.2; 6.8); 1.30–1.59 (m, 6H, 3 × CH_2); 0.93 (t, 3H, J = 7.0). MS(EI) *m/z*: 171 (100); 115 (14.26); 242 (12.88); 128 (12.70); 127 (8.27); 243 (7.19); 41 (6.50); 129 (5.88). Anal. calcd. for $C_{16}H_{18}O_2$ C%, 79.31; H%, 7.49. Found: C%, 78.85; H%, 7.27.

Product **3f**: m.p. 44–46°C; IR ν_{max}/cm^{-1}: 2928; 1714; 1616; 1605; 1258; 1189; 939; 863; 776. HNMR δ_H(ppm): 7.30–7.91 (m, 4H); 5.98 (s, 1H); 1.85 (ddd, 1H); 1.38–1.48 (m, 6H, 3 × CH_2); 1.19 (ddd, 1H); 1.09 (ddd, 1H); 0.98 (ddd, 1H); 0.92 (t, 3H, J = 7.1). MS(EI) *m/z*: 171 (100); 172 (62.62); 144 (48.23); 115 (47.03); 41 (26.54); 128 (25.65); 173 (20.34); 127 (17.56). Anal. calcd. for $C_{16}H_{18}O_2$ C%, 79.31; H%, 7.49. Found: C%, 79.42; H%, 7.24.

Product **3g**: m.p. 47–49°C; IR ν_{max}/cm^{-1}: 2925; 1715; 1616; 1603; 1448; 1257; 1184; 932; 863; 752. ^{1}HNMR δ_H(ppm): 7.27–7.90 (m, 4H); 5.99 (s, 1H); 1.84 (ddd, 1H); 1.32–1.49 (m, 8H, 4 × CH_2); 1.18 (ddd, 1H); 1.08 (ddd, 1H); 0.99 (ddd, 1H); 0.90 (t, 3H, J = 6.9). MS(EI) *m/z*: 171 (100); 172 (68.05); 144 (43.61); 43 (35.12); 115 (34.89); 41 (32.49); 173 (28.93); 128 (20.10). Anal. calcd. for $C_{17}H_{20}O_2$ C%, 79.65; H%, 7.86. Found: C%, 79.24; H%, 7.93.

Product **3h**: m.p. 50–52°C; IR ν_{max}/cm^{-1}: 2927; 1728; 1618; 1607; 1499; 1450; 1257; 1185; 938; 751. ^{1}HNMR δ_H(ppm): 7.30–7.90 (m, 4H); 5.98 (s, 1H); 1.87 (ddd, 1H); 1.29–1.49 (m, 10H, 5 × CH_2); 1.20 (ddd, 1H); 1.08 (ddd, 1H); 0.98 (ddd, 1H); 0.88 (t, 3H, J = 6.7). MS(EI) *m/z*: 171 (100); 172 (72.52); 173 (43.65); 144 (43.00); 115 (31.42); 41 (25.88); 128 (19.52); 43 (19.45). Anal. calcd. for $C_{18}H_{22}O_2$ C%, 79.96; H%, 8.20. Found: C%, 80.11; H%, 8.40.

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