JOC*Note*

Palladium-Catalyzed Cross-Coupling Reactions of 4-Tosyl-2(5*H*)-furanone with Boronic Acids: A Facile and Efficient Route to Generate 4-Substituted 2(5*H*)-Furanones

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Abstract: An efficient and facile synthesis of 4-substituted 2(5*H*)-furanones using palladium catalyzed cross-coupling reactions between 4-tosyl-2(5*H*)-furanone and boronic acids is reported herein.

As a privileged fragment, 4-substituted 2(5*H*)-furanone is a ubiquitous subunit in many butenolide-containing natural products with remarkable biological activities.[1] For example, butenolide **A** (see Figure 1),[1f] which was isolated from *P. syringae* pv. *tomato*, shows an interesting antimicrobial activity; Rubrolides **B**,[1g,h] a family of biologically active marine ascidian (tunicate) metabolites that have been isolated from *Ritterella rubra* and *Synoicum blochmanni*, are potent antibiotics and show moderate but selective inhibition of protein phosphatases 1 and 2A, significant cytotoxicity against P-388 suspension cultures of mouse lymphoid neoplasm and monolayer cultures of human lung carcinoma (A-549), human colon carcinoma (HT-29), and human melanoma (MEL-28). As a valuable synthetic intermediate,[2a−g] butenolide frequently is utilized as a key intermediate to construct complex molecules and also appears as a substructure in peptide analogues and HIV-1 protease inhibitors.[2h,i]

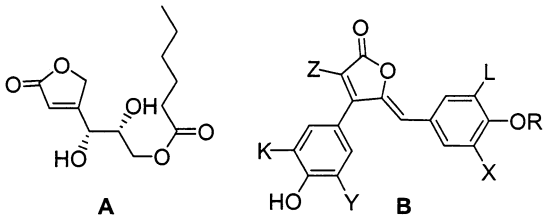

FIGURE 1. Butenolide chemistry.

In our ongoing combinatorial synthesis of natural product-like molecular libraries,[4d] we were interested in integrating this important fragment into our library synthesis either as a structural subunit or as a synthon to elaborate further complexity.

Synthetically, to generate 4-substituted 2(5*H*)-furanone is more challenging than its corresponding 3- or 5-substituted 2(5*H*)-furanone.[3] Currently, the most frequently used methods for synthesizing 4-substituted 2(5*H*)-furanone derivatives are based on the transition metal-catalyzed coupling methods.[3] For example, the first Suzuki reaction of tetronic acid triflate with 9-alkyl-9-BBN (51% yield) was adopted by Grigg[3p] during the total synthesis of (−)-isoseiridine, and later the reaction of

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alkenylboronic acid with tetronic acid triflate (48% yield) was described by Honda[3q] in the preparation of syributin. Very recently, Deng[3r] reported the palladium-catalyzed reactions of 4-triflate-2(*5H*)-furanone with cyclopropylboronic acids in the presence of $AsPh_3$ as a ligand (63−85% yields). Also, Boukouvalas[3n] and Rossi[3w] reported the coupling reactions by using 4-bromo-2(*5H*)-furanone as the substrate. However, the preparation of 4-bromo-2(*5H*)-furanone suffers harsh conditions, and highly toxic tin reagents were employed in the couplings. Another problem associated with the aforementioned synthetic methods is the stability of tetronic acid-derived triflate, which cannot be stored under normal conditions based on our experience.

Our desire to build up a furanone-based combinatorial library promoted us to search for a more facile method. The criteria for this replacement selection included the following considerations: (a) it must be stable at room temperature and in different solvents; (b) the reaction conditions must be very mild in order to be compatible with diversified substrates and our selected solid support;[4] and (c) the reaction should be reasonably fast at room temperature with high yield.

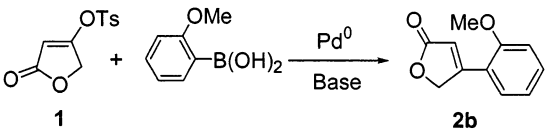
Recently, we have witnessed the important progress of using aryl sulfonates as electronphiles for the cross-coupling reactions.[5] In this field, we also reported the applications of 4-hydroxycoumarin-derived 4-tosyl-coumarin as a unique replacement for its corresponding triflate in the transition metal-catalyzed cross-coupling reactions with acetylenes, organozinc reagents, and arylboronic acids, respectively.[6]

The structural similarity of 4-hydroxycoumarin and tetronic acid led us to envisage that the 4-tosyl-2(*5H*)-furanone might be an ideal alternative for its corresponding triflate, since the 4-tosyl group attached to the electron-withdrawing α,*β*-unsaturated double bond in 4-tosyl-2(*5H*)-furanone may enhance its oxidative addition to the transition metals.

We therefore focused our attention on exploring the possibility of using 4-tosyl-2(*5H*)-furanone as a substrate in the palladium-catalyzed cross-coupling reaction. To permit an application of the above coupling reactions in drug discovery, it is of utmost importance to overcome the necessity of using highly toxic reagents. Due to the innocuous nature of boronic acids, which are generally nontoxic and thermally, air-, and moisture-stable, arylboronic acids would be the starting materials of choice, particularly for small-scale reaction. Thus, initial studies were carried out with 2-methoxyphenylboronic acid and 4-tosyl-2(*5H*)-furanone **1** (Scheme 1).

4-Tosyl-2(*5H*)-furanone **1** was prepared by simply mixing tetronic acid (1.0 equiv), tosyl chloride (1.0 equiv) and triethylamine (1.2 equiv) in dichloromethane at room temperature (See Experimental Section). As was expected, in contrast to the corresponding triflate, which is known to exhibit lability, **1** was remarkably stable as a crystalline solid, which could be stored at room temperature under air without protection from light. Under standard Suzuki conditions that we selected previously ($PdCl_2(PPh_3)_2$, THF, sodium carbonate),[6a] compound **1** underwent coupling reaction with *o*-methylphenylboronic acid to provide a 59% yield of desired product **2b** as expected. After further screening of different palladium catalysts and bases, 95% yield of **2b** was eventually obtained by combining potassium fluoride[7] and 5 mol % $PdCl_2(PPh_3)_2$ in a mixed solvent of THF−H_2O at 60 °C for 12 h. The ideal amount of catalyst is 5 mol %; however, with a significantly lower catalyst loading, the corresponding product with good yield was obtained by prolonging the reaction time to 48 h [$PdCl_2(PPh_3)_2$ (*0.5 mol %*), 60 °C, 92% yield]. Most importantly, this reaction can proceed even at room temperature to give 90% yield of coupling product, although the reaction needs 48 h to go to completion.

SCHEME 1. Tosylate-Based Suzuki Coupling Reaction



Encouraged by these results, the scope of this reaction was investigated by using various boronic acids and substrate **1**. The results are shown in Table 1.

From the results listed in Table 1, we can make the following observations. (1) Tosylate **1** can couple with all the selected boronic acids to provide the corresponding products in moderate to good yields. (2) Both electron-rich and electron-poor arylboronic acids gave similar yields (entries 2−5). (3) When 2-thiopheneboronic acid and 2-benzothiopheneboronic acid were coupled with **1**, only moderate yields of 49 and 48%, respectively, were obtained (entries 8 and 9). This may be due to a deteriorating effect of the sulfur on the palladium catalyst during the process of the reaction, which could cause the reduction of the efficiency of the catalyst. To broaden synthetic application of compound **1**, its coupling reaction with an alkenylboronic acid (entry 11) was also evaluated. As expected, 61% yield of desired product **2k** was obtained with retention of the double bond stereochemistry as evidenced from the ^1H NMR spectrum.

However, when the 3-phenyl-4-tosyl-2(*5H*)-furanone **3** was utilized as a substrate to couple with the boronic acids, only a trace amount of the desired product was detected, presumably due to the steric effect of C-3 phenyl group (Scheme 2). The reaction was still inactive even though different phosphine ligands such as P^tBu_3 and PCy_3 were added in the reaction.

Product **2** can be easily transformed to 4-substituted 5-[1-(aryl)methylidene]-2(*5H*)-furanones, another key subunit in natural products. For example, the reaction of compound **2c** with 4-chlorobenzaldehyde afforded the corresponding product **5a** in almost quantitative yield at room temperature by using a literature method[8] (Scheme 3).

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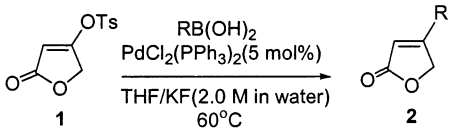
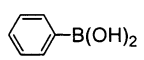
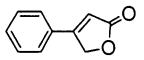
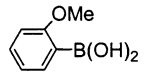
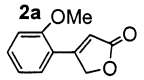
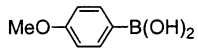
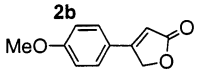
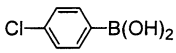
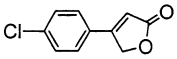
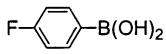
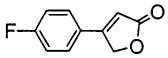
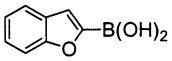
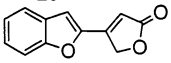
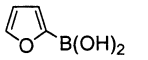
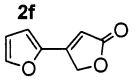
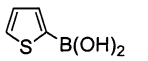
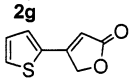
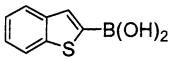
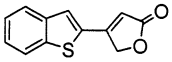
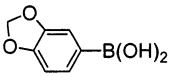
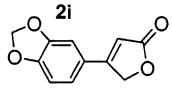
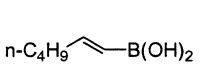
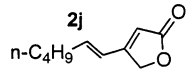
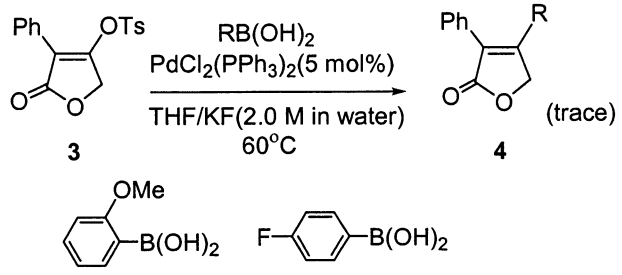
TABLE 1. Palladium-Catalyzed Cross-Coupling Reactions of 1 with Various Boronic Acids[a]



Entry	Boronic acid	Product	Yield (%)[b]
1		 **2a**	63
2		 **2b**	95
3		 **2c**	93
4		 **2d**	93
5		 **2e**	90
6		 **2f**	52
7		 **2g**	80
8		 **2h**	49
9		 **2i**	48
10		 **2j**	61
11		 **2k**	61

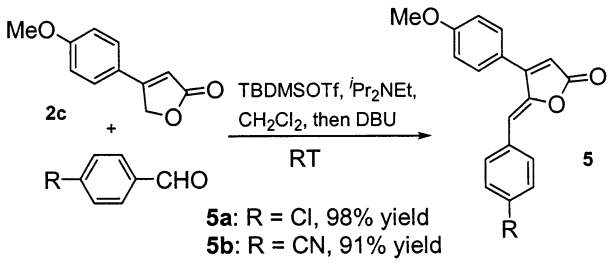
[a] Conditions: 4-tosyl-2(5*H*)-furanone (0.5 mmol), boronic acid (1.2 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), THF (2.0 mL), KF (2.0 M in water, 2.0 mL), 60 °C. [b] Isolated yield based on 4-tosyl-2(5*H*)-furanone.

SCHEME 2



In conclusion, we have reported herein the efficient and facile synthesis of 4-substituted 2(5*H*)-furanones using cross-coupling reactions between 4-tosyl-2(5*H*)-furanone (derived from commercially available tetronic acid) and boronic acids. The superiority of 4-tosyl-2(5*H*)-furanone versus its corresponding triflate in terms of its stability, the synthetic reagent cost, and easy preparation should make it an ideal synthon for organic synthesis, and further reports will be forthcoming.

SCHEME 3



Experimental Section

Procedure for Synthesis of 4-Tosyl-2(5*H*)-furanone (1). To a solution of tetronic acid (1.00 g, 10 mmol) and *p*-toluenesulfonyl chloride (2.00 g, 10.5 mmol) in dichloromethane (50 mL) was added triethylamine (1.67 mL, 12 mmol) under air at room temperature. The reaction mixture was stirred at room temperature for 2 h. Following completion of the reaction as monitored by TLC, the reaction mixture was concentrated to a residue that was purified by flash chromatography (silica gel, 4/1 (v/v) hexane/ethyl acetate) to give the corresponding product **1** (98% yield) as a white solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 2.45 (s, 3H), 4.89 (s, 2H), 5.98 (s, 1H), 7.56 (d, J = 8.5 Hz, 2H), 8.03 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125.7 MHz) δ (ppm) 22.0, 68.5, 99.9, 129.5, 130.4, 131.4, 148.2, 169.9, 171.7; MS [$C_{11}H_{10}O_5S$], m/z ($M^+ + 1$) calcd 255, found 255.

General Procedure for Synthesis of 4-Substituted 2(5*H*)-Furanones. To a solution of 4-tosyl-2(5*H*)-furanones (64 mg, 0.25 mmol), $PdCl_2(PPh_3)_2$ (8.8 mg, 5 mol %), and boronic acid (1.2 equiv) in THF (2 mL) was added potassium fluoride (2.0 M in water, 2 mL) under a nitrogen atmosphere. The reaction mixture was stirred at 60 °C overnight. Following completion of the reaction as monitored by TLC, the reaction mixture was diluted with ethyl acetate (20 mL) and separated. The solution was dried and filtered, and the filtrate was concentrated to a residue that was purified by flash chromatography (silica gel, 4/1 (v/v) hexane/ethyl acetate) to give the corresponding product.

4-Phenyl-2(5*H*)-furanone (**2a**),[9] 4-(2-methoxyphenyl)-2(5*H*)-furanone (**2b**),[10] 4-(4-methoxyphenyl)-2(5*H*)-furanone (**2c**),[9] 4-(4-chlorophenyl)-2(5*H*)-furanone (**2d**),[9] 4-(4-fluorophenyl)-2(5*H*)-furanone (**2e**),[11] and 4-thiophen-2-yl-5*H*-furan-2-one (**2h**)[9] are reported in the literature as known compounds.

4-Benzofuran-2-yl-5*H*-furan2-one (2f): 52% yield as a colorless oil; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 5.37 (s, 2H), 6.60 (s, 1H), 7.33 (t, J = 7.0 Hz, 1H), 7.47 (t, J = 7.0 Hz, 1H), 7.59 (s, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125.7 MHz) δ (ppm) 70.6, 111.3, 112.3, 113.0, 123.3, 124.7, 128.1, 128.2, 147.7, 154.3, 155.7, 173.8; MS [$C_{12}H_8O_3$], m/z ($M^+ + 1$) calcd 201, found 201.

2′*H*-[2,3′]Bifuranyl-5′-one (2g): 80% yield as a colorless oil; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 5.24 (s, 2H), 6.32 (s, 1H), 6.72−6.74 (m, 1H), 7.15 (d, J = 9.0 Hz, 1H), 8.00 (s, 1H); ^{13}C NMR (125.7 MHz) δ (ppm) 70.3, 109.7, 113.6, 115.6, 146.2, 147.6, 154.1, 174.1; MS [$C_8H_6O_3$], m/z ($M^+ + Na$) calcd 173, found 173.

4-Benzo[b]thiophen-2-yl-5*H*-furan-2-one (2i): 48% yield as a colorless oil; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 5.43 (s, 2H), 6.55 (s, 1H), 7.40−7.50 (m, 2H), 7.94 (t, J = 10.0, 8.0 Hz, 2H), 8.06 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125.7 MHz) δ (ppm) 71.7, 113.6, 123.6, 125.8, 126.1, 127.5, 127.6, 133.0, 139.8, 141.0, 159.0, 173.8.

4-Benzo[1,3]dioxol-5-yl-5*H*-furan-2-one (2j): 61% yield as a colorless oil; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 5.29 (s,

(9) Kagabu, S.; Shimizu, Y.; Ito, C.; Moriya, K. *Synthesis* **1992**, 830.
(10) Taniguchi, T.; Nagata, H.; Kanada, R. M.; Kadota, K.; Takeuchi, M.; Ogasawara, K. *Heterocycles* **2000**, *52*, 67.
(11) MacMillan, J. H.; Washburne, S. S. *J. Heterocycl. Chem.* **1975**, *12*, 1215.

2H), 6.11 (s, 2H), 6.59 (s, 1H), 7.04 (d, $J = 8.5$ Hz, 1H), 7.20 (d, $J = 8.0$ Hz, 1H), 7.38 (d, $J = 1.5$ Hz, 1H); ^{13}C NMR (125.7 MHz) δ (ppm) 71.7, 102.6, 107.7, 109.3, 111.4, 122.8, 124.5, 148.8, 150.8, 165.3, 174.6.

4-Hex-1-enyl-5*H*-furan-2-one (2k): 61% yield as a colorless oil; ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 0.87 (t, $J = 7.5$ Hz, 3H), 1.27−1.34 (m, 2H), 1.36−1.41 (m, 2H), 2.16−2.22 (m, 2H), 5.05 (s, 2H), 5.98 (s, 1H), 6.26−6.32 (m, 1H), 6.45 (d, $J = 16.0$ Hz, 1H); ^{13}C NMR (125.7 MHz) δ (ppm) 14.4, 22.3, 30.7, 32.9, 71.3, 113.5, 122.0, 142.8, 164.4, 174.5.

General Procedure for the Synthesis of (*Z*)-4-(4-Methoxyphenyl)-5-[1-(4-substituted-phenyl)methyli-dene]-2(5*H*)-furanone 5. A solution of compound **2c** (0.25 mmol) in dichloromethane (3.0 mL) was sequentially treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (1.2 equiv), diisopropylethylamine (3.0 equiv), and benzaldehyde (1.2 equiv), and the resulting mixture was stirred for 2 h at room temperature under argon. DBU (2.0 equiv) was then added, and the mixture was stirred at room temperature. Following completion of the reaction, the reaction mixture was filtered through a short pad of silica gel and the filtrate was concentrated to a residue that was purified by flash chromatography (silica gel, 6/1 (v/v) hexane/ethyl acetate) to give the corresponding product **5**.

5-(4-Chloro-benzylidene)-4-(4-methoxy-phenyl)-5*H*-furan-2-one (5a): ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 3.84 (s, 3H), 6.43 (s, 1H), 6.60 (s, 1H), 7.12 (d, $J = 7.0$ Hz, 2H), 7.52 (d, $J = 7.0$ Hz, 2H), 7.63 (dd, $J = 7.0$, 2.0 Hz, 2H), 7.84 (dd, $J = 7.0$, 2.0 Hz, 2H); ^{13}C NMR (125.7 MHz) δ (ppm) 56.2, 112.1, 114.1, 115.3, 122.6, 129.6, 131.2, 132.7, 132.8, 134.3, 148.5, 158.3, 161.9, 168.8; MS [$C_{18}H_{13}ClO_3$], m/z (M^++1) calcd 313, found 313.

5-(4-Cyano-benzylidene)-4-(4-methoxy-phenyl)-5*H*-furan-2-one (5b): ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 3.84 (s, 3H), 6.52 (s, 1H), 6.69 (s, 1H), 7.12 (d, $J = 9.0$ Hz, 2H), 7.64 (d, $J = 9.0$ Hz, 2H), 7.90 (d, $J = 8.5$ Hz, 2H), 8.00 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (125.7 MHz) δ (ppm) 56.2, 111.3, 111.4, 115.1, 115.4, 119.4, 122.4, 131.2, 131.6, 133.3, 138.4, 150.1, 158.2, 162.1, 168.6; MS [$C_{19}H_{13}NO_3$], m/z (M^++1) calcd 304, found 304.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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