# Facile Approach to 4-Substituted 2(5*H*)-Furanones

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The 2(5*H*)-furanone moieties are prevalent in a variety of natural products[1] and medicinally important compounds.[2] The compounds containing 2(5*H*)-furanone moiety have been considering as potential insectcides, fungicides, antimicrobial and antitumor agents,[3] *etc.* Therefore, in recent years, much attention has been paid to the preparation of various substituted 2(5*H*)-furanones. The recent patent[4] about the pharmacological effects of 4-alkyl-2(5*H*)-furanones in curing gastric ulcer and gastric hypersecretion actuated us to prepare their analogues.

In contrast with the 3-substituted or 5-substituted 2(5*H*)-furanones, the problem of the preparation of 4-substituted 2(5*H*)-furanones has not been solved satisfactorily yet.[5] In the existing limited methods to 4-substituted 2(5*H*)-furanones,[6] the transition metal-catalyzed coupling methodologies occupied the overwhelming majority.[7] Among them, the Stille coupling reaction was adopted frequently;[5,7a−e] however, its feasibility was limited due to the annoying preparation of organotin compounds and the difficult removal of the toxic organotin byproducts.[8] Due to the readily availability and environmentally friendly features of boronic acids, the Suzuki coupling reaction[9] came to attract ever-increasing attention recently. Because of the readily availability and the better electrophility of triflates, Suzuki and Miyaura investigated the palladium-catalyzed cross-coupling reaction of organoboranes and aryl, alkenylboronic acids with alkenyl, aryl triflates.[9c] The first Suzuki reaction of $\beta$-tetronic acid triflate with 9-alkyl-9-BBN (yield: 51%) was adopted by Grigg[10] during the total synthesis of (−)-isoseiridine, and later the reaction of alkenylboronic acid with $\beta$-tetronic acid triflate (yield: 48%) was described by Honda[11] in the preparation of syributin 1. Appearently, the yields of both reactions were unsatisfactory, and the further study of the coupling condition in detail was necessary.

Considering that the $\beta$-tetronic acid triflate could be prepared by the treatment of the readily available $\beta$-tetronic acid[12] with triflic anhydride in the presence of Hunig's base,[10] and in connection with our ongoing projects relating to the cross-coupling reactions of cyclopropylboronic acids,[13] we felt it significant to introduce the stereodefined cyclopropyl function into C-4 position of 2(5*H*)-furanones *via* the coupling reaction of $\beta$-tetronic acid triflate with cyclopropylboronic acids, and develop a convenient method to prepare 4-cyclopropyl-2(5*H*)-furanones, the special alkyl-substituted 2(5*H*)-furanones, which might have some potential bioactivity. In this paper, we wish to disclose our recent study in this research work.

The reaction of *trans*-pentylcyclopropylboronic acids with $\beta$-tetronic acid triflate was examined under an argon atmosphere to optimize the reaction conditions(Table 1). The reaction condition[14] established for cyclopropylboronic acids with activated alkenyl triflates did make the expected reaction take place, but the yield was poor (entry 1). Both the use of additive (entry 2), and the adoption of the reaction conditions used by Grigg[10] (entry 3) and Honda[11] (entry 4) could not improve the yield. The blank test of $\beta$-tetronic acid triflate alone in toluene solvent at 100 °C in the presence of $K_3PO_4$ indicated that $\beta$-tetronic acid triflate was sensitive to the strong base $K_3PO_4$. The reaction carried out in the weaker base KF (2 N aqueous solution) afforded only a trace of desired product and the massive $\beta$-tetronic acid, this fact suggested that the $\beta$-tetronic acid triflate was also sensitive to the water at 100 °C in the presence of the catalyst

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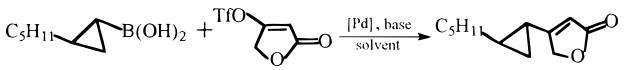
**Table 1. Effects of Solvent and Base on the Coupling of *trans*-Pentylcyclopropylboronic Acid with β-Tetronic Acid Triflate[a]**



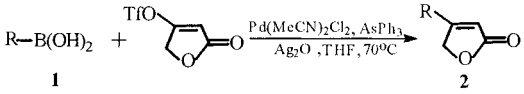

| entry | conditions | yield[b] (%) |
|---|---|---|
| 1 | toluene, $K_3PO_4 \cdot 3H_2O$, $Pd(PPh_3)_4$, 100 °C | 27 |
| 2 | toluene, $K_3PO_4 \cdot 3H_2O$, NaBr, $Pd(PPh_3)_4$, 100 °C | 25 |
| 3 | dioxane, $K_3PO_4$, $Pd(OAc)_2$, $PPh_3$ (2 equiv), 70 °C | 19 |
| 4 | THF, $K_3PO_4$, $Pd(PPh_3)_2Cl_2$, 70 °C | 22 |
| 5 | toluene, 2N KF, $Pd(PPh_3)_4$, 100 °C | trace[c] |
| 6 | toluene, KF, $Pd(PPh_3)_4$, 90 °C | 16 |
| 7 | toluene, $Ag_2O$, $Pd(PPh_3)_4$, 90 °C | 38 |
| 8 | toluene, $Ag_2O$, $PdCl_2$(dppf), 90 °C | 13 |
| 9 | toluene, $Ag_2O$, $Pd(MeCN)_2Cl_2$, $AsPh_3$ (4 equiv), 90 °C | 49 |
| 10 | toluene, $Ag_2O$, $Pd(MeCN)_2Cl_2$, $AsPh_3$ (4 equiv), 70 °C | 56 |
| 11 | THF, $Ag_2O$, $Pd(MeCN)_2Cl_2$, $AsPh_3$ (4 equiv), 70 °C | 77 |
| 12 | dioxane, $Ag_2O$, $Pd(MeCN)_2Cl_2$, $AsPh_3$ (4 equiv), 70 °C | 62 |

[a] Reactions were carried out using 0.05 mmol of catalyst. *trans*-2-Pentylcyclopropylboronic acid (1.1 mmol), triflate (1 mmol), and base (3 mmol) in 4 mL of solvent for 18 h. [b] Isolated yield based on triflate. [c] β-Tetronic acid was obtained.

and the base (entry 5 *vs* 6). To circumvent the sensitivity of β-tetronic acid triflate to both water and strong base, we turn to use the even weaker base $Ag_2O$, which was reported to have the characteristic of accelerating the coupling reaction rate.[15] As expected, this modification enhanced the yield to 38% (entry 7). To evaluate the effect of the catalysts on the reaction, some catalysts were examined. The results showed that the catalytic activity of $Pd(MeCN)_2Cl_2/AsPh_3$ was more effective than that of $Pd(PPh_3)_4$ and $PdCl_2$(dppf) (entry 9 *vs* 7, 8). The decrease of the reaction temperature made the yield increase to 56% (entry 10 *vs* 9). The investigation of solvent effect on the reaction indicated that etheral solvent THF and dioxane were preferred to the nonpolar solvent toluene-(entries 11, 12 *vs* 10).

After establishing the optimum reaction conditions (Table 1, entry 11), we evaluated the scope of the coupling reaction by investigating the reaction with various cyclopropylboronic acids (Table 2). As shown in Table 2, the optimized coupling reaction condition is applicable to both the racemic cyclopropylboronic acids (entry 1−5) and the optical active cyclopropylboronic acids[16] (entries 6, 7). The $^1H$ NMR spectrums of the products showed that products were pure *trans*-isomer, indicating that the configuration of cyclopropyl group was retained during the reaction. Together with the fact that the coupling products **2f** and **3** of the same (1*R*,2*R*)-2-phenylcyclopropylboronic acid **1f** had the same ee value and optical sense (Scheme 1), suggested that the absolute configuration of cyclopropyl group was retained during the reaction. As in our previous work it has been confirmed

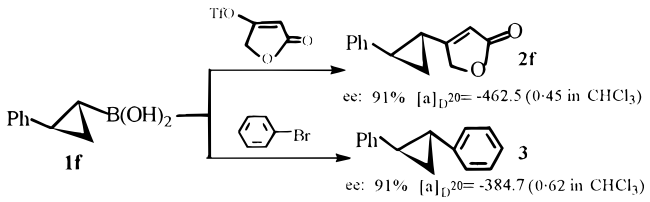
**Table 2. Coupling Reaction of Boronic Acids with β-Tetronic Acid Triflate[a]**




| Entry | Boronic acid **1** | R | Product **2** | Yield(%)[b] |
|---|---|---|---|---|
| 1 | **1a** | $C_5H_{11}$ | **2a** | 77 |
| 2 | **1b** | $C_4H_9$ | **2b** | 75 |
| 3 | **1c** | $C_6H_{13}$ | **2c** | 82 |
| 4 | **1d** | $C_7H_{15}$ | **2d** | 74 |
| 5 | **1e** | $C_6H_5$ | **2e** | 67 |
| 6[c] | **1f** | $C_6H_5$ | **2f** | 66 |
| 7[d] | **1g** | $C_6H_5$ | **2g** | 63 |
| 8 | **1h** | $C_5H_{11}$ | **2h** | 85 |
| 9 | **1i** | $C_6H_{13}$ | **2i** | 84 |

[a] Reactions were carried out at 70 °C using 0.05 mmol of $Pd(MeCN)_2Cl_2$, 0.20 mmol of $AsPh_3$, boronic (1.1 mmol), β-tetronic acid triflate (1.0 mmol), 3 equiv of $Ag_2O$ in 4 mL THF. [b] Isolated yields based on β-tetronic acid triflate. [c] ee: 91%, determined by HPLC(chiralcel OJ), $[\alpha]^{20}_D = -462.5$ (*c* 0.45 in $CHCl_3$). [d] ee: 93%, determined by HPLC(chiralcel OJ), $[\alpha]^{20}_D = +467.1$ (*c* 0.54 in $CHCl_3$).

**Scheme 1**




that the chiral cyclopropyl group was not racemized during the coupling reaction with aryl bromides.[16]

This coupling reaction condition was also suitable to the alkenylboronic acids (entries 8, 9), and judging from the $^1H$ NMR spectrums of the products, the configuration of alkenyl group was retained during the reaction. The yields of these cross-coupling products were moderate to good. Therefore, we have supplied here a better coupling condition than that of Grigg and Honda.

In summary, we have studied the palladium-catalyzed cross-coupling condition for β-tetronic acid triflate with sterodefined cyclopropyl (including the enantiomeric cyclopropyl), alkenylboronic acids in detail. The success of this reaction provides an efficient and convenient approach to 4-substituted 2(5*H*)-furanones. For the active alkenyl and cyclopropyl functions could be further elaborated,[17] our reaction procedure might opened a door to prepare many other types of 4-substituted 2(5*H*)-fura-

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(16) (1*R*,2*R*)-2-Phenylcyclopropylboronic acid (**1f**) and (1*S*,2*S*)-2-phenylcyclopropyl-boronic acid (**1g**) were prepared via the asymmetricly cyclopropanation of trans-tosylboronic acid ester of (+)-TMTA and (−)-TMTA, respectively, according to our previous procedure (see: Zhou, S.-M.; Deng, M.-Z.; Xia, L.-J.; Tang, M.-H. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2845−2847.)

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nones. The biological activities of these compounds are being studied.

## Experimental Section

All reactions were performed under an argon atmosphere. The $\beta$-tetronic acid triflate was prepared according to the literature procedure.[10] $^1$HNMR spectra were recorded using $CDCl_3$ as the solvent with TMS as an internal standard. The ee values were determined by chiral HPLC on Chiralcel OJ column.

General procedure for the coupling reaction: $\beta$-tetronic acid triflate (232 mg, 1.0 mmol), boronic acid (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 argon atmosphere, then 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 = 1:2−7) gave the corresponding products **2a**−**i**.

**Product 2a.** Liquid. IR $\nu_{max}$/cm$^{-1}$: 2934; 1775; 1736; 828. $^1$H NMR $\delta_H$(ppm): 5.61 (s, 1H); 4.66 (s, 2H); 1.28−1.44 (m, 9H, 4 × $CH_2$ + H); 1.09−1.18 (m, 1H); 0.86−1.03 (m, 5H, $CH_3$ + H + H). MS (EI) *m*/*z*: 181 (100); 111 (31.92); 41 (30.34). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.15; H, 9.51.

**Product 2b.** Liquid; IR $\nu_{max}$/cm$^{-1}$: 2932; 1778; 1739; 828. $^1$H NMR $\delta_H$(ppm): 5.62 (s, 1H); 4.66 (s, 2H); 1.28−1.44 (m, 7H); 1.09−1.18 (m, 1H); 0.85−1.04 (m, 5H). MS (EI) *m*/*z*: 181 (100); 182 (16.95); 41 (8.02). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.04; H, 8.87.

**Product 2c.** Liquid. IR $\nu_{max}$/cm$^{-1}$: 2934; 1778; 1742; 1628; 829. $^1$H NMR $\delta_H$(ppm): 5.62 (s, 1H); 4.66 (s, 2H); 1.26−1.45 (m, 11H); 1.10−1.19 (m, 1H); 0.86−1.04 (m, 5H). MS (EI) *m*/*z*: 111 (100); 43 (43.69); 209 (38.88); 79 (33.97). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.16; H, 10.07.

**Product 2d.** Liquid. IR $\nu_{max}$/cm$^{-1}$: 2935; 1780; 1743; 1631; 834. $^1$H NMR $\delta_H$(ppm): 5.63 (s, 1H); 4.67 (s, 2H); 1.27−1.47 (m, 13H); 1.10−1.20 (m, 1H); 0.86−1.04 (m, 5H). MS (EI) *m*/*z*: 94 (100); 43 (58.17); 223 (45.48). Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.71; H, 9.99.

**Product 2e.** Liquid. IR $\nu_{max}$/cm$^{-1}$: 3030; 1780; 1744; 1627; 1604; 699. $^1$H NMR $\delta_H$(ppm): 7.25−7.34 (m, 3H); 7.09−7.12 (m, 2H); 5.75 (s, 1H); 4.78 (s, 2H); 2.28−2.34 (ddd, 1H); 1.90−1.97 (ddd, 1H); 1.60−1.68 (ddd, 1H); 1.42−1.48 (ddd, 1H). MS (EI) *m*/*z*: 155 (100); 91 (62.70); 154 (54.40). Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.75; H, 5.92.

**Product 2f.** ee: 91%, determined by HPLC (chiralcel OJ). $[\alpha]^{20}_D = -462.5$ (*c* 0.45 in $CHCl_3$).

**Product 2g.** ee: 93%, determined by HPLC (chiralcel OJ). $[\alpha]^{20}_D = +467.1$ (*c* 0.54 in $CHCl_3$).

**Product 2h.** Liquid. IR $\nu_{max}$/cm$^{-1}$: 2934; 1782; 1753; 1649; 888. $^1$H NMR $\delta_H$(ppm): 6.39 (d, 1H, $J$ = 16.1 Hz); 6.14 (dt, 1H, $J$ = 6.9;16.1 Hz); 5.83 (s, 1H); 4.95 (s, 2H); 2.17−2.24 (dt, 2H, $J$ = 6.9); 1.34−1.46 (m, 2H); 1.24−1.32 (m, 4H); 0.88−0.93 (t, 3H, $J$ = 7.0 Hz). MS (EI) *m*/*z*: 111 (100); 67 (35.75); 43 (33.73). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.20; H, 9.21.

**Product 2i.** Liquid. IR $\nu_{max}$/cm$^{-1}$: 2934; 1782; 1753; 1649; 888. $^1$H NMR $\delta_H$(ppm): 6.39 (d, 1H, $J$ = 16.1 Hz); 6.14 (dt, 1H, $J$ = 6.9;16.1 Hz); 5.83 (s, 1H); 4.95 (s, 2H); 2.19−2.26(dt, 2H, $J$ = 6.9); 1.32−1.46 (m, 2H); 1.24−1.31 (m, 6H, 3 × $CH_2$); 0.87−0.92 (t, 3H, $J$ = 6.8 Hz). MS (EI) *m*/*z*: 111 (100); 79 (51.22); 43 (38.26); 77 (36.70); 112 (30.99). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.20; H, 9.58.

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