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A concise approach to 5-substituted-4-pyrones from kojic acid

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Abstract—A concise approach to 5-substituted-4-pyrones is described. This approach is based on manipulation of the 5-hydroxy group of readily available kojic acid. A number of 5-substituted-4-pyrones were synthesized from kojic acid utilizing Heck reaction, Suzuki coupling and Stille coupling.

The 4-pyrone unit is seen in a wide variety of biologically interesting natural products.[1] A number of approaches to 4-pyrones have been reported so far, and most of them involve acid-mediated cyclization of an appropriate triketone precursor.[2] In connection with our study toward the synthesis of actofunicone,[3] which reinforces the anti-*Candida albicans* activity of miconazole, we became interested in the use of readily available kojic acid (**1**) as a starting material. To the best of our knowledge, kojic acid has not been effectively utilized as a synthon in the synthesis of 5-substituted-4-pyrones. If it becomes possible to replace the 5-hydroxyl group of kojic acid with other groups, the methodology would provide a new entry to a variety of 5-substituted-4-pyrones (Fig. 1). This paper describes the transformation of kojic acid into triflate derivative **2** and stannane derivative **3** and their synthetic potential in C–C bond formation at C-5 of kojic acid.

First, we attempted the preparation of triflate derivative **2** and stannane derivative **3** considering that these derivatives could serve as versatile intermediates for introducing various substituents at C-5. Bis-TBS ether **4** was obtained in high yield by the reaction with TBSCl, imidazole and DMAP in DMF, and was treated with aqueous HF in acetonitrile to obtain the mono-TBS ether **5**[4] in 94% yield in 2 steps.[5] Triflate **2**[6] was obtained in 97% yield by the reaction with triflic anhydride in pyridine. Triflate **2** was further converted to the stannane derivative **3**[7] by the reaction with hexamethylditin in the presence of 1 mol% $Pd(OAc)_2$, 1 mol% PPh_3 and LiCl in 91% yield[8] (Scheme 1). With triflate **2** and stannane **3** in hand, we then attempted the Heck reaction,[9,10] the Suzuki coupling[11,12] and the Stille coupling[13] in order to demonstrate their synthetic potential by synthesizing several type of 5-substituted-4-pyrones.

Following the standard reaction protocol, Heck reaction of triflate **2** with ethyl acrylate proceeded smoothly in the presence of 1 mol% $Pd(OAc)_2$ and 1 mol% PPh_3 in DMF affording 5-alkenyl-4-pyrone **6** in 73% yield. The newly-introduced alkenyl group could be further manipulated by either an oxidative or a reductive reaction sequence to lead to various functionalized 5-substituted-4-pyrones.

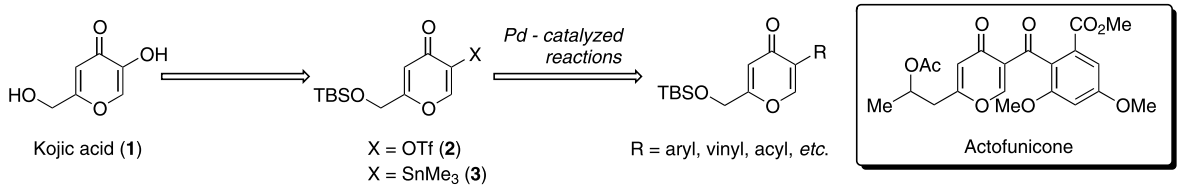

Figure 1. The strategy and actofunicone.

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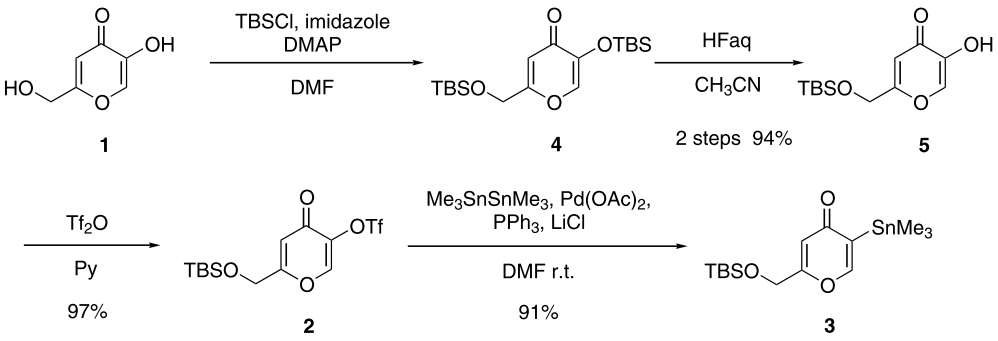
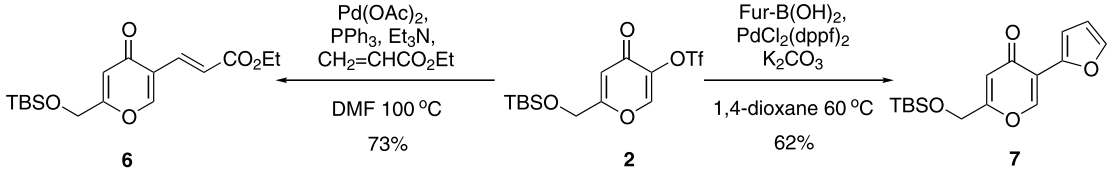
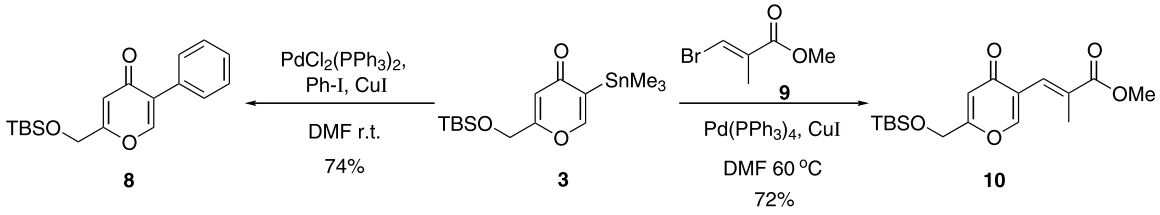


Scheme 1. Preparation of triflate **2** and stannane **3**.



Scheme 2. Heck reaction and Suzuki reaction of trifrate **2**.

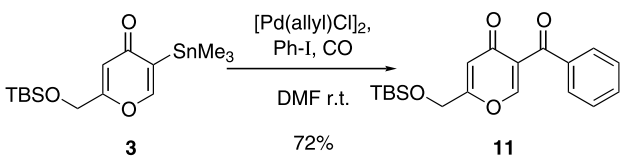


Scheme 3. Stille coupling of stannane **3**.

As an example of the Suzuki coupling, we examined the reaction of the triflate **2** with 2-furanboronic acid. The reaction also proceeded smoothly in dioxane at 60°C affording the corresponding 2-furyl-4-pyrone **7** in good yield (Scheme 2).

The Stille coupling of stannane **3** is shown in Scheme 3. Thus, the Stille coupling of stannane **3** with iodobenzene afforded **8** in 74% yield in the presence of $PdCl_2(PPh_3)_2$ and CuI. Addition of CuI was found to be critical to minimize the undesirable formation of a dimer. The Stille reaction with β-bromo-methacrylate **9** also proceeded smoothly affording the corresponding trisubstituted olefin **10** (Scheme 3).

Further, carbonylation[14] of **3** was also possible as demonstrated in Scheme 4. When stannane **3** was treated with iodobenzene and $[Pd(allyl)Cl]_2$ under the atmosphere of CO, 5-benzoyl-4-pyrone **11**[15] was isolated in 72% yield (Scheme 4).



Scheme 4. Acylation of stannane **3**.

In summary, we have prepared triflate **2** and stannane **3** as key intermediates for 5-substituted-4-pyrones. They were coupled with acrylate, aryl boronic acid, aryl halide and vinyl halide to produce a variety of 5-substituted-4-pyrones. Furthermore, 5-acyl-4-pyrone was obtained by the Pd-catalyzed reaction of stannane **3** with aryl halide in atmosphere of CO. These results strongly demonstrate the synthetic potential of triflate and stannane derivatives (**2** and **3**) of kojic acid for introducing various substituents at C-5 of 4-pyrones. Application to the synthesis of naturally-occurring biologically active compounds such as actofunicone is now in progress.

General experimental procedure

*Suzuki coupling of **2** with furanboronic acid*: To a solution of triflate **2** (50 mg, 0.13 mmol) in dioxane (2 ml), 2-furanboronic acid (28 mg, 0.26 mmol), K_2CO_3 (71.3 mg, 0.52 mmol), KBr (76.8 mg, 0.65 mmol) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (10.5 mg, 0.013 mmol) was added and the mixture was heated at 60°C overnight. After cooling to room temperature, the reaction mixture was treated with saturated aqueous NH_4Cl and extracted

with EtOAc (2 times). The combined organic phase was washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by preparative TLC (hexane–EtOAc, 4:1) to afford furylpyrone **7** (24.6 mg, 62%).

*Acylation of stannane **3***: To a solution of stannane **3** (28 mg, 0.069 mmol) in DMF (1 ml), iodobenzene (70.8 mg, 0.35 mmol) and $[Pd(allyl)Cl]_2$ (2.5 mg, 0.007 mmol) was added. The solution was stirred under carbon oxide (1 atm) overnight. The reaction mixture was treated with water and extracted with EtOAc (2 times). The combined organic phase was washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by preparative TLC (hexane–EtOAc, 4:1) to afford acylpyrone **11** (17.2 mg, 72%).

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5. Direct and selective mono-silylation[4] of kojic acid was unsuccessful, due to the formation of undesirable mono-silyl ether at C-5 in 67% yield.
6. Mp 35–36°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.14 (6H, s), 0.94 (9H, s), 4.52 (2H, s), 6.65 (1H, s), 8.07 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) −5.6, 18.2, 25.6, 60.8, 113.4, 118.6, 141.0, 148.8, 168.9, 170.8. IR (KBr): 3085, 2955, 2942, 2865, 1674, 1641, 1335, 1217, 1133 cm^{-1}. HR-EIMS: calcd for $C_{13}H_{19}O_6F_3SiS$ ($[M]^+$) 388.0624, found 388.0615.
7. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 0.11 (6H, s), 0.30 (9H, s), 0.93 (9H, s), 4.43 (2H, s), 6.33 (1H, s), 7.40 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) −9.4, −5.5, 18.3, 25.7, 61.4, 111.2, 127.6, 156.0, 167.6, 182.6. IR (KBr): 3050, 2952, 2856, 1650, 1600, 1260, 1131 cm^{-1}. HR-EIMS: calcd for $C_{15}H_{27}O_3SiSn$ ($[M-H]^+$) 403.0751, found 403.0771.
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15. Mp 56–58°C. ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 0.16 (6H, s), 0.96 (9H, s), 4.53 (2H, s), 6.57 (1H, s), 7.46 (2H, dd, J=7.5 Hz), 7.59 (1H, t, J=7.5 Hz), 7.85 (2H, d, J=7.5 Hz), 8.03 (1H, s). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) −5.5, 18.3, 25.7, 61.0, 114.1, 128.4, 129.5, 129.6, 133.7, 136.6, 156.6, 168.0, 175.9, 191.4. IR (KBr): 3066, 2952, 2932, 2856, 1660, 1618 cm^{-1}. HR-EIMS: calcd for $C_{19}H_{24}O_4Si$ ($[M]^+$) 344.1444, found 344.1453.