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Rapid access to 4-substituted-pyrones and 2(5*H*)-furanones via a palladium-catalyzed C–OH bond activation

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ABSTRACT

An efficient palladium-catalyzed cross-coupling reaction of 4-hydroxy-pyrone or 4-hydroxy-2(5*H*)-furanone with arylboronic acid is described, which affords the 4-substituted-pyrones and 2(5*H*)-furanones in good yields. This transformation proceeds through a C–OH bond activation under mild conditions.

1. Introduction

In drug development and drug discovery process, methodology development and combinatorial synthesis of natural product-like compounds with privileged scaffolds have attracted much attention.[1] Our continuous interest in the preparation of natural product-like compounds[2] prompts us to focus on the skeletons of 2-pyrone and 2(5*H*)-furanone (Fig. 1), which are important structural units in naturally occurring products, therapeutics, and synthetic analogs with interesting biological activities.[3–5] For instance, 3-alkyl-6-chloro-2-pyrones have been discovered as selective inhibitors of pancreatic cholesterol esterase. Rofecoxib as a COX-2 selective inhibitor has successfully reached the market, which is an anti-inflammatory drug launched by Merck.[3j] Additionally, they have been used as valuable synthetic intermediates in organic synthesis.[5]

In the past decades, reactions catalyzed by palladium have found widespread application in organic synthesis.[6] In this regard, palladium-catalyzed cross-coupling reactions continue to be a hot and attractive area because of its high efficiency in C–C bond formation.[7] In addition to the conventional cross-coupling methodology using organic halides and organometallic reagents, the metal-mediated C–H functionalization[8] and C–OH bond activation[9] have recently received great interest in organic synthesis. Kang reported a palladium-catalyzed C–OH bond activation of tautomerizable heterocycles with arylboronic acids in 2008.[9a] In this conversion, a phosphonium salt was employed as an activation reagent for a in situ activation of tautomerizable heterocycle. In the meantime, *p*-toluenesulfonyl chloride was successfully employed as an activator for functionalization of C–OH bond.[9b–d] Recently, Shi and co-workers developed cross-coupling reactions via C–OH bond activation by using metal salts as activation reagents.[10] Prompted by the achievement of palladium-catalyzed cross-coupling reactions via a C–OH bond activation, we envisioned that a small library of 4-substituted 2-pyrones and 2(5*H*)-furanones could be constructed starting from 4-hydroxy-2-pyrone and 4-hydroxy-2(5*H*)-furanone, due to their easy availability. We expected that some promising lead compounds would be generated from their evaluations against various biological screens. Herein, we wish to disclose our recent efforts for the preparation of

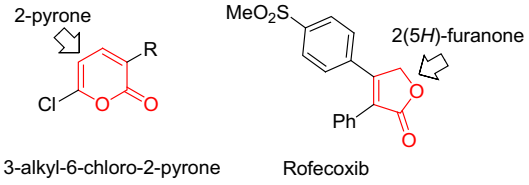

Fig. 1. Scaffolds of pyrone and 2(5*H*)-furanone.

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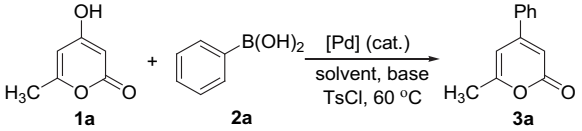
4-substituted 2-pyrones and 2(5*H*)-furanones via a palladium-catalyzed direct arylation of 4-hydroxy-2-pyrone and 4-hydroxy-2(5*H*)-furanone with arylboronic acids.

2. Results and discussion

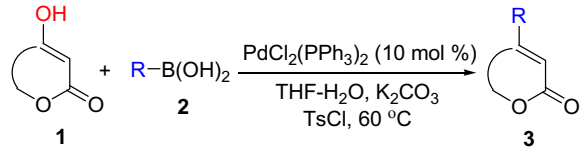
During our initial studies, 4-hydroxy-2-pyrone **1a** and phenylboronic acid **2a** were selected as the substrates for reaction development (Scheme 1). At the outset, the reaction was catalyzed by 5 mol % of $PdCl_2$ in the presence of K_2CO_3 (3.0 equiv) and *p*-toluenesulfonyl chloride (1.1 equiv) in a mixed solvent of THF and water at 60 °C. We conceived that a vinyl tosylate would be generated as the key intermediate for further coupling reactions. In the last decades, vinyl/aryl tosylate has been demonstrated as a good electrophile in transition metal-catalyzed cross-coupling reactions.[11] Gratifyingly, the expected 6-methyl-4-phenyl-2*H*-pyran-2-one **3a** was isolated in 35% yield. Further screens of various bases (NaOH, Na_2CO_3, Cs_2CO_3, Et_3N, K_3PO_4) could not improve the final outcome. The yield was increased to 57% when 10 mol % of $PdCl_2$ was used in the reaction. The reactivity was diminished when the reaction was performed at room temperature. The palladium source was subsequently surveyed [$PdCl_2(MeCN)_2$, $Pd(PPh_3)_4$, $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, $Pd_2(dba)_3$]. We discovered that the reaction worked efficiently when 10 mol % of $PdCl_2(PPh_3)_2$ was utilized as the catalyst, which afforded the desired product **3a** in 83% yield. No better results were obtained when other solvents (toluene, MeCN, DMF) were employed in the reaction.

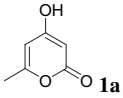
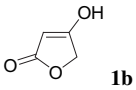
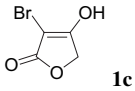


Scheme 1. Initial studies for a palladium-catalyzed cross-coupling reaction of 4-hydroxy-2-pyrone **1a** and phenylboronic acid **2a**.

Under the optimized conditions [$PdCl_2(PPh_3)_2$ (10 mol %), K_2CO_3 (3.0 equiv), *p*-toluenesulfonyl chloride (1.1 equiv), THF/H_2O, 60 °C], the palladium-catalyzed cross-coupling reactions of 4-hydroxy-2-pyrone or 4-hydroxy-2(5*H*)-furanone with various arylboronic acids were then carried out to define the protocol generality. The results are shown in Table 1. 4-Hydroxy-2-pyrone **1a** reacted with arylboronic acids **2** leading to the desired products **3a**–**j** in good to excellent yields. It is noteworthy that different functional groups attached to the aromatic ring of arylboronic acids could be readily accommodated. For example, reaction of 4-hydroxy-2-pyrone **1a** with 4-(dimethylamino)phenylboronic acid **2g** afforded the corresponding product **3g** in 64% yield (Table 1, entry 7). When ester-substituted arylboronic acid **2j** was employed in the reaction of 4-hydroxy-2-pyrone **1a**, the desired product **3j** was isolated in 81% yield (Table 1, entry 10). Additionally, the reactions worked smoothly as well when sterically hindered arylboronic acid, such as 2-methylphenylboronic acid **2b** or 2-methoxyphenylboronic acid **2e** was utilized as a reactant in the reaction (Table 1, entries 2 and 5). Reactions of 4-hydroxy-2(5*H*)-furanone **1b** with various arylboronic acids were examined subsequently. As expected, all reactions proceeded smoothly to furnish the desired products in good yield (Table 1, entries 11–17). However, only a trace amount of product was detected when 3-bromo-4-hydroxyfuran-2(5*H*)-one **1c** was employed in the coupling reaction under the standard conditions (Table 1, entries 18–20). The reaction stopped at the formation of 3-bromo-4-tosyoxyfuran-2(5*H*)-one. We thus explored the palladium-catalyzed coupling reaction of phenylboronic acid with 3-bromo-4-tosyoxyfuran-2(5*H*)-one under different conditions. However, no desired product was detected. This result was similar to the previous report.[12] We reasoned that the inert

Table 1
Palladium-catalyzed cross-coupling reactions of 4-hydroxy-2-pyrone or 4-hydroxy-2(5*H*)-furanone with various arylboronic acids

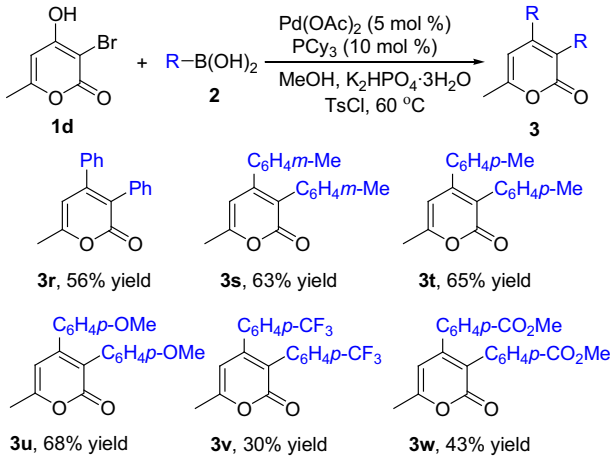


Entry	Substrate **1**	R	Product	Yield[a] (%)
1	 **1a**	C_6H_5 (**2a**)	**3a**	83
2	**1a**	2-MeC_6H_4 (**2b**)	**3b**	71
3	**1a**	3-MeC_6H_4 (**2c**)	**3c**	85
4	**1a**	4-MeC_6H_4 (**2d**)	**3d**	91
5	**1a**	2-$MeOC_6H_4$ (**2e**)	**3e**	80
6	**1a**	4-$MeOC_6H_4$ (**2f**)	**3f**	90
7	**1a**	4-$Me_2NC_6H_4$ (**2g**)	**3g**	64
8	**1a**	4-ClC_6H_4 (**2h**)	**3h**	80
9	**1a**	4-$CF_3C_6H_4$ (**2i**)	**3i**	62
10	**1a**	4-$MeO_2CC_6H_4$ (**2j**)	**3j**	81
11	 **1b**	C_6H_5 (**2a**)	**3k**	65
12	**1b**	2-MeC_6H_4 (**2b**)	**3l**	71
13	**1b**	3-MeC_6H_4 (**2c**)	**3m**	75
14	**1b**	4-MeC_6H_4 (**2d**)	**3n**	77
15	**1b**	2-$MeOC_6H_4$ (**2e**)	**3o**	81
16	**1b**	4-$MeOC_6H_4$ (**2f**)	**3p**	85
17	**1b**	4-$Me_2NC_6H_4$ (**2g**)	**3q**	40
18	 **1c**	C_6H_5 (**2a**)	—	Trace
19	**1c**	4-$MeOC_6H_4$ (**2f**)	—	Trace
20	**1c**	4-$CF_3C_6H_4$ (**2i**)	—	Trace

[a] Isolated yield based on 4-hydroxy-2-pyrone or 4-hydroxy-2(5*H*)-furanone.

reactivity of 3-bromo-4-tosyoxyfuran-2(5*H*)-one might be due to its steric hinder in the coupling reactions.

In the meantime, palladium-catalyzed coupling reactions of 3-bromo-4-hydroxy-2-pyrone **1d** were examined. Under the conditions shown in Table 1, only the intermediate 3-bromo-4-tosyloxy-2-pyrone was obtained as well, and no further conversion was observed. Therefore, the coupling reactions of 3-bromo-4-hydroxy-2-pyrone **1d** with arylboronic acids were re-investigated. After screening the effects of palladium catalysts, ligands, bases, and solvents, we finally realized that the reaction worked efficiently catalyzed by palladium acetate and tricyclohexylphosphine in the presence of $K_2HPO_4 \cdot H_2O$ as the base in methanol (Scheme 2). Since vinyl bromide is more reactive than the corresponding vinyl tosylate intermediate, thus 3,4-disubstituted 2-pyrone **3** was afforded as the product. In these cases, 2.5 equiv of arylboronic acid was utilized in the transformation. For instance, 3-bromo-4-hydroxy-2-pyrone **1d** reacted with phenylboronic acid **2a**, giving rise to 6-methyl-3,4-diphenyl-2*H*-pyran-2-one **3r** in 56% yield. A lower yield was obtained when arylboronic acids with electron-withdrawing groups attached on the aromatic ring. For example, reaction of 3-bromo-4-hydroxy-2-pyrone **1d** with 4-methoxyphenylboronic acid **2f** afforded the 3,4-disubstituted 2-pyrone **3u** in 68% yield; while compound **3v** was obtained in 30% yield when 4-trifluoromethylphenylboronic acid **2i** was used as a replacement in the reaction. Again, the ester group could be tolerated under the conditions, and the corresponding product **3w** was isolated in 43% yield. However, the reaction was unsuccessful when 3-bromo-



Scheme 2. Palladium-catalyzed cross-coupling reactions of 3-bromo-4-hydroxy-2-pyrone with various arylboronic acids.

4-hydroxyfuran-2(5*H*)-one **1c** was employed as a substrate under the conditions.

3. Conclusions

In conclusion, we have developed an efficient and facile route for the preparation of 4-substituted 2-pyrones and 2(5*H*)-furanones under mild conditions, utilizing a palladium-catalyzed cross-coupling reaction via a C–OH bond activation. The starting materials are easily available and the method readily accommodates a wide variety of functionality. Application of this strategy in library construction is ongoing currently.

4. Experimental section

4.1. General experimental procedure for palladium-catalyzed cross-coupling reactions of 4-hydroxy-2-pyrone or 4-hydroxy-2(5*H*)-furanone with arylboronic acids

A solution of 4-hydroxy-2-pyrone or 4-hydroxy-2(5*H*)-furanone **1** (0.3 mmol), *p*-toluenesulfonyl chloride (0.33 mmol, 1.1 equiv), arylboronic acid **2** (0.36 mmol, 1.2 equiv), K_2CO_3 (0.9 mmol, 3.0 equiv), and $PdCl_2(PPh_3)_2$ (10 mol %) in THF/H_2O (v/v 20:1, 4.2 mL) was stirred at 60 °C for a period of time. After completion of reaction as indicated by TLC, the reaction was quenched by the addition of saturated aqueous NH_4Cl (5.0 mL), and the mixture was extracted with EtOAc (4.0 mL×3). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel to provide the desired product **3**.

*4.1.1. 6-Methyl-4-phenyl-2H-pyran-2-one (**3a**)*[13]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 6.24 (s, 1H), 6.27 (s, 1H), 7.40 (t, *J*=4.0 Hz, 3H), 7.49 (d, *J*=4.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 103.4, 108.1, 126.6, 129.1, 130.6, 135.8, 155.5, 162.1, 163.4. HRMS (ESI) calcd for $C_{35}H_{40}N_4O_2S$: 581.2950 (M+H^+), found: 599.2940.

*4.1.2. 6-Methyl-4-o-tolyl-2H-pyran-2-one (**3b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.33 (s, 3H), 6.04 (s, 1H), 6.10 (s, 1H), 7.18 (d, *J*=8.0 Hz, 1H), 7.26 (t, *J*=8.0 Hz, 2H), 7.31 (d, *J*=4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 22.7, 106.1, 111.3, 126.2, 127.9, 129.2, 130.9, 134.7, 137.1, 157.8, 161.4, 163.1. HRMS (ESI) calcd for $C_{13}H_{13}O_2$ (M+H^+) 201.0916; found, 201.0912.

*4.1.3. 6-Methyl-4-m-tolyl-2H-pyran-2-one (**3c**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.42 (s, 3H), 6.31 (s, 1H), 6.34 (s, 1H), 7.27 (t, *J*=4.0 Hz 1H), 7.36–7.37 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 21.4, 103.6, 108.0, 123.8, 127.3, 129.0, 131.3, 135.8, 138.9, 155.7, 162.0, 163.5. HRMS (ESI) calcd for $C_{13}H_{13}O_2$ (M+H^+) 201.0916; found, 201.0902.

*4.1.4. 6-Methyl-4-p-tolyl-2H-pyran-2-one (**3d**)*[13]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 2.32 (s, 3H), 6.23 (s, 1H), 6.25 (s, 1H), 7.19 (d, *J*=8.0 Hz, 2H), 7.39 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 20.3, 102.3, 106.2, 125.5, 128.8, 131.7, 140.1, 154.3, 160.9, 162.5.

*4.1.5. 4-(2-Methoxyphenyl)-2-methyl-2H-pyran-2-one (**3e**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H), 3.79 (s, 3H), 6.20 (s, 1H), 6.24 (s, 1H), 6.89–6.96 (m, 2H), 7.22 (d, *J*=8.0 Hz, 1H), 7.33 (t, *J*=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 55.6, 106.0, 111.1, 111.4, 121.0, 125.6, 129.6, 131.4, 154.5, 156.7, 160.4, 163.7. HRMS (ESI) calcd for $C_{13}H_{13}O_3$ (M+H^+) 217.0865; found, 217.0861.

*4.1.6. 4-(4-Methoxyphenyl)-6-methyl-2H-pyran-2-one (**3f**)*[14]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.86 (s, 3H), 6.29 (s, 2H), 6.97 (d, *J*=8.0 Hz, 2H), 7.54 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 55.4, 103.1, 106.4, 114.5, 127.8, 128.1, 154.7, 161.7, 161.8, 163.7.

*4.1.7. 4-(4-(Dimethylamino)phenyl)-6-methyl-2H-pyran-2-one (**3g**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 3H), 2.90 (s, 6H), 6.20 (s, 1H), 6.24 (s, 1H), 6.64 (d, *J*=8.0 Hz, 2H), 7.43 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 40.1, 102.7, 103.9, 111.9, 121.9, 127.9, 152.0, 154.7, 161.2, 164.2. HRMS (ESI) calcd for $C_{14}H_{16}NO_2$ (M+H^+) 230.1181; found, 230.1175.

*4.1.8. 4-(4-Chlorophenyl)-6-methyl-2H-pyran-2-one (**3h**)*[13]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 6.28 (s, 1H), 6.32 (s, 1H), 7.45 (d, *J*=8.0 Hz, 2H), 7.51 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 103.1, 108.1, 128.2, 130.0, 134.1, 136.8, 154.2, 162.5, 163.2.

*4.1.9. 6-Methyl-4-(4-(trifluoromethyl)phenyl)-2H-pyran-2-one (**3i**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 6.30 (s, 1H), 6.38 (s, 1H), 7.67–7.76 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 103.1, 109.3, 126.1, 127.1, 139.4, 154.1, 162.8, 162.8. HRMS (ESI) calcd for $C_{13}H_{10}F_3O_2$ (M+H^+) 255.0633; found, 255.0602.

*4.1.10. Methyl-4-(6-methyl-2-oxo-2H-pyran-4-yl)benzoate (**3j**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 3.96 (s, 3H), 6.32 (s, 1H), 6.39 (s, 1H), 7.63 (d, *J*=8.0 Hz, 2H), 8.13 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.2, 52.4, 103.2, 109.1, 126.7, 130.3, 131.8, 140.0, 154.4, 162.6, 163.0, 166.2. HRMS (ESI) calcd for $C_{14}H_{13}O_4$ (M+H^+) 245.0814; found, 245.0802.

*4.1.11. 4-Phenylfuran-2(5H)-one (**3k**)*[12]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (s, 2H), 6.39 (s, 1H), 7.46–7.53 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.0, 113.0, 126.4, 129.3, 129.6, 131.8, 163.9, 173.9.

*4.1.12. 4-o-Tolylfuran-2-(5H)-one (**3l**)*[15]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H), 5.20 (s, 2H), 6.28 (s, 1H), 7.27–7.38 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 72.7, 117.1, 126.5, 127.2, 129.6, 130.7, 131.9, 137.3, 163.8, 174.0.

*4.1.13. 4-m-Tolylfuran-2-(5H)-one (**3m**)*[16]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (s, 3H), 5.22 (s, 2H), 6.36 (s, 1H), 7.32–7.37(m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 71.1, 112.8, 123.6, 127.0, 129.1, 129.5, 132.6, 139.1, 164.1, 174.0.

*4.1.14. 4-p-Tolylfuran-2-(5H)-one (**3n**)*[15]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 5.13 (s, 2H), 6.24 (s, 1H), 7.20 (d, *J*=8.0 Hz, 2H), 7.33 (d,

J=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 70.0, 110.9, 125.3, 125.8, 128.9, 141.5, 162.9, 173.1.

*4.1.15. 4-(2-Methoxy phenyl)furan-2(5H)-one (**3o**)*[12]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 5.16 (s, 2H), 6.46 (s, 1H), 6.92–6.97 (m, 2H), 7.32–7.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 72.7, 111.7, 114.8, 118.7, 120.9, 128.3, 132.9, 158.4, 161.0, 174.7.

*4.1.16. 4-(4-Methoxy phenyl)furan-2(5H)-one (**3p**)*[12]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 5.13 (s, 2H), 6.18 (s, 1H), 6.90 (d, J=8.0 Hz, 2H), 7.39 (d, J=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.5, 70.9, 110.5, 114.6, 122.2, 128.2, 162.3, 163.5, 174.3.

*4.1.17. 4-(4-(Dimethylamino)phenyl)furan-2(5H)-one (**3q**)*[17]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.06 (s, 6H), 5.18 (s, 2H), 6.11 (s, 1H), 6.69 (d, J=8.0 Hz, 2H), 7.37 (d, J=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.0, 70.9, 107.4, 111.6, 118.7, 128.0, 152.4, 164.2, 177.6.

4.2. General experimental procedure for palladium-catalyzed cross-coupling reactions of 3-bromo-4-hydroxy-2-pyrone with arylboronic acids

A solution of 3-bromo-4-hydroxy-6-methyl-2*H*-pyran-2-one **1d** (0.3 mmol), *p*-toluenesulfonyl chloride (0.33 mmol, 1.1 equiv), $K_2HPO_4\cdot 3H_2O$ (0.9 mmol, 3.0 equiv), $Pd(OAc)_2$ (5 mol %), PCy_3 (10 mol %), and $ArB(OH)_2$ (0.75 mmol, 2.5 equiv) in methanol (4.0 mL) was stirred at 60 °C for a period of time. After completion of reaction as indicated by TLC, the reaction was quenched by the addition of saturated aqueous NH_4Cl (5.0 mL), and the mixture was extracted with EtOAc (4.0 mL×3). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography on silica gel to provide the desired product **3**.

*4.2.1. 6-Methyl-3,4-diphenyl-2H-pyran-2-one (**3r**)*[18]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 6.09 (s, 1H), 7.00 (d, J=8.0 Hz, 4H), 7.13 (d, J=8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 107.1, 122.0, 127.5, 127.9, 128.2, 128.6, 130.8, 133.8, 137.5, 152.7, 160.1.

*4.2.2. 6-Methyl-3,4-di-m-tolyl-2H-pyran-2-one (**3s**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 6H), 2.31 (s, 3H), 6.16 (s, 1H), 6.82–6.88 (m, 2H), 6.93 (s, 1H), 7.00–7.07 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 21.3, 21.4, 107.1, 122.0, 125.8, 127.8, 127.8, 128.0, 128.3, 129.2, 129.3, 131.3, 133.8, 137.3, 137.4, 137.8, 152.7, 159.8, 163.7. HRMS (ESI) calcd for $C_{20}H_{19}O_2$ ($M+H^+$) 291.1385; found, 291.1354.

*4.2.3. 6-Methyl-3,4-di-p-tolyl-2H-pyran-2-one (**3t**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 6H), 2.30 (s, 3H), 6.14 (s, 1H), 6.98 (d, J=8 0.0 Hz, 4H), 7.02 (t, J=5.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 19.8, 21.2, 107.2, 121.6, 128.6, 128.7, 128.9, 130.6, 130.9, 131.0, 134.7, 137.1, 138.6, 152.2, 159.6, 163.8, HRMS (ESI) calcd for $C_{20}H_{19}O_2$ (M+H), 291.1385; found, 291.1346.

*4.2.4. 3,4-Bis(4-methoxyphenyl)-6-methyl-2H-pyran-2-one (**3u**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 3H), 3.67 (s, 6H), 6.07 (s, 1H), 6.65–6.70 (m, 4H), 6.95–7.01 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 55.1, 55.2, 107.1, 113.6, 113.7, 120.7, 126.4, 129.8, 130.3, 132.0, 151.7, 158.8, 159.4, 159.8, 163.9, HRMS (ESI) calcd for $C_{20}H_{19}O_4$ (M+H), 323.1283; found, 323.1285.

*4.2.5. 6-Methyl-3,4-bis(4-(trifluoromethyl)phenyl)-2H-pyran-2-one (**3v**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 6.18 (s, 1H), 7.21 (d, J=8.0 Hz, 2H), 7.26 (d, J=8.0 Hz, 2H), 7.49–7.54 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 106.6, 121.2, 122.2, 124.9, 125.1, 125.5, 127.4, 127.6, 127.9, 128.9, 129.4, 129.7, 130.1, 130.4, 130.9, 131.2, 131.5, 137.0, 152.0, 161.6, 162.6. HRMS (ESI) calcd for $C_{20}H_{13}F_6O_2$ (M+H), 399.0820; found, 399.0792.

*4.2.6. 6-Methyl-3,4-bis(4-methylbenzoatyl)-2H-pyran-2-one (**3w**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.88 (s, 6H), 6.20 (s, 1H), 7.15 (d, J=8.0 Hz, 2H), 7.21 (d, J=8.0 Hz, 2H), 7.87–7.90 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.0, 52.1, 52.2, 106.6, 121.5, 128.6, 129.2, 129.3, 129.6, 130.4, 130.9, 138.3, 141.5, 152.4, 161.3, 162.6, 166.2, 166.6. HRMS (ESI) calcd for $C_{22}H_{19}O_6$ (M+H), 379.1182; found, 379.1156.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.07.048. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. (a) Walsh, D. P.; Chang, Y.-T. *Chem. Rev.* **2006**, *106*, 2476; (b) Arya, P.; Chou, D. T. H.; Baek, M.-G. *Angew. Chem., Int. Ed.* **2001**, *40*, 339; (c) Schreiber, S. L. *Science* **2000**, *287*, 1964; (d) Pinilla, C.; Appel, J. R.; Houghten, R. A. *Nat. Med.* **2003**, *9*, 118.
2. For recent selected examples, see: (a) Li, S.; Wu, J. *Org. Lett.* **2011**, *13*, 712; (b) Chen, Z.; Zheng, D.; Wu, J. *Org. Lett.* **2011**, *13*, 848; (c) Luo, Y.; Pan, X.; Wu, J. *Org. Lett.* **2011**, *13*, 1150; (d) Ren, H.; Luo, Y.; Ye, S.; Wu, J. *Org. Lett.* **2011**, *13*, 2552; (e) Li, S.; Luo, Y.; Wu, J. *Org. Lett.* **2011**, *13*, 3190; (f) Luo, Y.; Hong, L.; Wu, J. *Chem. Commun.* **2011**, 5298; (g) Chen, Z.; Ye, C.; Gao, L.; Wu, J. *Chem. Commun.* **2011**, 5623; (h) Qiu, G.; Ding, Q.; Gao, K.; Peng, Y.; Wu, J. *ACS Comb. Sci.* **2011**, *13*, 13; (i) Ye, S.; Wang, H.; Wu, J. *ACS Comb. Sci.* **2011**, *13*, 120.
3. (a) Midland, S. L.; Sims, J. J. *J. Org. Chem.* **1995**, *60*, 1118; (b) Miao, S. W.; Andersen, R. J. *J. Org. Chem.* **1991**, *56*, 6275; (c) Ortega, M. J.; Zubia, E.; Ocafia, J. M.; Naranjo, S.; Salva, J. *Tetrahedron* **2000**, *56*, 3963; (d) Ducharme, Y.; Gauthier, J. Y.; Prasit, P.; Leblanc, Y.; Wang, Z.; Leger, S.; Therien, M. PCT Int. Appl. WO 95 00,501, 1995; *Chem. Abstr.* **1996**, *124*, 55954y; (e) Lee, G. C. M.; Garst, M. E. PCT Int. Appl. WO 91 16,055, 1991; *Chem. Abstr.* **1992**, *116*, 59197m; (f) Honda, T.; Mizutani, H.; Kanai, K. *J. Org. Chem.* **1996**, *61*, 9374; (g) Bellina, F.; Anselmi, C.; Viel, S.; Mannina, L.; Rossi, R. *Tetrahedron* **2001**, *57*, 9997 and references cited therein; (h) For dihydroxerulin, xerulin, and xerulinic acid, see: Kuhnt, D.; Anke, T.; Besl, H.; Bross, M.; Herrmann, R.; Mocek, U.; Steffan, B.; Steglich, W. *J. Antiobiot.* **1990**, *43*, 1413; (i) For (−)-dysiolide, see: Gunaskera, G. P.; McCarthy, P. J.; Borges, M. K.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc.* **1996**, *118*, 8759; (j) Palomer, A.; Cabre, F.; Pascual, J.; Campos, J.; Trujillo, M. A.; Entrena, A.; Gallo, M. A.; Garcia, L.; Mauleon, D.; Espinosa, A. *J. Med. Chem.* **2002**, *45*, 1402 and references cited therein.
4. (a) Hayashi, Y.; Yuki, Y.; Matsumoto, T. *Tetrahedron Lett.* **1977**, *41*, 3637; (b) Chen, K. K.; Kovarikova, A. *J. Pharm. Sci.* **1967**, *56*, 1535; (c) Kupchan, S. M.; Moniot, J. L.; Sigel, C. W.; Hemingway, R. J. *J. Org. Chem.* **1971**, *36*, 2611; (d) For a synthesized α-pyrone with anti-HIV activity, see: Prasad, J. V. N.; Para, K. S.; Lunney, E. A.; Ortwine, D. F.; Dunbar, J. B.; Ferguson, D.; Tummino, P. J.; Hupe, D.; Tait, B. D.; Domagala, J. M.; Humblet, C.; Bhat, T. N.; Liu, B.; Guenin, D. M. A.; Baldwin, E. T.; Erickson, J. W.; Sawyer, T. K. *J. Am. Chem. Soc.* **1994**, *116*, 6989; (e) Sunazuka, T.; Handa, M.; Nagai, K.; Shirahata, T.; Harigaya, Y.; Otoguro, K.; Kuwajima, I.; Omura, S. *Org. Lett.* **2002**, *4*, 367 and references cited therein; (f) Chen, C.-H.; Liao, C.-C. *Org. Lett.* **2000**, *2*, 2049.
5. For example: (a) Renard, M.; Ghosez, L. A. *Tetrahedron* **2001**, *57*, 2597; (b) Concellon, J. M.; Riego, E.; Bernad, P. L. *Org. Lett.* **2002**, *4*, 1303; (c) Makabe, H.; Hattori, Y.; Tanaka, A.; Oritani, T. *Org. Lett.* **2002**, *4*, 1083; (d) Chio, Y.; Choo, H.; Chong, Y.; Lee, S.; Olgen, S.; Schinazi, R. F.; Chu, C. K. *Org. Lett.* **2002**, *4*, 305; (e) Roush, W. R.; Limberakis, C.; Kunz, R. K.; Barda, D. A. *Org. Lett.* **2002**, *4*, 1543; (f) Ghosh, N.; McKee, S. P.; Thompson, W. J.; Darke, P. L.; Zugory, J. C. *J. Org. Chem.* **1993**, *58*, 1025; (g) Wender, P. A.; Ihle, N. C.; Correia, C. R. D. *J. Am. Chem. Soc.* **1988**, *110*, 5904; (h) Hanessian, S.; Park, H.; Yang, R. Y. *Synlett* **1997**, 351; (i) Hanessian, S.; Park, H.; Yang, R. Y. *Synlett* **1997**, 353; (j) Sulikowski, G. A.; Agnelli, F.; Spencer, P.; Koomen, J. M.; Russell, D. H. *Org. Lett.* **2002**, *4*, 1447.
6. (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318; (b) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731; (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

7. (a) *Palladium Reagents and Catalysts*, 2nd ed.; Tsuji, J., Ed.; John Wiley: Chichester, UK, 2004; (b) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; John Wiley: Weinheim, Germany, 2004.
8. Recent reviews: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174; (b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200; (c) Campeau, L. C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35; (d) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173; (e) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222; (f) Lewis, L. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013; (g) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013; (h) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074; (i) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087; (j) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094; (k) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792; (l) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, 677; (m) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147; (n) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2096; (o) Satoh, T.; Miura, M. *Synthesis* **2010**, 3395; (p) Ackermann, L. *Chem. Commun.* **2010**, 4866; (q) Hirano, K.; Miura, M. *Synlett* **2011**, 294.
9. (a) Kang, F.-A.; Sui, Z.; Murray, W. V. *J. Am. Chem. Soc.* **2008**, *130*, 11300; (b) Ackermann, L.; Mulzer, M. *Org. Lett.* **2008**, *10*, 5043; (c) Luo, Y.; Wu, J. *Tetrahedron Lett.* **2009**, *50*, 2103; (d) Luo, Y.; Wu, J. *Tetrahedron* **2009**, *65*, 6810.
10. Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Acc. Chem. Res.* **2010**, *43*, 1486.
11. For selected examples, see: (a) So, C. M.; Lau, C. P.; Chan, A. S. C.; Kwong, F. Y. *J. Org. Chem.* **2008**, *73*, 7731; (b) So, C. M.; Lee, H. W.; Lau, C. P.; Kwong, F. Y. *Org. Lett.* **2009**, *11*, 317; (c) Albaneze-Walker, J.; Raju, J.; Vance, J. A.; Goodman, A. J.; Reeder, M. R.; Liao, J.; Maust, M. T.; Irish, P. A.; Espino, P.; Andrews, D. R. *Org. Lett.* **2009**, *11*, 1463; (d) So, C. M.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 8059; (e) Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 13848; (f) Fors, B. P.; Watson, D. A.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 13552; (g) So, C. M.; Zhou, Z.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 6402; (h) Munday, R. H.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 2754; (i) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818; (j) Tang, Z.-Y.; Hu, Q.-S. *J. Am. Chem. Soc.* **2004**, *126*, 3058; (k) Hansen, A. L.; Ebran, J.-P.; Ahlquist, M.; Norrby, P.-O.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3349; (l) Zhang, L.; Wu, J. *J. Am. Chem. Soc.* **2008**, *130*, 12250; (m) Fernández-Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180.
12. Wu, J.; Zhu, Q.; Wang, L.; Fathi, R.; Yang, Z. *J. Org. Chem.* **2003**, *68*, 670.
13. Wu, J.; Zhang, L.; Gao, K. *Eur. J. Org. Chem.* **2006**, 5260.
14. Kuroda, J.-i.; Inamoto, K.; Hiroya, K.; Doi, T. *Eur. J. Org. Chem.* **2009**, 2251.
15. Tang, Z.-Y.; Hu, Q.-S. *Adv. Synth. Catal.* **2004**, *346*, 1635.
16. Ciattini, P. G.; Ortar, G. *Synthesis* **1986**, 70.
17. Melamed, J. Y.; Egbertson, M. S.; Varga, S.; Vacca, J. P.; Moyer, G.; Gabryelski, L.; Felock, P. J.; Stillmock, K. A.; Witmer, M. V.; Schleif, W.; Hazuda, D. J.; Leonard, Y.; Jin, L.; Ellis, J. D.; Young, S. D. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5307.
18. Henry, W. P.; Hughes, R. P. *J. Am. Chem. Soc.* **1986**, *108*, 7862.