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Facile Access to 4-Aryl-2(5*H*)-furanones by Suzuki Cross Coupling: Efficient Synthesis of Rubrolides C and E

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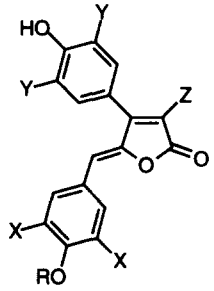
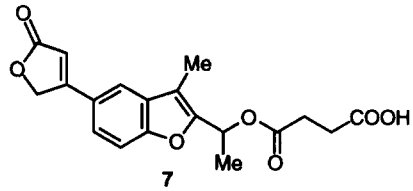
Abstract: The Pd(0)-catalyzed cross coupling between 4-bromo-2(5*H*)-furanones and arylboronic acids provides the corresponding 4-aryl-2(5*H*)-furanones in yields of 61-85%. By using this method in conjunction with furanolate chemistry, the marine antibiotics rubrolide C and E have been synthesized in highly efficient fashion (4 steps, overall yield = 61 and 56% respectively) from β-tetronic acid.

The 4-aryl-2(5*H*)-furanone unit characterizes many naturally occurring[1] and medicinally important compounds.[2] Noteworthy examples are the potent antibiotics rubrolide A-F (**1-6**), isolated by Andersen and Miao from the colonial tunicate *Ritterela rubra*,[1b,3] and the synthetic drug benfurodil hemisuccinate (Eucilat®; **7**) which is used for the chronic treatment of congestive heart failure.[4] Moreover, several simple 4-aryl-3-methyl-2(5*H*)-furanones are highly effective in controlling fungal diseases in plants of agronomic importance.[5]

1 R = Z = H, X = Y = Br
2 R = H, X = Y = Br, Z = Cl
3 R = Y = Z = H, X = Br
4 R = X = Z = H, Y = Br
5 R = X = Y = Z = H
6 R = Me, X = Y = Z = H





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Traditionally, 4-aryl-2(5*H*)-furanones have been prepared by multistep routes involving *de novo* construction of the furanone ring.[2a,4,6-9] A notable exception is the recently described Stille coupling of 4-tributylstannyl-2(5*H*)-furanone with aryl iodides.[10] Although arylation proceeds with reasonable efficiency (58-72%), the utility of this method is limited by the availability of the requisite stanyllactone[10,11] and the toxicity of organotin by-products which are difficult to remove, especially on a large scale. In search of a more utilitarian means for installing a C-4 aryl substituent onto the furanone ring, we decided to explore the Suzuki-type cross coupling of arylboronic acids with suitably activated butenolides.[12] We now report our preliminary results which demonstrate that such a pathway provides an exceptionally concise and convenient synthesis of a wide variety of 4-aryl-2(5*H*)-furanones. We further describe the utilization of this methodology in conjunction with furanolate chemistry for a straightforward synthesis of rubrolides C and E.

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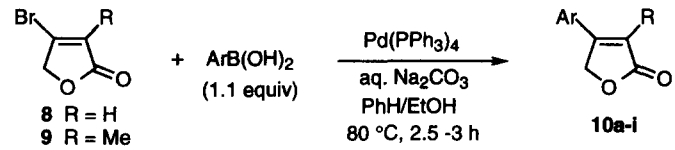
The highly crystalline 4-bromo-2(5*H*)-furanone (**8**), prepared by Vilsmeier bromination of commercially available β-tetronic acid (86% yield, 30g-scale),[13a] was viewed as a stable, readily accessible building block[14] and its reaction with phenylboronic acid was briefly investigated. The best results were obtained by adaptation of the original Suzuki regimen for aryl-aryl cross coupling[15] ($Pd(PPh_3)_4$ /aq. $NaHCO_3$ / PhH / EtOH, 80 °C, 2.5 h) which provided 4-phenyl-2(5*H*)-furanone (**10a**) in 78% yield (entry 1, Table 1). This procedure worked equally well with other aryl and heteroaryl boronic acids to furnish the corresponding furanones (**10b-g**) in yields of 61-79% after purification by flash chromatography (entries 2-7). Likewise, the easily prepared 4-bromo-3-methyl-2(5*H*)-furanone (**9**)[13b] was converted to the fugicidal agent **10h**[5,16] and its analogue **10i**[8] in yields of 85 and 71%, respectively (entries 8-9). Clearly, the presence of a C3-methyl in the furanone component does not compromise the efficiency of cross coupling (*cf.* entry 1 vs. 8, and 4 vs. 9, Table 1).

Table 1. Pd(0)-Catalyzed Cross Coupling of Bromobutenolides with Arylboronic Acids.



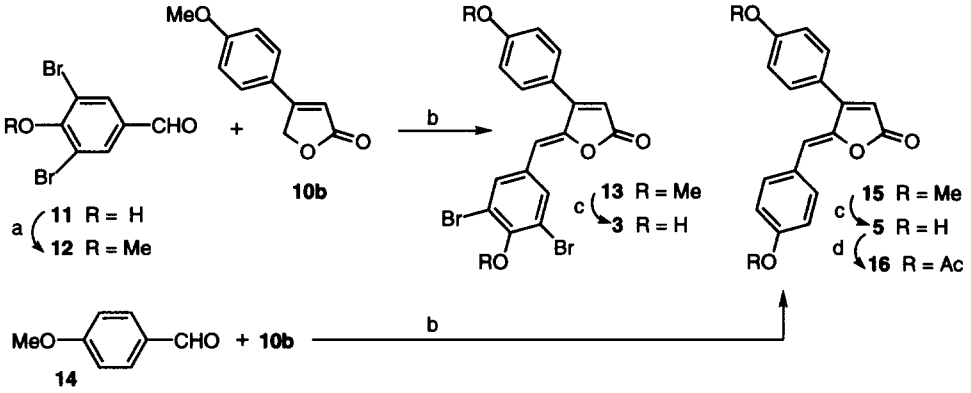
Entry	R	Ar	% Yield[a] of **10**	mp °C
1	H	Ph	78[b] (**10a**)	92.5-93.5 (lit.[10b] 91-93)
2	H	4-$MeOC_6H_4$	79 (**10b**)	119-119.5 (lit.[9a] 119-120.5)
3	H	3-ClC_6H_4	73 (**10c**)	98.5-99.5
4	H	4-BrC_6H_4	66[c] (**10d**)	165-167 (lit.[7] 163)
5	H	1-naphthyl	72 (**10e**)	98.5-99.5 (lit.[7] 99)
6	H	2-thienyl	76[d] (**10f**)	96-97 (lit.[10b] 94-96)
7	H	3-thienyl	61 (**10g**)	129-130
8	Me	Ph	85 (**10h**)	120-121 (lit.[16] 115-117)
9	Me	4-BrC_6H_4	71[c] (**10i**)	178-180 (lit.[8] 174)

[a]Yields refer to chromatographically isolated, spectroscopically homogeneous products. [b]The use of $Pd(OAc)_2$ together with $Ba(OH)_2$ (EtOH, 25 °C) or Ph_3P/Et_3N (DMF, 120 °C) led to a lower yield of **10a** (45-46%). [c]A small amount of the corresponding 4-(4'-bromobiphenylyl) furanone was also obtained. [d]1.5 equiv of 2-thienylboronic acid was used.

Having established a viable means for installing an aryl group at the C-4 position of furanone, the subsequent appendage of a C-5 arylmethylene substituent (*cf.* **10b** →**13**, Scheme 1) was explored *en route* to rubrolides C and E (**3** and **5**). The requisite aldehyde **12** was prepared in 90% yield by O-methylation of commercially available phenol **11**.[17] Initial attempts to prepare **13** by aldol condensation of **12** with **10b** under Knoevenagel conditions[18] (e.g. piperidine/MeOH or piperidine/pyridine) proved unrewarding. Much to our delight, it was ultimately discovered that the one-pot version of a previously reported three-step sequence[19] provided a highly effective solution. Thus, treatment of **10b** with the appropriate aldehyde (**12** or **14**) in the

presence of TBDMSOTf and diisopropylethylamine, followed by DBU-mediated β-elimination *in situ* led uniquely to the corresponding *Z*-arylmethylenebutenolide (**13** or **15**) with high efficiency (Scheme 1).[20] Exposure of **13** to boron tribromide in dichloromethane afforded rubrolide C (**3**; 95%) whose ^1H and ^{13}C NMR properties were in excellent agreement with those reported for the natural product.[1b] Similarly, demethylation of **15** gave rubrolide E (**5**; 98%)[21] whose identity was firmly established by conversion to diacetate **16** and spectral comparison of the latter with the diacetate of natural rubrolide E.[1b]

Scheme 1



a) MeI, K_2CO_3, Me_2CO, 55 °C, 6h (90%); b) TBDMSOTf (1.2 equiv), *i*-Pr_2NEt (3 equiv), CH_2Cl_2, rt, 1-2 h, then DBU (2 equiv), rt, 3 h (**13** 95%, **15** 84%); c) BBr_3 (3 equiv), CH_2Cl_2, - 78 → 25 °C, 24 h (**3** 95%, **5** 98%); d) Ac_2O, Et_3N, THF, rt, 16 h (81%).

In conclusion, a distinctly short and efficient synthesis of the marine antibiotics rubrolide C and E from β-tetronic acid (4 steps, overall yield = 61 and 56% respectively) has been achieved through the combined use of Suzuki cross coupling and furanolate chemistry. The attractiveness of the present approach stems from the generality of the Suzuki reaction (*cf.* Table 1) and the serviceability of a newly devised 'one-pot' method for C5-arylmethylenation of 4-aryl-2(5*H*)-furanones.[22] Further applications of this technology to the construction of structurally related natural products are under investigation.

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20. Representative procedure: To a solution of lactone **10b** (205 mg, 1.08 mmol) in anhydrous CH_2Cl_2 (5 mL), TBDMSOTf (300 μL, 1.31 mmol) was added at rt followed by *p*-anisaldehyde (160 μL, 1.31 mmol) and *i*-Pr_2NEt (560 μL, 3.21 mmol). After stitrring for 1 h at rt, DBU (325 μL, 2.17 mmol) was added. After 3 h, CH_2Cl_2 (100 mL) was added and the mixture was washed successively with aq. HCl (3N, 2x50 mL) and brine (12x50 mL). The organic layer was dried ($MgSO_4$) and concentrated and the residue was recrystallized from CH_2Cl_2-hexanes to give pure lactone **15** (mp 139-140 °C; 278 mg, 84%).
21. Data for synthetic rubrolide E (**5**): pale yellow crystals mp 279-280 °C (acetone-hexanes); R_f 0.64 (EtOAc); ^1H NMR (300 MHz, DMSO-d_6) δ 10.06 (br. s, 2H), 7.70 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 6.93 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 6.38 (s, 1H), 6.32 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.4, 161.5, 160.4, 159.8, 147.1, 134.3, 132.1, 126.0, 122,4, 117.6, 115.2, 112.6; HRMS m/z 280.0733 (Calcd for $C_{17}H_{12}O_4$ 280.0736).
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