

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

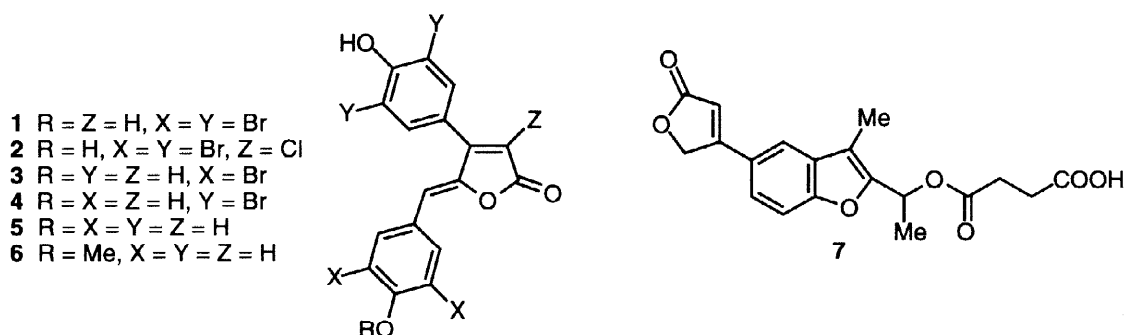
John Boukouvalas\*, Nicolas Lachance, Michel Ouellet and Martin Trudeau

Département de Chimie, Université Laval, Québec G1K 7P4, Canada

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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  $\beta$ -tetronic acid. © 1998 Elsevier Science Ltd. All rights reserved.

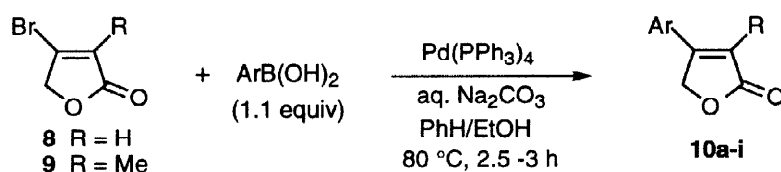
The 4-aryl-2(5*H*)-furanone unit characterizes many naturally occurring<sup>1</sup> and medicinally important compounds.<sup>2</sup> Noteworthy examples are the potent antibiotics rubrolide A–F (**1–6**), isolated by Andersen and Miao from the colonial tunicate *Ritterella rubra*,<sup>1b,3</sup> and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



Traditionally, 4-aryl-2(5*H*)-furanones have been prepared by multistep routes involving *de novo* construction of the furanone ring.<sup>2a,4,6–9</sup> A notable exception is the recently described Stille coupling of 4-tributylstannyl-2(5*H*)-furanone with aryl iodides.<sup>10</sup> Although arylation proceeds with reasonable efficiency (58–72%), the utility of this method is limited by the availability of the requisite stanyllactone<sup>10,11</sup> 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.<sup>12</sup> 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.

The highly crystalline 4-bromo-2(5*H*)-furanone (**8**), prepared by Vilsmeier bromination of commercially available  $\beta$ -tetronic acid (86% yield, 30g-scale),<sup>13a</sup> was viewed as a stable, readily accessible building block<sup>14</sup> 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<sup>15</sup> ( $\text{Pd(PPh}_3)_4$  / aq.  $\text{NaHCO}_3$  / 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**)<sup>13b</sup> was converted to the fungicidal agent **10h**<sup>5,16</sup> and its analogue **10i**<sup>8</sup> 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 <sup>a</sup> of <b>10</b>	mp °C
1	H	Ph	78 <sup>b</sup> ( <b>10a</b> )	92.5-93.5 (lit. <sup>10b</sup> 91-93)
2	H	4-MeOC <sub>6</sub> H <sub>4</sub>	79 ( <b>10b</b> )	119-119.5 (lit. <sup>9a</sup> 119-120.5)
3	H	3-ClC <sub>6</sub> H <sub>4</sub>	73 ( <b>10c</b> )	98.5-99.5
4	H	4-BrC <sub>6</sub> H <sub>4</sub>	66 <sup>c</sup> ( <b>10d</b> )	165-167 (lit. <sup>7</sup> 163)
5	H	1-naphthyl	72 ( <b>10e</b> )	98.5-99.5 (lit. <sup>7</sup> 99)
6	H	2-thienyl	76 <sup>d</sup> ( <b>10f</b> )	96-97 (lit. <sup>10b</sup> 94-96)
7	H	3-thienyl	61 ( <b>10g</b> )	129-130
8	Me	Ph	85 ( <b>10h</b> )	120-121 (lit. <sup>16</sup> 115-117)
9	Me	4-BrC <sub>6</sub> H <sub>4</sub>	71 <sup>c</sup> ( <b>10i</b> )	178-180 (lit. <sup>8</sup> 174)

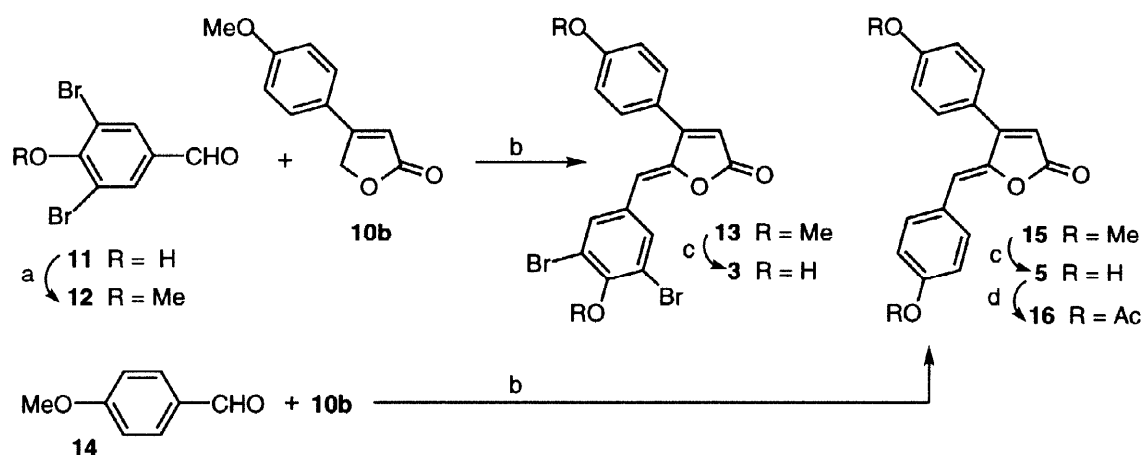
<sup>a</sup>Yields refer to chromatographically isolated, spectroscopically homogeneous products.

<sup>b</sup>The use of  $\text{Pd(OAc)}_2$  together with  $\text{Ba(OH)}_2$  (EtOH, 25 °C) or  $\text{Ph}_3\text{P/Et}_3\text{N}$  (DMF, 120 °C) led to a lower yield of **10a** (45-46%). <sup>c</sup>A small amount of the corresponding 4-(4'-bromo-biphenyl) furanone was also obtained. <sup>d</sup>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**.<sup>17</sup> Initial attempts to prepare **13** by aldol condensation of **12** with **10b** under Knoevenagel conditions<sup>18</sup> (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<sup>19</sup> 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  $\beta$ -elimination *in situ* led uniquely to the corresponding *Z*-arylmethylenebutenolide (**13** or **15**) with high efficiency (Scheme 1).<sup>20</sup> Exposure of **13** to boron tribromide in dichloromethane afforded rubrolide C (**3**; 95%) whose <sup>1</sup>H and <sup>13</sup>C NMR properties were in excellent agreement with those reported for the natural product.<sup>1b</sup> Similarly, demethylation of **15** gave rubrolide E (**5**; 98%)<sup>21</sup> whose identity was firmly established by conversion to diacetate **16** and spectral comparison of the latter with the diacetate of natural rubrolide E.<sup>1b</sup>

Scheme 1



a) MeI, K<sub>2</sub>CO<sub>3</sub>, Me<sub>2</sub>CO, 55 °C, 6 h (90%); b) TBDMSOTf (1.2 equiv), *i*-Pr<sub>2</sub>NEt (3 equiv), CH<sub>2</sub>Cl<sub>2</sub>, rt, 1-2 h, then DBU (2 equiv), rt, 3 h (**13** 95%, **15** 84%); c) BBr<sub>3</sub> (3 equiv), CH<sub>2</sub>Cl<sub>2</sub>, -78 → 25 °C, 24 h (**3** 95%, **5** 98%); d) Ac<sub>2</sub>O, Et<sub>3</sub>N, THF, rt, 16 h (81%).

In conclusion, a distinctly short and efficient synthesis of the marine antibiotics rubrolide C and E from  $\beta$ -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-arylmethylation of 4-aryl-2(5*H*)-furanones.<sup>22</sup> 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<sub>2</sub>Cl<sub>2</sub> (5 mL), TBDMSOTf (300  $\mu$ L, 1.31 mmol) was added at rt followed by *p*-anisaldehyde (160  $\mu$ L, 1.31 mmol) and *i*-Pr<sub>2</sub>NEt (560  $\mu$ L, 3.21 mmol). After stirring for 1 h at rt, DBU (325  $\mu$ L, 2.17 mmol) was added. After 3 h, CH<sub>2</sub>Cl<sub>2</sub> (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<sub>4</sub>) and concentrated and the residue was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>-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<sub>f</sub> 0.64 (EtOAc); <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>)  $\delta$  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); <sup>13</sup>C NMR (75 MHz, DMSO-d<sub>6</sub>)  $\delta$  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<sub>17</sub>H<sub>12</sub>O<sub>4</sub> 280.0736).
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