

Syntheses of 4-(1-alkynyl)-2(5H)-furanones and coumarins via the palladium catalyzed cross-coupling reactions of potassium alkynyltrifluoroborates

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Abstract—An efficient synthesis of 4-(1-alkynyl)-2(5H)-furanones has been developed utilizing a palladium catalyzed coupling reaction of β -tetronic acid bromide with potassium alkynyltrifluoroborates in the absence of base. 4-Alkynylcoumarins were also synthesized using this method. The reactions are straightforward and the yields are excellent.

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Unsaturated five-membered lactones are important synthetic targets because they are core units in many natural products¹ and medicinally important materials.² Compounds containing the 2(5H)-furanone moiety have been evaluated as insecticides, fungicides, antitumor agents, allergy inhibitors, cyclooxygenase inhibitors, and phospholipase A₂ inhibitors.³ Examples of alkynyl-substituted heterocycles that exhibit significant cytotoxicity have also been reported.⁴ Recently, 4-(1-alkynyl)-2(5H)-furanones were found to exhibit potent cytotoxicity.⁵ Syntheses of 2(5H)-furanones with varying substitution patterns have been reported.^{6,7} However, synthetic routes to 4-alkynyl-substituted 2(5H)-furanones are limited.⁸ Existing methods involve transition metal catalyzed coupling methodologies such as the Sonogashira^{8c} and Stille^{5,8b} reactions. These methods have limitations. The Sonogashira reaction requires a catalyst mixture and a strong base, in addition, brominated substrates generate only modest yields of the desired products. The Stille reaction involves the use of organotin compounds, which are often difficult to separate from the desired product.

Due to their ready availability and chemical stability, potassium organotrifluoroborates have attracted signif-

icant attention.⁹ In connection with our ongoing studies of the cross-coupling reactions of potassium organotrifluoroborates,¹⁰ we developed an efficient synthesis of 4-alkynyl-substituted 2(5H)-furanones using alkynyltrifluoroborates. In this paper, we wish to disclose the results of this study.

The reaction of β -tetronic acid bromide with potassium (3,3-dimethyl-1-butyn-1-yl)trifluoroborate was first examined in an effort to optimize the reaction conditions. Pd(OAc)₂ afforded a moderate yield (Table 1, entry 3). Pd(PPh₃)₂Cl₂ and Pd(PPh₃)₄ produced only modest yields of the expected product (Table 1, entries 1 and 2). Molander successfully coupled potassium alkynyltrifluoroborates with aryl halides using Pd(dppf)Cl₂.^{9b} We found that lesser quantities of Pd(dppf)Cl₂ catalyzed the new reaction effectively (Table 1, entries 5 and 6).

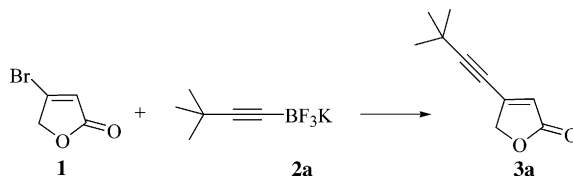
The base-free conditions were applied to a variety of potassium alkynyltrifluoroborates. Typical results are summarized in Table 2. Under these optimized conditions, the reaction resulted in high isolated yields of the desired products.

Coumarins are found in nature and act as structural subunits of more complex natural products.¹¹ The new method was applied to the synthesis of 4-alkynylcoumarins.

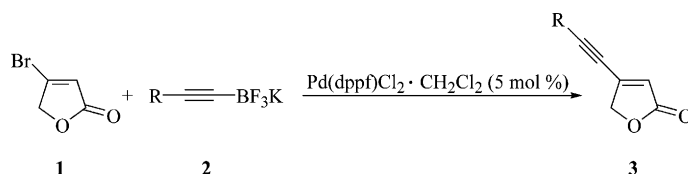
Interestingly, the reaction of 4-bromocoumarin with potassium alkynyltrifluoroborates requires the presence

Keywords: β -Tetronic acid bromide; 4-Bromocoumarin; Potassium alkynyltrifluoroborates; Palladium catalyzed; Cross-coupling.

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Table 1. Reaction of β -tetronic acid bromide with (3,3-dimethyl-1-butyn-1-yl)trifluoroborate

Entry	Reaction conditions	Isolated yield (%)
1	Pd(PPh ₃) ₂ Cl ₂ (5 mol%), PPh ₃ (10 mol%), 3 Cs ₂ CO ₃ , THF/H ₂ O (20:1), reflux, 8 h	15
2	Pd(PPh ₃) ₂ Cl ₂ (5 mol%), Cs ₂ CO ₃ , THF/H ₂ O (20:1), reflux, 7 h	12
3	Pd(OAc) ₂ (5 mol%), Cs ₂ CO ₃ , THF/H ₂ O (20:1), reflux, 4 h	52
4	Pd(dppf)Cl ₂ ·CH ₂ Cl ₂ (9 mol%), Cs ₂ CO ₃ , THF/H ₂ O (20:1), 50 °C, 2 h	95
5	Pd(dppf)Cl ₂ ·CH ₂ Cl ₂ (5 mol%), Cs ₂ CO ₃ , THF/H ₂ O (20:1), 50 °C, 2 h	95
6	Pd(dppf)Cl ₂ ·CH ₂ Cl ₂ (5 mol%), THF, 3 h	95

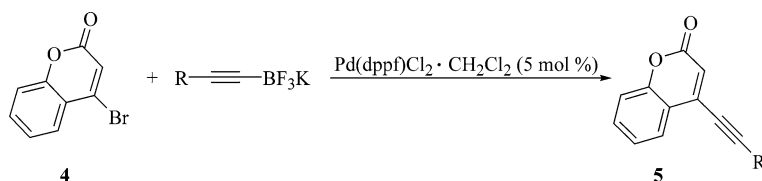
Table 2. Cross-coupling of β -tetronic acid bromide with potassium alkynyltrifluoroborates^a

Entry	R	Time (h)	Product ^b	Yield (%) ^c
1	<i>t</i> -Butyl	3	3a	95
2	<i>n</i> -Butyl	4	3b	95
3	Isopropenyl	3	3c	88
4	3-Chloropropyl	3	3d	89
5	1-Cyclohexenyl	5	3e	80
6	Phenyl	6	3f	91
7	<i>p</i> -Tolyl	6	3g	87
8	TMS	4	3h	71

^a Reactions were carried out using Pd(dppf)Cl₂·CH₂Cl₂ (5 mol%) in THF at room temperature.

^b All products were characterized by ¹H, ¹³C NMR spectroscopy and elemental analysis.

^c Isolated yields.

Table 3. Cross-coupling reactions of 4-bromocoumarin with various potassium alkynyltrifluoroborates^a

Entry	R	Time (h)	Product ^b	Yield (%) ^c
1	<i>t</i> -Butyl	1	5a	97
2	<i>n</i> -Butyl	1.5	5b	91
3	1-Cyclohexenyl	1.5	5c	82
4	Phenyl	2	5d	92
5	<i>p</i> -Tolyl	2	5e	85

^a Reactions were carried out using Pd(dppf)Cl₂·CH₂Cl₂ (5 mol%) and Cs₂CO₃ (3 equiv) in THF/H₂O (20:1) at 50 °C.

^b All products were characterized by ¹H, ¹³C NMR spectroscopy and elemental analysis.

^c Isolated yields.

of base. The reactions of 4-bromocoumarin with various potassium alkynyltrifluoroborates are summarized in Table 3.

In conclusion, we have developed an efficient method for the synthesis of 4-(1-alkynyl)-2(5H)-furanones utilizing the Pd-catalyzed coupling reaction of β -tetronic acid

bromide with potassium alkynyltrifluoroborates in the absence of base under mild conditions. 4-Alkynylcoumarins were also successfully synthesized via coupling reactions of 4-bromocoumarin with potassium alkynyltrifluoroborates in the presence of Cs₂CO₃. The reaction procedures are straightforward and the yields are excellent.

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