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Facile access to 4-(1-alkynyl)-2(5*H*)-furanones by Sonogashira coupling of terminal acetylenes with β-tetronic acid bromide: efficient synthesis of cleviolide

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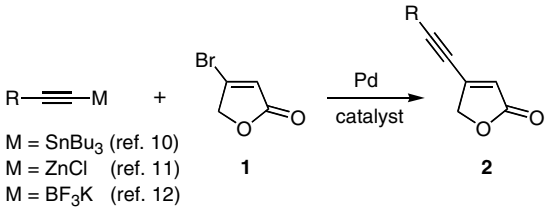
Abstract—A mild and convenient synthesis of 4-(1-alkynyl)-2(5*H*)-furanones has been achieved by Sonogashira or Heck-type alkynylation of β-tetronic acid bromide. As an illustration of this methodology, the natural product cleviolide was prepared in two steps and 78% overall yield.

The development of practical methods for constructing 4-substituted 2(5*H*)-furanones is a prominent objective in synthetic chemistry due to the significant biological activities of many natural and unnatural products containing this moiety.[1] An appealing approach to these compounds, suitable for parallel synthesis, involves the attachment of a C4-substituent onto a preformed furanone ring. This is best accomplished by cross-coupling tactics,[2] as first demonstrated by Negishi and co-workers during a total synthesis of the 4-homoallyl-2(5*H*)-furanone makupalide.[3] Recently, new protocols have been developed for installing a variety of C4-substituents including aryl,[4] alkenyl,[5] alkyl,[6] benzyl[4d,7] and cyclopropyl[8] among others.[9]

A few simple 4-(1-alkynyl)-2(5*H*)-furanones (**2**) have also been prepared in this manner, notably by palladium-catalysed cross-coupling of β-tetronic acid bromide (**1**) with tributylstannylacetylenes,[10] 1-alkynylzinc chlorides,[11] and more recently, potassium alkynyltrifluoroborates[12] (Scheme 1). For example, the structurally unusual monoterpene cleviolide (**2**, R = $Me_2C{=}CH$), a constituent of the plant *Senecio clevelandii*[13] and an attractive target for testing new methodologies,[14] has been synthesized using the Stille coupling reaction depicted in Scheme 1[10b] as well as its inverse variant.[15]



Scheme 1.

Although some of these methods have been shown to be efficient,[10,12] the preparation of the requisite tin or boron acetylides is an obvious inconvenience, especially when other sensitive functional groups are present. In addition, the frequently used Stille reaction produces toxic organotin by-products which are difficult to remove even on a small scale.

Intrigued by the lack of literature reports on the alkynylation of bromide **1** with terminal acetylenes,[16,17] we decided to explore this process as a potentially more utilitarian, direct pathway to 4-(1-alkynyl)-2(5*H*)-furanones (**2**). Herein we report, that under the appropriate conditions, a variety of terminal acetylenes undergo smooth coupling with **1** at room temperature to provide **2** in good to high yields (Table 1). We also describe an application of this methodology to an exceptionally simple and efficient synthesis of cleviolide.

Initial attempts to couple **1** with phenylacetylene under classical conditions used for the Sonogashira reaction, for example, treatment of the coupling partners with

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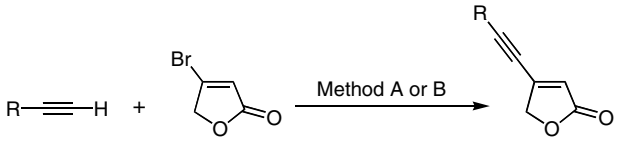
Table 1. Preparation of 4-(1-alkynyl)-2(5*H*)-furanones from β-tetronic acid bromide and terminal acetylenes



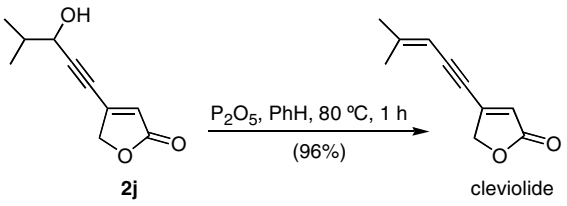
1 **2a-j**

Entry	R	Product	Method[a]	Isolated yield[b] (%)
1	Ph	**2a**	A	71
2	*p*-F–Ph	**2b**	A	74
3	*n*-octyl	**2c**	A	80
4	*t*-Bu	**2d**	A	73
5		**2e**	A	65
6	$THPOCH_2$	**2f**	A	77
7	*t*-BuOCHMe	**2g**	A	86
8	$HOCH_2CH_2$	**2h**	A	50
9			B	63
10		**2i**	A	62
11			B	78
12		**2j**	B	81

[a] Method A: bromide (**1**), $PdCl_2(PPh_3)_2$ (10 mol %), CuI (2 mol %), THF, 0.5 h, rt, then *i*-Pr_2NH, 1-alkyne, 16 h, rt. Method B: $Pd(OAc)_2$ (3 mol %), TPPMS (5 mol %), Et_3N, $MeCN/H_2O$ (15:1), 20 h, rt.
[b] All yields refer to isolated products after flash chromatography.

$PdCl_2(PPh_3)_2$, CuI and diisopropylamine in THF at various temperatures, or heating **1** with the metal salts and base in THF before adding the acetylene,[18] provided the desired product **2a** in only 10–20% yield.[19] Further experimentation revealed that by simply altering the order of addition (Table 1, method A),[20] the yield of **2a** could be substantially improved without a need for heating, strong bases or expensive phosphine additives. Using this procedure, several 4-(1-alkynyl)-2(5*H*)-furanones (**2a**–**i**)[20] were readily prepared in a single step from commercially available acetylenes. Yields were generally good with aryl, alkyl, alkenyl and protected hydroxyalkyl acetylenes (65–86%), but less so with substrates bearing a free hydroxyl group (50–62%; entries 8 and 10). However, we were able to prepare hydroxyalkynylfuranones **2h** and **2i** more efficiently (entries 9 and 11) by Heck-type alkynylation of **1** (a.k.a. copper-free Sonogashira reaction) using the procedure of Genêt et al.[21] which employs palladium acetate in conjunction with an inexpensive water-soluble ligand such as sodium triphenylphoshine monosulfonate (TPPMS, method B).[22] Likewise, alcohol **2j** was prepared from bromide **1** and 4-methyl-1-pentyn-3-ol in 81% yield (entry 12).[22] Heating **2j** with phosphorus pentoxide in benzene cleanly provided cleviolide (96% yield, Scheme 2) whose mp (63–64 °C) and NMR data were in excellent agreement with those reported in the literature.[10b,15b]

In conclusion, we have developed a methodology that allows direct and easy access to a variety of 4-(1-alkynyl)-2(5*H*)-furanones from commercial acetylenes. The foregoing alkynylation procedures are operationally simple, do not require strong bases and work well at room temperature. Moreover, the effectiveness of the water-soluble $Pd(OAc)_2$–TPPMS catalyst, as demonstrated by the straightforward synthesis of cleviolide, renders this methodology both 'green' and practical for potential large-scale applications.



2j cleviolide

Scheme 2.

Acknowledgements

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20. *Typical procedure (method A)*: To a solution of **1** (448 mg, 2.75 mmol) in THF (4 mL) was added CuI (10 mg, 0.05 mmol) and $PdCl_2(PPh_3)_2$ (193 mg, 0.27 mmol). After stirring the mixture for 30 min at room temperature, a solution of tetrahydro-2-(2-propynyloxy)-2*H*-pyran (385 μL, 2.75 mmol) and *N*,*N*-diisopropylamine (775 μL, 5.48 mmol) in THF (4 mL) was added. Stirring continued for 16 h (rt) and the reaction mixture was quenched with saturated aq ammonium chloride, extracted with 1:1 ethyl acetate/hexanes (×3), and the combined extracts were dried (Na_2SO_4) and evaporated in vacuo. Purification by flash chromatography (ethyl acetate/hexanes: 1/4) afforded **2f** as an oil (476 mg, 77%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.13 (t, $J = 1.9$ Hz, 1H), 4.75 (d, $J = 1.9$ Hz, 2H), 4.72 (t, $J = 2.9$ Hz, 1H), 4.48–4.35 (m, 2H), 3.80–3.72 (m, 1H), 1.81–1.46 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 146.5, 122.8, 101.8, 97.2, 75.8, 72.7, 61.9, 54.3, 29.9, 25.1, 18.7. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.52; H, 6.56. Data for other new compounds: Compound **2b**: mp 70–71 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (m, 2H), 7.08 (m, 2H), 6.24 (t, $J = 1.9$ Hz, 1H), 4.88 (d, $J = 1.9$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 163.5 (d, $J = 253$ Hz), 146.8, 134.1 (d, $J = 8.7$ Hz), 122.1, 116.1 (d, $J = 22$ Hz), 103.8, 79.0, 72.8; HRMS *m*/*z* 202.0435 (calcd for $C_{12}H_7FO_2$ 202.0430). Compound **2c**: mp 106–108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (t, $J = 1.6$ Hz, 1H), 4.75 (d, $J = 1.6$ Hz, 2H), 2.43 (t, $J = 7.1$ Hz, 2H), 1.58 (q, $J = 7.1$ Hz, 2H), 1.41–1.08 (m, 10H), 0.87 (t, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 148.1, 121.3, 108.2, 73.1, 71.4, 31.7, 29.0, 28.9, 28.8, 27.8, 22.5, 19.8, 13.9; HRMS *m*/*z* (MH^+) 221.1540 (calcd for $C_{14}H_{21}O_2$ 221.1541). Compound **2g**: mp 73–74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.13 (t, $J = 1.7$ Hz, 1H), 4.77 (d, $J = 1.9$ Hz, 2H), 4.47 (q, $J = 6.7$ Hz, 1H), 1.43 (d, $J = 6.7$ Hz, 3H); 1.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 146.7, 121.6, 108.5, 74.7, 73.1, 72.4, 57.4, 27.4, 23.1; HRMS (MH^+) *m*/*z* 209.1181 (calcd for $C_{12}H_{17}O_3$ 209.1178). Compound **2h**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15 (s, 1H), 4.78 (d, $J = 1.6$ Hz), 3.83 (t, $J = 6.3$ Hz, 2H), 2.74 (t, $J = 6.3$ Hz, 2H), 1.72 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 148.0, 121.7, 105.0, 74.9, 73.2, 60.1, 24.0; HRMS *m*/*z* 152.0481 (calcd for $C_8H_8O_3$ 152.0473). Compound **2i**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00 (t, $J = 1.9$ Hz, 1H), 4.66 (d, $J = 1.9$ Hz, 2H), 3.73 (s, 1H), 1.91–1.57 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 147.6, 121.6, 110.3, 74.1, 73.0, 72.8, 41.9, 23.3; HRMS (MH^+) *m*/*z* 193.0863 (calcd for $C_{11}H_{12}O_3$ 193.0865).
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22. *Typical procedure (method B)*: 4-Methyl-1-pentyn-3-ol (321 μL, 3.04 mmol), triethylamine (564 μL, 4.05 mmol), $Pd(OAc)_2$ (14 mg, 0.06 mmol) and TPPMS (37 mg, 0.10 mmol) were added to a solution of **1** (330 mg, 2.02 mmol) in $MeCN/H_2O$ (15:1, 5 mL) and the mixture was stirred for 20 h at room temperature, filtered through Celite, and diluted with water before extraction with ethyl acetate (×3). The combined extracts were dried (Na_2SO_4), evaporated in vacuo, and the crude product was purified by flash chromatography (Et_2O) to deliver **2j** as an oil (296 mg, 81%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15 (s, 1H), 4.78 (s, 2H), 4.36 (d, $J = 5.6$ Hz, 1H), 2.75 (br s, 1H), 1.93 (m, 1H), 0.98 and 0.99 (2d, $J = 6.6$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 146.8, 122.5, 105.9, 75.3, 72.9, 68.0, 34.2, 17.9, 17.5; HRMS *m*/*z* 180.0784 (calcd for $C_{10}H_{12}O_3$ 180.0786).