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Palladium-Mediated Intramolecular Carbonylative Annulation of *o*-Alkynylphenols To Synthesize Benzo[*b*]furo[3,4-*d*]furan-1-ones

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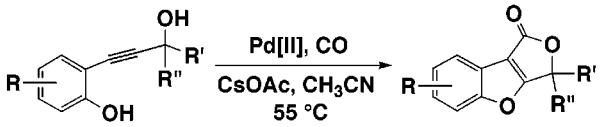
ABSTRACT



The carbonylative annulation of *o*-alkynylphenols mediated by $PdCl_2(PPh_3)_2$ and dppp in the presence of CsOAc at 55 °C in acetonitrile under a balloon pressure of CO generates functionalized benzo[*b*]furo[3,4-*d*]furan-1-ones in good yields. This novel synthetic approach provides a highly efficient method for diversification of the benzofuran scaffold for combinatorial synthesis.

As a result of recent advances in chemical biology,[1] there is a strong desire to develop efficient methods and strategies for combinatorial syntheses of small molecule libraries based on naturally occurring products.[2] Therefore, development of a truly practical and efficient method[3] for combinatorial synthesis of these natural product libraries is both essential and necessary. One of the best ways to address this objective is to develop processes that afford enhancement of target-relevant molecular complexity at minimal cost.[4] Among the many effective ways to reach the goal, the tandem process,[5] which integrates multistep processes in a single operation, is very attractive.

In this Letter, we would like to report our recent efforts for the tandem synthesis of benzo[*b*]furo[3,4-*d*]furan-1-ones by palladium-mediated intramolecular carbonylative annulation of *o*-alkynylphenols.

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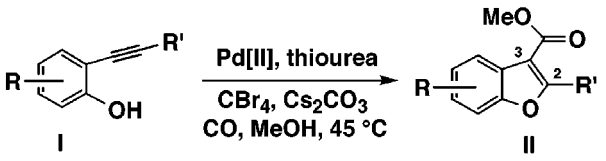
Benzo[*b*]furo[3,4-*d*]furan-1-ones share a common scaffold with many naturally occurring products,[6] which have a wide range of biological effects.[7]

Several methods are known for synthesizing this type of molecule;[8] however, all of them focused on individual targets. Consequently, there is a need for new and powerful methods that offer greater flexibility and synthetic ease to diversity-oriented synthesis[9] of this type of molecule.

The transition metal-catalyzed carbonylative annulation of alkynols or alkeneols provides convenient and effective one-step processes for the syntheses of pyran or furan carboxylates, lactones, and other interesting scaffolds, and significant progress has been made in this fertile area.[10]

We previously demonstrated that palladium−thiourea is an effective cocatalyst for the syntheses of 2,3-disubstituted benzo[*b*]furans by carbonylative annulation of *o*-alkynylphenols under very mild conditions (at 45 °C under a balloon pressure of CO) [see Scheme 1].[11]

Scheme 1. Palladium-Catalyzed Carbonylative Annulation

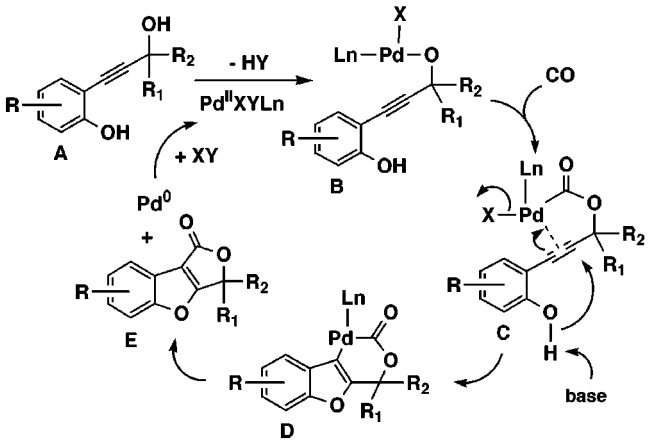


Our continuing interest in this field grew out of a desire to create a cascade reaction which would exhibit broad versatility with maximum toleration of diversified functional groups for a combinatorial synthesis of benzo[*b*]furo[3,4-*d*]-furan-1-ones from *o*-alkynylphenols.

On the basis of our previous mechanistic interpretation for the palladium-catalyzed carbonylative annulation to synthesize 2,3-disubstituted benzo[*b*]furans,[11] we envisage that benzo[*b*]furo[3,4-*d*]furan-1-ones could also be generated from *o*-alkynylphenols **A** via the following multistage process shown in Scheme 2.

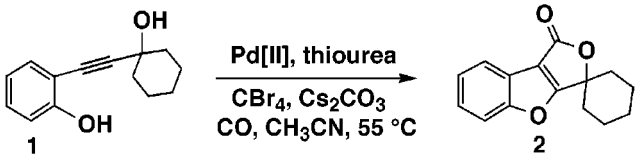
We speculated that the overall process may involve attack of alcohol **A** on the $Pd^{II}XYLn$ to generate complex **B**, followed by insertion of CO to give intermediate **C**. Intramolecular nucleophilic addition of the phenolic oxide to the resulting acyl−palladium complex **C** leads to formation of intermediate **D**, which might undergo reductive elimination to produce the five-membered lactone **E** and palladium(0). The palladium(0) is then oxidized to palladium-(II), completing the cycle.

Scheme 2. Proposed Mechanism of the Palladium-Catalyzed Carbonylative Cyclization of *o*-Alkynylphenols



We therefore set up the experiments to pursue this proposed cascade reaction. The reaction of *o*-alkynylphenols **1** in the presence of palladium−thiourea and CBr_4 in acetonitrile under conditions similar to those of our previous annulation conditions[11] resulted in formation of the desired product **2** in 17% yield (Scheme 3).

Scheme 3. Synthesis of Benzo[*b*]furo[3,4-*d*]furan-1-one **2**



To find the optimal reaction conditions, we studied the effect of various reaction parameters (palladium catalyst, solvent, base, etc.) on the outcome of the reaction. It was found that among the catalysts tested [$PdCl_2$, PdI_2, $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, $PdCl_2(PPh_3)_2$−thiourea, PdI_2−thiourea, $PdCl_2$-$(PPh_3)_2$−dppp], $PdCl_2(PPh_3)_2$−dppp proved to be the most efficient. Among the solvents used [THF, benzene, DMF, CH_3CN], CH_3CN was the best choice. Between the bases CsOAc and Cs_2CO_3, CsOAc gave a better result. Taken together, a 68% yield of compound **2** was eventually obtained when a stoichiometric amount of $PdCl_2(PPh_3)_2$−dppp (1:1) was utilized at 55 °C under a balloon pressure of CO.

Although a variety of oxidative agents, such as $CuCl_2$ and CBr_4, were tested for the turnover of Pd(0) to Pd(II) in order to carry out a palladium-catalyzed process, current results using these oxidative agents gave only a 38% yield of the desired product **2** under conditions identical to those discussed above. Further investigation to find other oxidative agents is being carried out in our lab.

To assess the generality of the optimal reaction conditions, other *o*-alkynylphenols were prepared by Sonogashira coupling[12] (see Scheme 4) and annulated.

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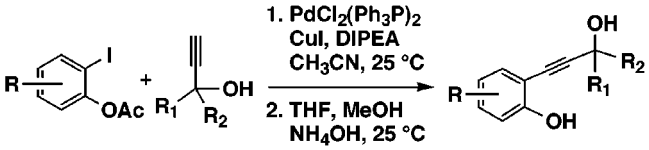
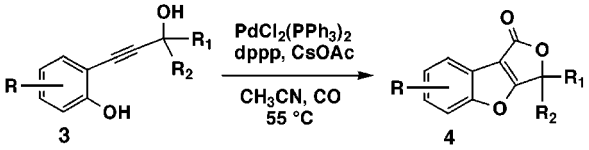
Scheme 4. Synthesis of *o*-Alkynylphenols from the Corresponding Iodophenol Acetate and Terminal Acetylenes



The Sonogashira reaction was carried out by mixing phenyl iodide, acetylene, CuI ,and $PdCl_2(Ph_3P)_2$ in dry acetonitrile, followed by treatment with DIPEA, and then stirring the solution at 25 °C for 24 h to give the *o*-alkynylphenol acetate, which was treated with NH_2NH_2 in THF to afford the desired product *o*-alkynylphenol. The detailed experimental data are summarized in the Supporting Information.

To delineate the scope of this annulation, particularly in regard to our future combinatorial library construction, we investigated the annulation of various *o*-alkynylphenols with more complex and sterically hindered substitutes, and most of them have a side chain attached to the TBS silyl protecting group. As we expected, all the selected substrates gave

Table 1. $PdCl_2(PPh_3)_2$−dppp Promoted Carbonylative Annulation of *o*-Alkynylphenols



3 4

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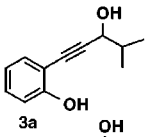
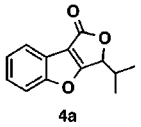
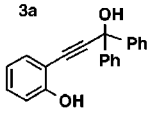
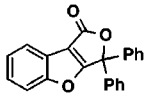
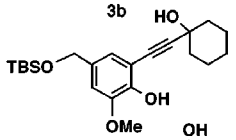
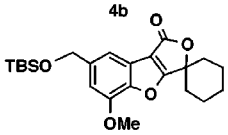
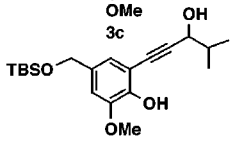
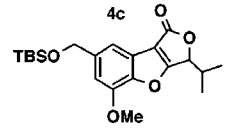
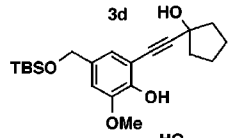
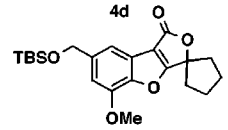
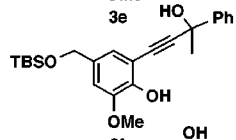
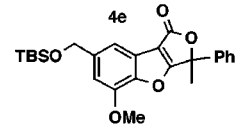
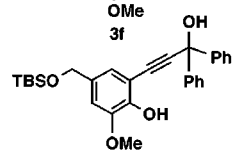
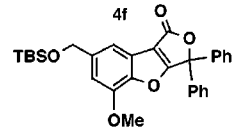
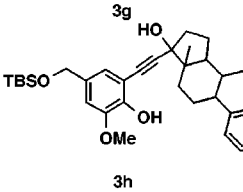
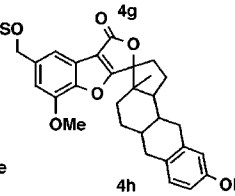
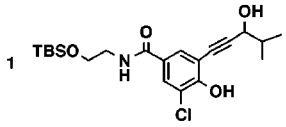
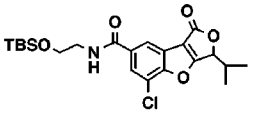
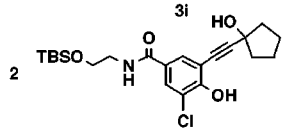
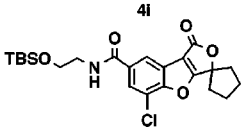
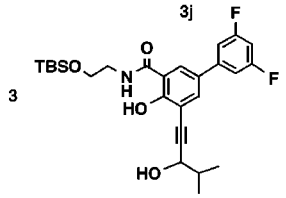
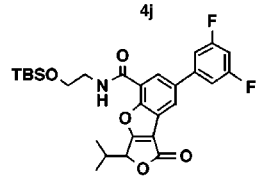
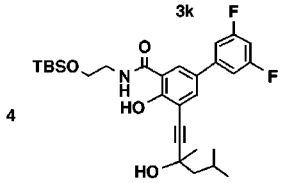
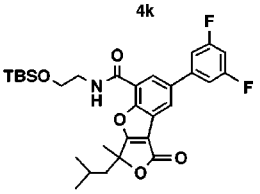
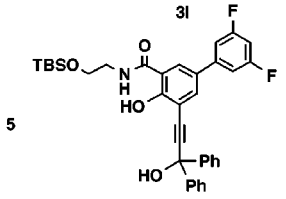
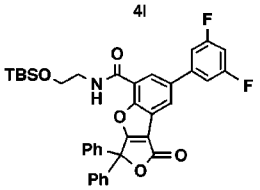
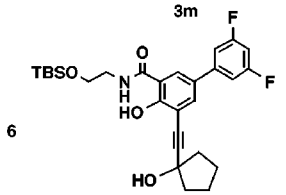
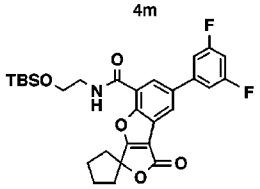
1	 3a	12	 4a	53
2	 3b	12	 4b	52
3	 3c	12	 4c	67
4	 3d	12	 4d	62
5	 3e	2	 4e	92
6	 3f	12	 4f	70
7	 3g	12	 4g	73
8	 3h	12	 4h	85

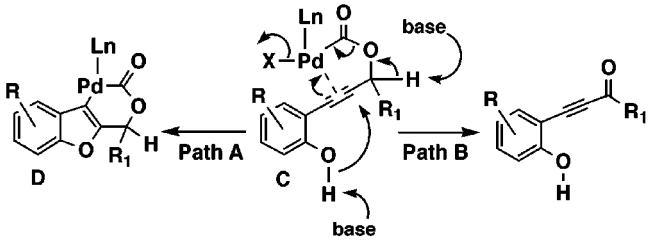
entry	phenylacetylene	time (h)	product	% yield[a]
1	 3i	12	 4i	52
2	 3j	12	 4j	83
3	 3k	12	 4k	55
4	 3l	12	 4l	69
5	 3m	12	 4m	67
6	 3n	12	 4n	76

[a] Pure product after flash chromatography and refers to a single run.

satisfactory yields and the reaction went to completion at 55 °C in less than 12 h using the conditions described.[14] Furthermore, the TBS protecting group (see products **4c**−**4n**) was found to be stable under these reaction conditions. This result is particularly important since we plan to build up a benzo[*b*]furo[3,4-*d*]furan-1-one library on silyl linker based polystyrene macrobeads.[13,14]

From the results in Table 1, we can make the following observations. (1) Considering the substitution effects of a five-membered ring (see **4e**, **4h**, **4j**, and **4n** in Table 1) and a six-membered ring (compound **2** in Scheme 2 and **4c** in Table 1) on the outcome of the cyclization, it is interesting to note that the five-membered ring based substrates give higher yields of cyclization products than that of the six-membered ring based substrates. (2) In comparison to tertiary propargylic alcohols (see **3c**, **3e**−**h**, **3j**, and **3l**−**n** in Table 1), secondary propargylic alcohols (**3a**, **3d**, **3i**, and **3k** in Table 1) gave lower yields of cyclization products, a result presumably due to the oxidation of the secondary propargylic alcohols to ketones (see Scheme 5).

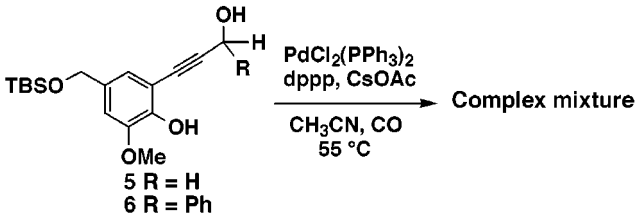
Scheme 5. Oxidation of the Secondary Propargylic Alcohols



We reasoned that two competitive paths would account for these low yields. Accordingly, the secondary propargylic alcohol based acyl−palladium complex **C** (see Scheme 5) could either undergo an intramolecular nucleophilic addition of a phenolic oxide to the acetylene to provide intermediate **D** (Path A) or be converted to a ketone by deprotonation of the α hydrogen in the propargylic alcohol portion of the molecule (Path B).

To prove this assumption, we selected two types of propargylic alcohol based *o*-alkynylphenols (Scheme 6) to carry out the annulations under conditions identical to those listed in Table 1. As expected, these two easily oxidized propargylic alcohols (primary propargylic alcohol **5** and benzylic alcohol **6**) gave unidentified complex reaction mixtures, presumably due to the decomposition of the newly generated aldehyde or ketone.

Scheme 6. Oxidation of Primary and Secondary Alcohols with Palladium(II) Species



In summary, we have developed a highly efficient synthetic methodology for carbonylative cyclization of *o*-alkynylphenols to construct the corresponding benzo[*b*]-furo[3,4-*d*]furan-1-ones, and all the products listed in Table 1 were synthesized, for the first time, with good to excellent yields. Such an efficient manipulation of multiple steps (three carbon−oxygen bonds and one carbon−carbon bond) in this particular reaction cycle combined with mild reaction conditions will make this method a general approach to the syntheses of benzo[*b*]furo[3,4-*d*]furan-1-ones.

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Supporting Information Available: Experimental procedures and ^{1}H and C^{13} NMR spectra for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Liao, Y.; Fathi, R.; Reitman, M.; Zhang, Y.; Yang, Z. *Tetrahedron Lett.* **2001**, *42*, 1815−1818.

(14) **Typical procedure used in the synthesis of benzo[*b*]furo[3,4-*d*]-furan-1-ones:** A mixture of *o*-alkylnylphenol (1.0 mmol), dppp (1.0 mmol), CsOAc (4.0 mmol), and $PdCl_2(PPh_3)_2$ (1.0 mmol) was dissolved in dry acetonitrile (5.0 mL), and the reaction mixture was degassed by CO for 10 min and then stirred at 55 °C under a balloon pressure of CO for 12 h. The reaction mixture was concentrated and the residue was filtered through a pad of silica gel and washed by EtOAc. The filtrate was concentrated, and the residue was purified by silica gel flash chromatography.