JOC Note

Palladium-Catalyzed Oxidative Alkoxylation of α-Alkenyl β-Diketones To Form Functionalized Furans

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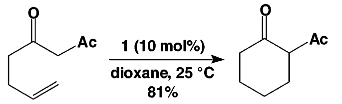
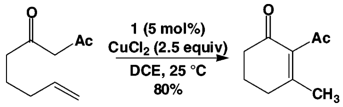
Abstract: Treatment of 4-allyl-2,6-dimethyl-3,5-heptanedione with a catalytic amount of $PdCl_2(CH_3CN)_2$ (5 mol %) and a stoichiometric amount of $CuCl_2$ (2.2 equiv) in dioxane at 60 °C for 12 h formed 3-isobutyryl-2-isopropyl-5-methylfuran in 77% isolated yield. A number of α-alkenyl β-diketones underwent oxidative alkoxylation under these conditions to form 2,3,5-trisubsituted furans in moderate to good yield.

Functionalized furans are a common component of naturally occurring and biologically active molecules,[1] pharmaceuticals,[1] and fragrance and flavoring compounds[2] and are useful building blocks for the synthesis of complex organic molecules.[3] For these reasons, the development of new and efficient methods for the synthesis of functionalized furans remains an area of current interest.[4] A particularly effective approach to the synthesis of functionalized furans is through the transition-metal-catalyzed cyclization of an alkynyl or allenyl ketone,[5] alcohol,[6] or epoxide.[7] In contrast, the transition-metal-catalyzed conversion of an alkenyl ketone, alcohol, or epoxide to a substituted furan has not been demonstrated.[8] Although olefins are significantly less reactive toward transition-metal complexes than are alkynes or allenes, olefins are more readily accessible and more easily manipulated than are alkynes or allenes. Furthermore, utilization of alkenyl substrates in the transition-metal-catalyzed synthesis of functionalized furans would significantly expand the scope of suitable starting materials for these transformations. Here, we report the palladium-catalyzed oxidative alkoxylation of α-alkenyl β-diketones to form 2,3,5-trisubstituted furans.

We have recently reported the palladium-catalyzed intramolecular hydroalkylation of 3-butenyl β-diketones to form 2-acylcyclohexanones.[9,10] For example, treatment of 7-octene-2,4-dione with a catalytic amount of $PdCl_2(CH_3CN)_2$ (**1**) formed 2-acetylcyclohexanone in 81% isolated yield (eq 1).[9] Similarly, we have reported the palladium-catalyzed intramolecular oxidative alkylation of 4-pentenyl β-diketones to form 2-acyl-2-cyclohexenones.[11] As an example, reaction of 8-nonene-2,4-dione with a catalytic amount of **1** and a stoichiometric amount of $CuCl_2$ led to the isolation of 2-acetyl-3-methyl-2-cyclohexenone in 80% yield (eq 2).[11]



eq 1



eq 2

In an effort to expand the scope of palladium-catalyzed olefin alkylation, we studied the reaction of **1** with alkenyl β-diketones in which the alkenyl group was tethered to the α-carbon atom of the β-diketone moiety. However, reaction of α-alkenyl β-diketones with **1** led not to olefin alkylation, but rather to oxidative alkoxylation to form substituted furans. For example, treatment of 4-allyl-2,6-dimethyl-3,5-heptanedione (**2**) with a catalytic amount of **1** (5 mol %) and stoichiometric amount of $CuCl_2$ (2.2 equiv) in dioxane at 60 °C for 12 h led to the isolation of 3-isobutyryl-2-isopropyl-5-methylfuran (**3**) in 77% yield (eq 3).

Palladium was required for furan formation; stirring a suspension of 4-allyl-3,5-heptanedione (**4**) and $CuCl_2$

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(8) A related transformation involving the palladium-catalyzed addition of an enolic oxygen atom to a pendant olefin terminated by β-hydroxide elimination has been previously reported,[8a] as has the synthesis of benzofurans via the palladium-catalyzed addition of a phenolic oxygen atom to a pendant olefin.[8b] (a) Tenaglia, A.; Kammerer, F. *Synlett* **1996**, 576. (b) Hosokawa, T.; Murahashi, S.-I. *Heterocycles* **1992**, *33*, 1079.

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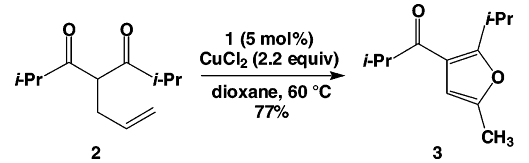
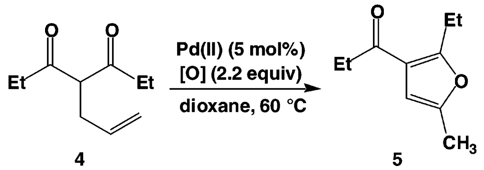


2 **3** eq 3

(2.2 equiv) in dioxane in the absence of **1** produced no detectable amounts of 2-ethyl-5-methyl-3-propionylfuran (**5**) after 21 h at 60 °C. In addition to **1**, both Pd(OAc)$_2$ and Pd(CH$_3$CN)$_4$(BF$_4$)$_2$ served as effective catalysts for the oxidative alkoxylation of α-allyl β-diketone **4** to form furan **5** (Table 1, entries 1−3). Conversely, Pd(II) sources such as PdBr$_2$, PdI$_2$, Pd(acac)$_2$, and Pd(OCOCF$_3$)$_2$ were less effective than was **1** for the conversion of **4** to **5** (Table 1, entry 4−7). 1,4-Benzoquinone also served as a terminal oxidant for the conversion of **4** to **5** catalyzed by **1**, but was inferior to CuCl$_2$ (Table 1, entry 8).

TABLE 1. Effect of Pd Source and Oxidant on Conversion of 4 to 5 in Dioxane at 60 °C



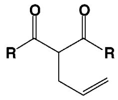
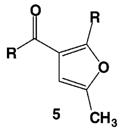
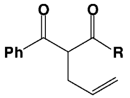
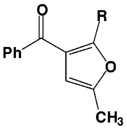
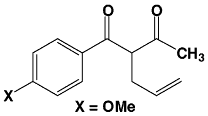
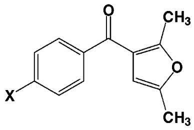
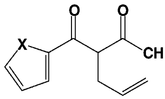
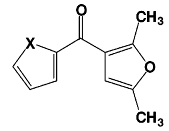
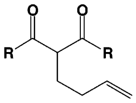
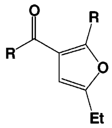
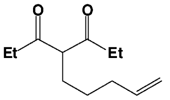
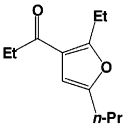
4 **5**

entry	Pd(II) source	time (h)	[O]	yield[a] (%)
1	**1**	17	CuCl$_2$	80
2	Pd(OAc)$_2$	19	CuCl$_2$	78
3	Pd(CH$_3$CN)$_4$(BF$_4$)$_2$	17	CuCl$_2$	80
4	PdBr$_2$	22	CuCl$_2$	61
5	PdI$_2$	22	CuCl$_2$	14
6	Pd(acac)$_2$	17	CuCl$_2$	62
7	Pd(OCOCF$_3$)$_2$	19	CuCl$_2$	58
8	**1**	22	*p*-benzoquinone	63

[a] As determined by GC analysis of the crude reaction mixture.

A number of α-allyl β-diketones in addition to **2** and **4** underwent oxidative alkoxylation in the presence of a catalytic amount of **1** and a stoichiometric amount of CuCl$_2$ to form substituted furans (Table 2, entries 1−9). Noteworthy was that palladium-catalyzed cyclization of 2-allyl-1-phenyl-1,3-butanedione led to exclusive incorporation of the acetyl group into the furan ring to form 3-benzoyl-2,5-dimethylfuran in 63% isolated yield (Table 2, entry 3). The palladium-catalyzed oxidative alkoxylation of 2-allyl-1-aryl-1,3-diones was general and tolerated a variety of alkyl and aryl groups (Table 2, entries 4−9). Palladium dichloride complexes catalyze olefin isomerization,[12] and it is likely for this reason that β-diketones that possessed either an α-3-butenyl or α-4-pentenyl group underwent palladium-catalyzed oxidative alkoxylation to form 5-ethyl or 5-propyl furans, respectively, in modest yield (Table 2, entries 10−12). In contrast to α-allyl β-diketones, α-allyl β-keto esters failed to undergo palladium-catalyzed oxidative alkoxylation, presumably due to the lower reactivity of a β-keto ester relative to a β-diketone.[13]

TABLE 2. Oxidative Alkoxylation of α-Alkenyl β-Diketones Catalyzed by 1 (5 mol %) in the Presence of CuCl$_2$ (2.2 equiv) in Dioxane at 60 °C

entry	diketone	furan	yield (%)[a]
			
1	R = Et (**4**)	**5**	68
2	R = Ph		72
			
3	R = Me		63
4	R = *n*-pentyl		62
5	R = (CH$_2$)$_3$OMe		61
			
6	X = OMe		63
7	X = CF$_3$		65
			
8	X = O		71
9	X = S		63
			
10	R = Et		46[b]
11	R = *i*-Pr		43[b]
12			42[b]

[a] Isolated material of ≥95% purity with ≥98% isomeric purity. [b] The remainder of the reaction mixture consisted of isomerized and reduced starting materials as determined by GC/MS analysis.

We have formulated a working mechanism for the palladium-catalyzed oxidative alkoxylation of α-allyl β-diketones that is based on the proposed mechanism of the Wacker oxidation.[14] Attack of enolic oxygen atom on the palladium-complexed olefin of **I** coupled with loss of HCl would form the palladium dihydrofurylmethyl intermediate **II**. Intermediate **II** could undergo β-hydride elimination to form palladium 2-methylene-2,3-dihydrofuran complex **III** (Scheme 1). Because formation of a transition metal tertiary alkyl bond via β-hydride addition is slow,[15] and because 2-methylene-2,3-dihydrofurans undergo facile acid-catalyzed isomerization,[16] it appears unlikely that conversion of the initially formed 2-methylene-2,3-dihydrofuran of intermediate **III** to furan **B**

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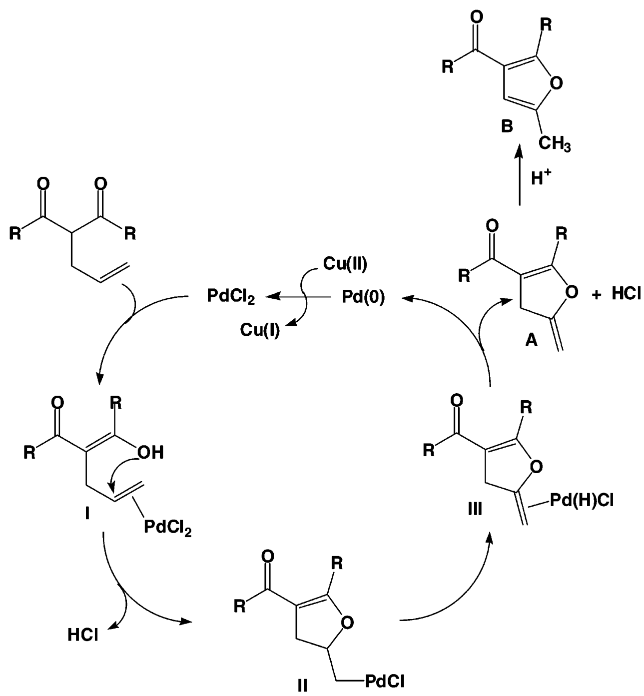
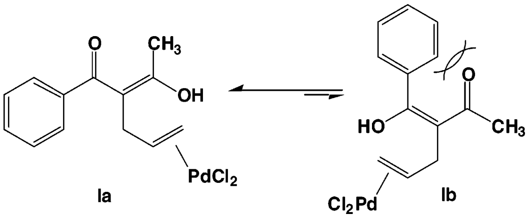
SCHEME 1



SCHEME 2



occurs within the coordination sphere of palladium (Scheme 1). Rather, we propose that furan **B** is formed via displacement of 2-methylene-2,3-dihydrofuran (**A**) from palladium olefin complex **III** followed by acid-catalyzed isomerization of **A** to **B** (Scheme 1).

Palladium-catalyzed cyclization of 2-allyl-1-aryl-1,3-diones, such as 2-allyl-1-phenyl-1,3-butanedione, led to exclusive incorporation of the alkyl carbonyl group into the furan ring (Table 1, entries 3−9). Because β-diketones exist predominantly as the enol tautomer in nonpolar solvents,[13] and because a β-diketone group was required for effective cyclization, it appears likely that C−O bond formation involves attack of an enol hydroxyl oxygen atom, rather than a carbonyl oxygen atom, on the pendant olefin (Scheme 1). On the basis of this assumption, we propose that exclusive incorporation of the alkyl carbonyl group into the furan ring results from the predominant formation of palladium olefin intermediate **Ia** in preference to **Ib** (Scheme 2). Unfavorable steric interaction between the aryl group and alkyl carbonyl group of **Ib** likely precludes conjugation of the aryl group with the enolic π-system. Because no such steric interaction is present in intermediate **Ia**, **Ia** should form in preference to **Ib**, which will lead to preferential incorporation of the alkyl carbonyl group into the furan ring provided that intermediates **Ia** and **Ib** cyclize at comparable rates.

In summary, we have developed an efficient, one-pot procedure for the conversion of α-alkenyl β-diketones to 2,3,5-trisubstituted furans. Because a diverse range of α-alkenyl β-diketones can be easily prepared, the palladium-catalyzed oxidative alkoxylation of α-alkenyl β-diketones represents an attractive means for the synthesis of highly substituted furans.

Experimental Section

3-Isobutyryl-2-isopropyl-5-methylfuran (3). A suspension of 4-allyl-2,6-dimethyl-3,5-heptanedione (**2**) (99 mg, 0.51 mmol), $PdCl_2(MeCN)_2$ (**1**) (7 mg, 0.026 mmol), and $CuCl_2$ (151 mg, 1.12 mmol) in dioxane (5.1 mL) was stirred at 60 °C for 12 h. The reaction mixture was cooled to room temperature, filtered through a plug of silica gel, and eluted with ether. The filtrate was concentrated under vacuum and chromatographed (hexanes−ether = 15:1) to give 3-isobutyryl-2-isopropyl-5-methylfuran (**3**) (75 mg, 77%) as a colorless oil. TLC: $R_f = 0.67$. ^{1}H NMR: δ 6.16 (br s, 1 H), 3.72 (septet, $J = 6.8$ Hz, 1 H), 3.02 (septet, $J = 6.8$ Hz, 1 H), 2.25 (d, $J = 1.2$ Hz, 3 H), 1.22 (d, $J = 6.8$ Hz, 6 H), 1.12 (d, $J = 6.8$ Hz, 6 H). ^{13}C{^{1}H} NMR: δ 201.4, 166.2, 149.9, 119.0, 106.0, 38.6, 27.7, 21.0, 19.0, 13.6. IR (neat, cm^{-1}): 1673 ($\nu_{C=O}$). Anal. Calcd (found) for $C_{12}H_{18}O_2$: C, 74.19 (74.06); H, 9.34 (9.42).

The remaining furans were synthesized employing a procedure similar to that used to synthesize **3**; isolated yields are given in Table 2.

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Supporting Information Available: Experimental procedures and spectroscopic data for new compounds and furans and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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