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Furan Synthesis

Tetrasubstituted Furans by a Pd^{II}-Catalyzed Three-Component Michael Addition/Cyclization/Cross-Coupling Reaction **

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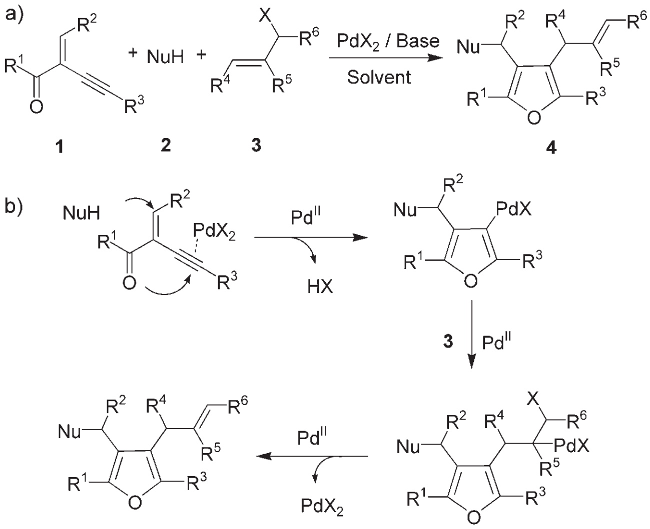
The design and discovery of new reactions for the synthesis of highly substituted furans has been stimulated by their appearance in many bioactive natural products and important pharmaceuticals.[1,2] There has been recent focus on the development of metal-catalyzed one- or two-component reactions for synthesis of these types of compounds, including the cyclization of allenyl ketones,[3] 3-alkyn-1-ones,[3k,4] 1-(1-alkynyl)-cyclopropyl ketones,[5] (*Z*)-2-en-4-yn-1-ols,[6] and 2-(1-alkynyl)-2-alken-1-ones,[7] and cycloisomerization of cyclopropyl ketones[8]/cyclopropenyl ketones.[9] Recently, the design of multicomponent reactions[10] that preserve atom economy in a one-pot reaction has attracted attention becasue of the application to efficient construction of molecular structures. Herein we report results of a Pd^{II}-catalyzed three-component Michael addition/cycliztion/cross-coupling reaction to afford highly functionalized tetrasubstituted furans.[11]

As a continuation of our interest in the design and discovery of new reactions for the synthesis of highly substituted furans,[5,8,9b] we envisioned that 2-(1-alkynyl)-2-alken-1-ones might react with nucleophiles and an allyl halide in the presence of a catalytic Pd^{II} species that might exhibit dual roles, serving simultaneously as a Lewis acid and a transition metal (Scheme 1). First, Pd^{II} acts as a Lewis acid and a transition metal to facilitate both the nucleophilic addition step and the cyclization step[12] to afford a furanyl–palladium intermediate, which then reacts with the allyl halide by insertion and subsequent β-halide elimination to provide product furans and regenerate the PdX_2 catalyst. To the best of our knowledge, only one example of $Pd(OAc)_2$ serving as a dual role catalyst exists.[13] Herein we present our recent results on the $[PdCl_2(CH_3CN)_2]$-catalyzed three-component Michael addition/cyclization/cross-coupling of 2-(1-alkynyl)-2-alken-1-ones **1** with various nucleophiles and allyl chlorides.



Scheme 1. a) General reaction scheme for the Pd^{II}-catalyzed three-component reaction to afford highly substituted furans. b) Propsed reaction pathway for the reaction in (a). In the first step the Pd^{II} serves as a Lewis acid and a transition metal, and in subsequent steps the Pd^{II} serves as a transition metal.

First, we examined the reaction of 2-phenylethynyl-3-phenyl-2-butylene-1-one (**1a**) with MeOH and allyl chloride (**3a**) under different reaction conditions. After numerous attempts, we isolated the desired product **4aaa** in 75% yield after running the reaction for 24 hours at room temeprature in CH_3CN with $[PdCl_2(CH_3CN)_2]$ (5 mol%) as the catalyst, methanol (4.0 equiv) as the nucleophile, allyl chloride (4.0 equiv) as the allylating reagent, and K_2CO_3 (4.0 equiv) as the base. Only trace amounts (<1%) of the furan generated by the competitive side reaction from protonation could be detected by ^1H NMR spectra analysis (Table 1, entry 6). Alternate conditions, such as lowering the equivalents of the base, MeOH, or allylic chloride or changing the solvent or the base lead to a lower yield of the product (Table 1, entries 1–12). Surprisingly, when allyl bromide (even 10 equiv) was used instead of allyl chloride, the reaction proceeded slowly to give the desired furan in 37% yield (determined by ^1H NMR spectroscopy) after 48 hours. We deduced that relative to $[PdCl_2(CH_3CN)_2]$, the weak Lewis acid $[PdBr_2(CH_3CN)_2]$ that is generated in the reaction is not strong enough to activate the substrate. To support this deduction, two control reactions were carried out under the standard conditions with the exception that 20 mol% of Ph_3P (Table 1, entry 14) or 1 equivalent of KBr (Table 1, entry 15) was added; neither of the reactions worked well and the yield of the product was not more than 20%, thus, further verifying that $[PdCl_2(CH_3CN)_2]$ is a stronger Lewis acid than [PdBr$_2$-

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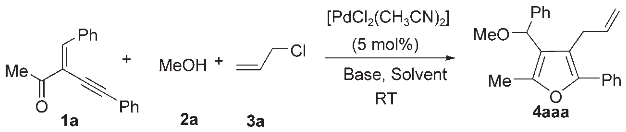
Table 1: Screening of reaction conditions for the three-component Michael addition/cyclization/cross-coupling reaction.[a]



Entry	Base (equiv)	**2a/3a** [equiv]	Solvent	*t* [h]	Yield [%][b]
1	none	4.0/4.0	CH_3CN	36	0
2	Na_2CO_3(4.0)	4.0/4.0	CH_3CN	36	41
3	$NaHCO_3$(4.0)	4.0/4.0	CH_3CN	36	50
4	K_3PO_4 (4.0)	4.0/4.0	CH_3CN	36	62
5	Cs_2CO_3 (4.0)	4.0/4.0	CH_3CN	24	42
6	K_2CO_3(4.0)	4.0/4.0	CH_3CN	24	88(75)
7	K_2CO_3(2.0)	4.0/4.0	CH_3CN	24	80
8	K_2CO_3(2.0)	2.0/2.0	CH_3CN	24	53
9	K_2CO_3(2.0)	2.0/4.0	CH_3CN	24	62
10	K_2CO_3(4.0)	4.0/4.0	THF	24	52
11	K_2CO_3(4.0)	4.0/4.0	1,4-dioxane	24	68
12	K_2CO_3(4.0)	4.0/4.0	DMF	24	69
13[c]	K_2CO_3(4.0)	4.0/4.0	CH_3CN	24	0
14[d]	K_2CO_3(4.0)	4.0/4.0	CH_3CN	24	0
15[e]	K_2CO_3(4.0)	4.0/4.0	CH_3CN	24	20
16[f]	K_2CO_3(4.0)	4.0/4.0	CH_3CN	48	37
17[g]	K_2CO_3(4.0)	4.0/4.0	CH_3CN	48	78

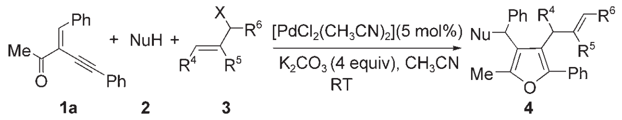
[a] Reactions run with **1a** (0.5 mmol) at room temperature. [b] Yields were determined by ^1H NMR spectroscopy using CH_2Br_2 as an internal standard; yields of isolated product are shown in parentheses. [c] 5 mol% of $[Pd(PPh_3)_4]$ was used. [d] 20 mol% of Ph_3P was added. [e] 1.0 equiv of KBr was added. [f] 10 equiv of allyl bromide used instead of allyl chloride. [g] 5 mol% of allylpalladium chloride dimer was used.

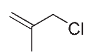
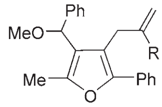
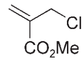
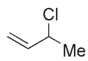
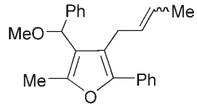
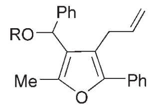
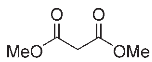
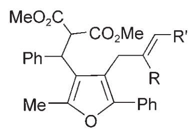
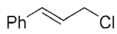
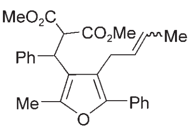
$(CH_3CN)_2]$ and $[PdCl_2(PPh_3)_2]$ (generated by adding Ph_3P to the mixture). In addition, no reaction occurred when $[Pd(PPh_3)_4]$ was employed as the catalyst instead of $[PdCl_2(CH_3CN)_2]$. All these observations indicate that $[PdCl_2(CH_3CN)_2]$, acting simultaneously as a Lewis acid and a transition-metal catalyst, is the key to making this transformation work well.[14]

To determine the scope of this transformation, we studied the reaction of **1a** with various nucleophiles **2** and allyl chlorides **3**, and the results are listed in Table 2. Notably: 1) Alcohols other than methanol, such as isopropanol, benzyl alcohol, and phenol, can act as O nucleophiles to give tetrasubstituted furans in moderate to excellent yields (Table 2, entries 1–6); 2) Dimethyl malonate can act as a nucleophilic component to allow the introduction of more functional groups (Table 1, entries 7–11); 3) Substituted allyl chlorides, such as **3b–d**, can be used as allylating reagents to give more functionalized furans in good yields (Table 2, entries 1–3, 8–11); 4) The coupling occurs exclusively at the less substituted terminus of the allyl chloride and the configuration of the C=C bond in 3-phenyl-2-propenyl chloride **3e** remained intact when it was introduced as the allylating agent (Table 2, entry 10), a result that was consistent with previous findings.[3g]

This transformation can be successfully extended to a variety of 2-(1-alkynyl)-2-alken-1-ones **1** leading to the generation of the corresponding tetrasubstituted furan in 40–91% yield (Table 3, entries 1–7). The substituents on the

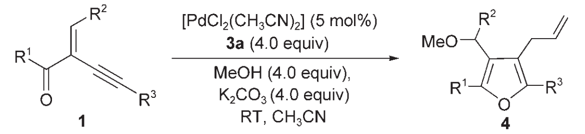
Table 2: Scope of the $[PdCl_2(CH_3CN)_2]$-catalyzed three-component Michael addition/cyclization/cross-coupling of **1a**.[a]

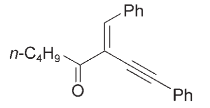
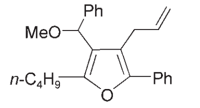
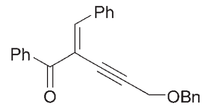
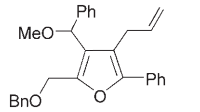
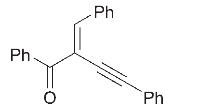
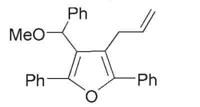
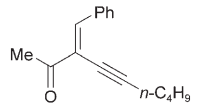
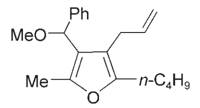
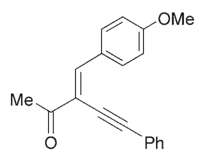
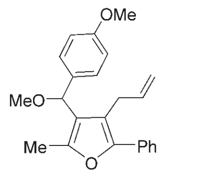
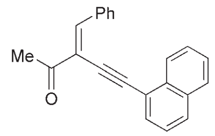
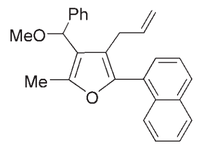
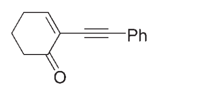
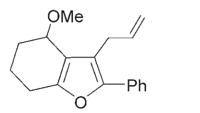
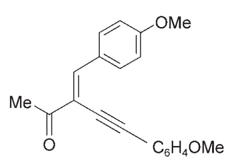
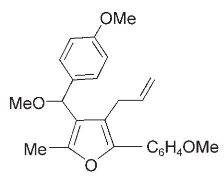


Entry	NuH (**2**)	**3**	*t* [h]	Yield (**4**)[a]
1	MeOH **2a**	 **3b**	14	 R = Me, **4aab**,[f] 66%
2[b]	**2a**	 **3c**	36	R = CO_2Me, **4aac**, 70%
3	**2a**	 **3d**	48	 **4aad**, 89%
4[b,c]	*i*PrOH **2b**	**3a**	72	 R = *i*Pr, **4aba**, 42%
5	BnOH **2c**	**3a**	24	R = Bn, **4aca**, 63%
6	PhOH **2d**	**3a**	24	R = Ph, **4ada**, 66%
7[d]	 **2e**	**3a**	10	 R = H, R' = H, **4aea**, 91%
8[d]	**2e**	**3b**	12	R = Me, R' = H, **4aeb**, 62%
9[d]	**2e**	**3c**	20	R = CO_2Me, R' = H, **4aec**, 54%
10[d,e]	**2e**	 **3e**	24	R = H, R' = Ph, **4aee**, 79%
11[d]	**2e**	**3d**	24	 **4aed**, 85%

[a] Unless otherwise specified, reactions were carried out under standard conditions. Reported yields are of the isolated product. [b] Additional $[PdCl_2(CH_3CN)_2]$ (5 mol%) was added after the reaction was stirred for 24 h. [c] Used *i*PrOH (6.0 equiv) and allyl chloride (6.0 equiv). [d] 2.0 equiv of dimethyl malonate were used. [e] Additional 0.5 equiv of dimethyl malonate was added after the reaction was stirred for 12 h. [f] The designation **4aab** for the product indicates that the reactants used were **1a**, **2a**, and **3b**, respectively.

Table 3: $[PdCl_2(CH_3CN)_2]$-catalyzed three-component Michael addition/cyclization/cross-coupling of various 2-(1-alkynyl)-2-alken-1-ones **1** with MeOH and allyl chloride.[a]



Entry	1	t [h]	Yield 4[b]
1	 **1b**	30	 **4baa**, 77%
2	 **1c**	24	 **4caa**, 80%
3	 **1d**	24	 **4daa**, 91%
4[c]	 **1e**	43	 **4eaa**, 40%
5	 **1f**	36	 **4faa**, 73%
6	 **1g**	18	 **4gaa**, 65%
7	 **1h**	24	 **4haa**, 57%
8	 **1i**	72	 **4iaa**, 63%

[a] Unless otherwise noted the reactions were performed under standard conditions. [b] Yield of isolated product. [c] Reaction conditions: MeOH (8.0 equiv), allyl chloride (8.0 equiv), K_2CO_3 (6.0 equiv), and $[PdCl_2(CH_3CN)_2]$ (10 mol%).

alkynes can affect the reaction; for example, alkynes bearing aryl groups afford relatively higher yields than those bearing alkyl groups (Table 3, compare entry 1 to entry 4). The type of nucleophile also affects the yield and the rate of the reaction (compare entries 4–7 in Table 2). Cyclic substrate **1h** also affords a fused furan in 57% yield under these reaction conditions (Table 3, entry 7). The results in Tables 2 and 3 clearly show that our new approach to tetrasubstituted furans allows easy introduction of various functional groups, such as alkoxy groups, aryloxy groups, and dimethyl malonate groups, as well as various types of allylic groups directly incorporated into the furan ring. The new method provides opportunities for further elaboration of the functional groups on the polysubstitued furans.

In conclusion, we have developed a $[PdCl_2(CH_3CN)_2]$-catalyzed three-component Michael addition/cyclization/cross-coupling reaction that provides an efficient route to functionalized tetrasubstituted furans. We found that $[PdCl_2(CH_3CN)_2]$ plays a dual role in this transformation. This finding will be helpful to other cases in which activation of a carbonyl group or related functional group, such as enone (Lewis acid role), and activation of a double or triple bond (transition-metal role) are desired to occur simultaneously. As all three starting materials are readily available, this method may allow the synthesis of more complex furans. Further studies on the scope and synthetic applications of this methodology are currently being carried out in our laboratory.

Experimental Section

Typical procedure for the synthesis of **4aaa** (Table 1, entry 6): $[PdCl_2(CH_3CN)_2]$ (6.0 mg, 0.025 mmol) was added to a mixture of **1a** (123.0 mg, 0.5 mmol), MeOH (64.0 mg, 2.0 mmol), allyl chloride (153.0 mg, 2.0 mmol), and K_2CO_3 (276.0 mg, 2.0 mmol) in CH_3CN (2.0 mL) at room temperature. The reaction mixture was stirred for 24 h, at which time **1a** was consumed completely according to TLC analysis, and then concentrated in vacuo after filtration. The residue was purified by column chromatography on silica gel (petroleum ether/Et_2O = 10:1) to give desired product **4aaa** (119 mg) in 75% yield as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) : δ = 7.66–7.59 (m, 2H), 7.40–7.34 (m, 6H), 7.28–7.20 (m, 2H), 5.90–5.78 (m, 1H), 5.29 (s, 1H), 5.04–4.96 (m, 2H), 3.41 (s, 3H) 3.29–3.25 (m, 2H), 2.30 ppm (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 149.04, 148.00, 141.30, 135.86, 131.43, 128.43, 128.20, 127.19, 126.72, 126.64, 125.36, 120.86, 118.36, 115.45, 77.38, 56.78, 28.29, 12.58 ppm; MS (70 eV): m/z (%):318 (3.10) [M^+], 105 (100) $[C_6H_5CO]^+$, HRMS calcd for $C_{22}H_{22}O_2$: 318.1620, found: 318.1620.

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