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Palladium-Catalyzed Formation of C=C Bonds: A Regioselective Strategy for the Synthesis of 2-Vinylfurans by 1,2-H Shift of Palladium–Carbene Complexes

Haiying Zhan,[a] Xiulian Lin,[a] Yanying Qiu,[a] Zuodong Du,[a] Peixian Li,[a] Yongjian Li,[a] and Hua Cao*[a]

Keywords: Synthetic methods / Palladium / Oxygen heterocycles / Carbenes / Ene–yne ketones / Cyclization

A convenient method to synthesize vinylfurans through a palladium-catalyzed cyclization/1,2-H shift sequence under mild conditions is described. This is an efficient strategy to synthesize 2-vinylfurans from ene–yne ketones, and the corresponding products are obtained in good yields.

Introduction

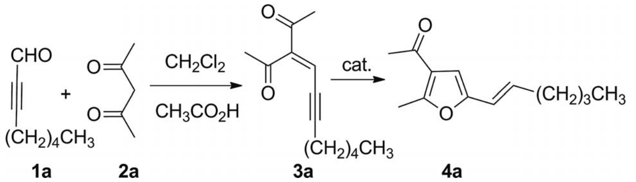
Furans represent a ubiquitous structural motif in nature and are also present in many natural products.[1] Furans and related compounds belong to one of the most important members of the family of heterocycles, and they find a variety of applications in pharmaceuticals, flavors, and fragrances.[2] Currently, two general approaches are commonly used for the construction of multisubstituted furan derivatives: (1) Paal–Knorr synthesis and (2) transition-metal-catalyzed cyclization of allenyl ketones,[3] alkynyl ketone,[4] alkynyl epoxides,[5] enynols,[6] or propargyl ethers.[7] Prominent among these processes are palladium-catalyzed organic transformations.[8] The historical, mechanistic, theoretical, and practical aspects of these processes have been amply discussed.[9] In addition, the development of new methodologies to synthesize multisubstituted furan derivatives under mild conditions is of extraordinary interest.

Recently, elegant studies were reported by Herndon,[10] Uemura,[11] and Vicente and López[12] for the synthesis of furans through the cyclization of ene–yne ketones. In particular, Herndon described an efficient method for the coupling of enyne aldehydes or ketones with methylcarbene complexes for the synthesis of vinylfurans. However, palladium-catalyzed direct synthesis of vinylfurans from ene–yne ketones has not been disclosed. Here, we report a more direct approach with the use of ene–yne ketones as starting materials for the synthesis of 2-vinylfurans through a palladium-catalyzed cyclization/1,2-H shift sequence.

Results and Discussion

Initially, oct-2-ynal (**1a**) and pentane-2,4-dione (**2a**) were used as model substrates to optimize the reaction conditions (Table 1). The intermediate product, **3a**, was easily prepared through Knoevenagel condensation of **1a** with **2a** in the presence of AcOH in DMF at room temperature for 1 h. Subsequently, our study focused on the cyclization of

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	T [°C]	t [h]	Solvent	Yield [%][b]
1	$Pd(OAc)_2$	60	12	DMF	16
2	$PdCl_2$	60	12	DMF	9
3	$Pd(dba)_2$	60	12	DMF	trace
4	$Pd(CH_3CN)Cl_2$	60	12	DMF	11
5	$Pd(OAc)_2$	80	12	DMF	6
6	$Pd(OAc)_2$	100	12	DMF	trace
7	$Pd(OAc)_2$	r.t.	12	DMF	81
8	$Pd(OAc)_2$	r.t.	24	DMF	80
9	$Pd(OAc)_2$	r.t.	6	DMF	81
10	$Pd(OAc)_2$	r.t.	4	DMF	74
11	$Pd(OAc)_2$	r.t.	6	toluene	79
12	$Pd(OAc)_2$	r.t.	6	CH_2Cl_2	84
13	$Pd(OAc)_2$	r.t.	6	CH_3OH	87
14	$Pd(OAc)_2$	r.t.	6	CH_3CN	82
15	$Pd(OAc)_2$	r.t.	6	dioxane	77
16	–	r.t.	6	CH_3OH	n.p.[c]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), catalyst (2.5 mol-%), solvent (2.0 mL), r.t. to 100 °C. [b] GC yield. [c] n.p. = no product.

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[a] School of Chemistry and Chemical Engineering, Guangdong Pharmaceutical University,
Guangzhou 510006, P. R. China
Fax: +86-760-88207939
E-mail: caohua@gdput.edu.cn
Homepage: http://www.gdpu.edu.cn/

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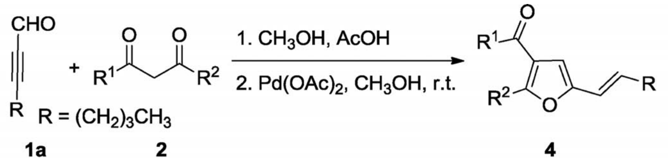
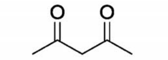
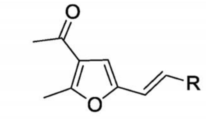
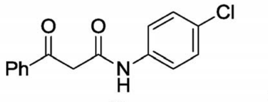
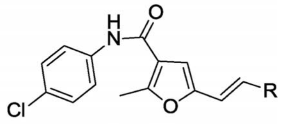
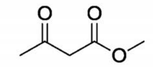
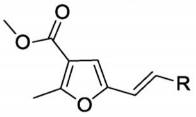
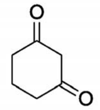
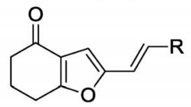
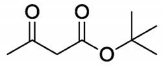
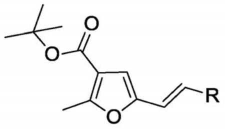
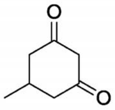
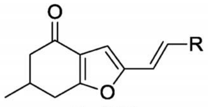
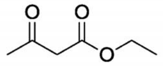
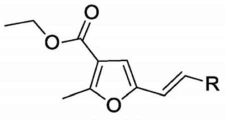
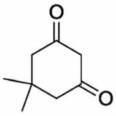
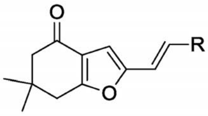
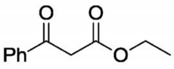
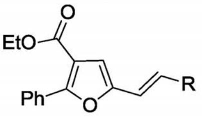
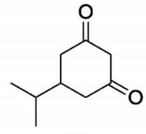
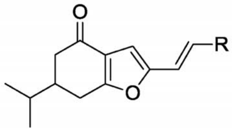
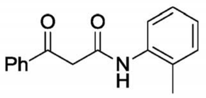
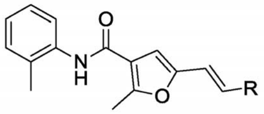
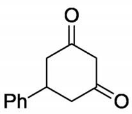
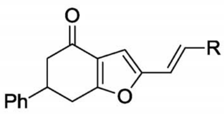
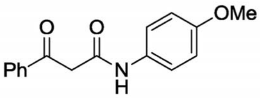
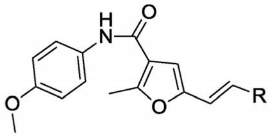
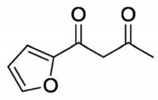
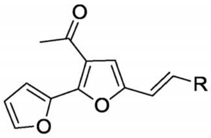
3a by testing various Pd catalysts (Table 1, entries 1–4). $Pd(OAc)_2$ was a better Pd catalyst than other Pd catalysts, and it gave corresponding product **4a** in 16% yield (Table 1, entry 1). We thought that product **4a** was obtained in very low yield because of the decomposition of intermediate product **3a** at the high temperature at which the reaction was performed. Thus, the effects of the temperature were next examined (Table 1, entries 5–7). To our delight, when the reaction was carried out at room temperature with $Pd(OAc)_2$ (2.5 mol-%) in DMF, product **4a** was formed in 81% yield (Table 1, entry 7). Thus, this transformation is temperature sensitive. Subsequently, we attempted to improve the yields by adjusting the reaction time and the solvent. It was pleasing to find that **4a** was generated in 81% yield after only 6 h. Among the solvents tested, including DMF, toluene, CH_2Cl_2, THF, CH_3CN, and 1,4-dioxane, CH_3OH was clearly the best solvent (Table 1, entry 13). These preliminary results revealed that $Pd(OAc)_2$ acts as a good catalyst for the cyclization of **3a** in CH_3OH at 60 °C for 6 h.

Table 2. Pd-catalyzed synthesis of furans.[a]



Entry	2	Product (% yield)[b]	Entry	2	Product (% yield)[b]
1	 **2a**	 **4a** (80)	8	 **2h**	 **4h** (87)
2	 **2b**	 **4b** (81)	9	 **2i**	 **4i** (79)
3	 **2c**	 **4c** (84)	10	 **2j**	 **4j** (82)
4	 **2d**	 **4d** (81)	11	 **2k**	 **4k** (84)
5	 **2e**	 **4e** (82)	12	 **2l**	 **4l** (78)
6	 **2f**	 **4f** (84)	13	 **2m**	 **4m** (84)
7	 **2g**	 **4g** (86)	14	 **2n**	 **4n** (80)

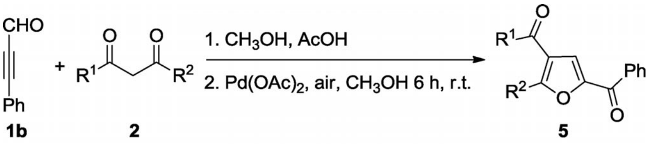
[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), $Pd(OAc)_2$ (2.5 mol-%), CH_3OH (2 mL), r.t., 6 h. [b] Isolated yield.

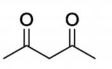
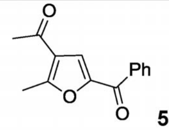
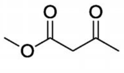
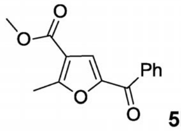
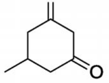
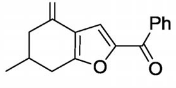
With the optimal reaction conditions in hand, we explored the scope of this $Pd(OAc)_2$-catalyzed approach, and the results are outlined in Table 2. We used **1a** as a fixed substrate to examine the reactions with various types of 1,3-dicarbonyl compounds. First, open-chain 1,3-dicarbonyl compounds were treated with **1a** under the optimized reaction conditions, and the desired vinylfurans were obtained in good yields (Table 2, entries 1–8). Notably, when substrates **2f**, **2g**, and **2h** were employed in the reaction, corresponding products **4f**, **4g**, and **4h** were obtained in 84, 86, and 87 % yield, respectively (Table 2, entries 6–8). All these cases showed high functional group tolerance [R^2 = CH_3, CH_3O, EtO, $(CH_3)_3CO$, *o*-CH_3-PhNH, *p*-CH_3O-PhNH, *p*-Cl-PhNH; R^3 = CH_3, Ph]. We were next interested in evaluating the scope of this $Pd(OAc)_2$-catalyzed transformation by using commercially available cyclohexane 1,3-diones as substrates. It was pleasing to find that the reactions of cyclic 1,3-dicarbonyl compounds **2i**–**m** proceeded smoothly in CH_3OH with $Pd(OAc)_2$ at room temperature to afford the corresponding products in good yields (Table 2, entries 9–13). These results indicated that both open and cyclic 1,3-dicarbonyl compound are suitable partners in this process and that the catalytic system is applicable for this cyclization strategy to prepare 2-vinylfurans. Importantly, when the reaction was performed with unsymmetrical 1,3-dione **2n**, product **4n** was obtained in 80 % yield with complete control of regiochemistry (Table 2, entry 14). No other regioisomers were detected in the process, which clearly shows that this cyclization is regioselective and chemoselective.

Extending the investigation further, substrate **1b** was also tested, and the results showed that the cycloisomerization/carbene oxidation sequence allowed the formation of the corresponding α-carbonyl furan, which represents a new approach to the construction of C–O bonds. Interestingly, this strategy was achieved perfectly by treatment of intermediate products **3** in the presence of $Pd(OAc)_2$ (2.5 mol-%) at room temperature in CH_3OH (Table 3). Both open-chain 1,3-dicarbonyl compounds and a cyclohexane 1,3-dione were suitable for this transformation, and corresponding products **5a**, **5b**, and **5c** were obtained in 48, 42, and 41 % yield, respectively. These results were obtained because **1a** possesses two hydrogen atoms at C-4, which undergo 1,2-H shift, whereas substrate **1b** does not contain any hydrogen atoms at this position. Thus, the shift is difficult in **1b**, as it would destroy conjugation of the benzene ring, and instead carbene oxidation occurs easily.

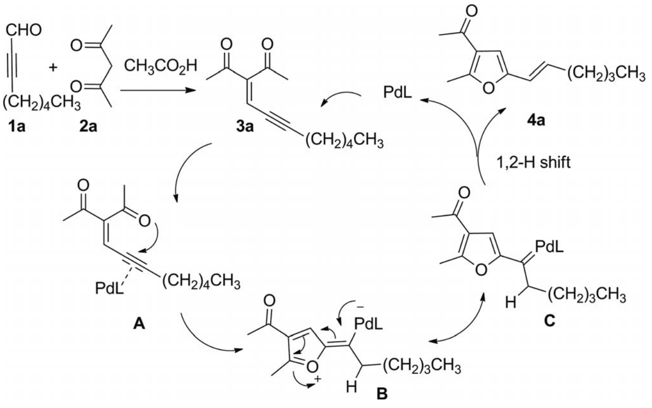
The most plausible Pd-catalyzed reaction mechanism for the cyclization of the ene–yne ketones is illustrated in Scheme 1. Intermediate product **3a** is easily formed by AcOH-catalyzed intermolecular dehydration of **1a** with **2a**. Product **3a** reacts with palladium metal to generate the palladium(II)–alkyne complex, which undergoes nucleophilic attack by the carbonyl oxygen atom to afford zwitterionic vinylpalladium complex **B**, which is a resonance structure of **C**. Finally, product **4a** is formed by 1,2-H migration of Pd–carbene complex **C**.[13] A similar carbene intermediate and transformation has been mentioned in previous studies.[14]

Table 3. Formation of 2-carbonylfurans.



Entry	2	Product (% yield)[a]
1		 **5a** (48)
2		 **5b** (42)
3		 **5c** (41)

[a] Isolated yield.



Scheme 1. Proposed mechanism.

Conclusions

In conclusion, we have developed an efficient one pot $Pd(OAc)_2$-catalyzed cyclization reaction of ene–yne ketones. This is a new approach for synthesis of α-vinylfurans through a palladium-catalyzed cyclization/1,2-H shift sequence. The reaction provides a convergent approach to the formation of C=C and C–O bonds for the synthesis of furan derivatives in good to excellent yields. Further studies will focus on utilizing ene–yne ketones in organic synthesis and will be reported in future publications.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterizations of compounds **4a**–**4n**, **5a**–**5b**.

Acknowledgments

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