Tetrahedron Letters 50 (2009) 4744–4746

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Palladium(II) catalyzed carbonylative dimerization of allenyl ketones: efficient synthesis of difuranylketones

Keisuke Kato [a,*], Tomoyuki Mochida [b], Hiroyuki Takayama [c], Masayuki Kimura [c], Hiroshi Moriyama [d], Akihito Takeshita [d], Yuichro Kanno [a], Yoshio Inouye [a], Hiroyuki Akita [a,*]

[a] Faculty of Pharmaceutical Sciences, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan
[b] Department of Chemistry, Faculty of Science, Kobe University, Rokkodai, Nada, Kobe 657-8501, Japan
[c] School of Pharmacy, Nihon Pharmaceutical University, 10281, Komuro, Inamachi, Kita-Adachigun, Saitama, Japan
[d] Department of Chemistry, Faculty of Science, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274-8510, Japan

ARTICLE INFO

Article history:
Received 5 May 2009
Revised 30 May 2009
Accepted 5 June 2009
Available online 7 June 2009

Keywords:
Palladium
Carbonylative dimerization
Difuranylketone

ABSTRACT

Palladium(II) catalyzed carbonylation of 1,2-allenyl ketones **1** in the presence of *p*-benzoquinone (1 equiv) under a CO atmosphere (balloon) afforded difuranylketones **4** in moderate to good yields. Mechanistically, the electron-withdrawing nature of the acyl group should enhance the electrophilicity of the acylpalladium species **B**, and thus promote the oxypalladation of an additional molecule of **1**, leading to the difuranyl ketone **4**.

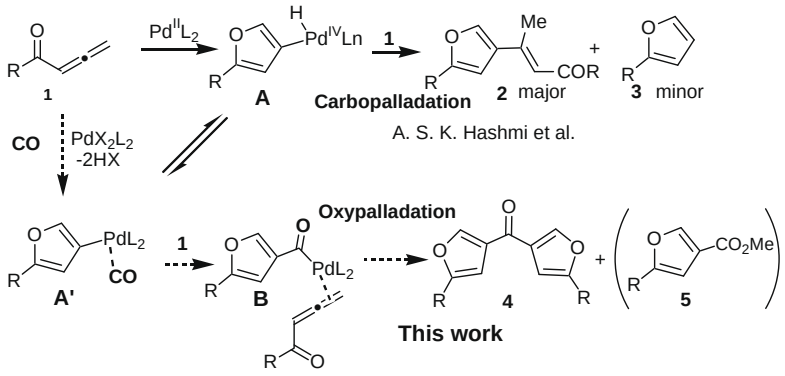
Furan rings are a common structure in a range of biologically active natural products and important pharmaceuticals.[1] Diarylketones are also frequently found in natural products and pharmaceuticals.[2] In addition, they are good precursors for non-steroidal antiestrogen drugs, such as tamoxifen,[3] and for diarylmethyl compounds, such as histamine H_1 antagonists,[4a] antitubercular compounds,[4b] and inhibitors of tubulin polymerization.[4c] Transition-metal-catalyzed reaction of unsaturated systems has recently proven to be a powerful method for the construction of a variety of carbo- and heterocycles.[5] In particular, transition-metal-catalyzed cycloisomerization of 1,2-allenyl ketones leading to furan derivatives has been extensively studied.[6] Among such reactions, Hashmi et al. demonstrated the palladium-catalyzed dimeric cyclization of 1,2-allenyl ketones (Scheme 1).[6c,d]

In that study, the authors suggested that a possible pathway toward formation of **2** and **3** was through a furyl hydridopalladium(IV) species **A** obtained via the intramolecular oxypalladation of a palladium-coordinated allene. The intermediate **A** can form either product **3** by reductive elimination or product **2** by carbopalladation of an additional molecule of **1** followed by reductive elimination. Recently, we reported on the intramolecular- and intermolecular-oxycarbonylation of several types of alkynes[7] as well as the tandem carbonylative cyclization of propargyl acetates with 1,4-diyne[8a] and 1,5-diyne structures.[8b] In these reactions, the insertion of CO into the vinylpalladium species was faster than the intramolecular insertion of the second triple bond.[8] Based on our previous findings, we have hypothesized that treatment of 1,2-allenyl ketones **1** with Pd^{II} under CO atmosphere[9] may form the acylpalladium species **B** as a result of CO insertion into the furyl palladium species **A'** (Scheme 1). The electron-withdrawing nature of the acyl group should enhance the electrophilicity of the acylpalladium species **B**, and thus promote the oxypalladation of an additional molecule of **1**, leading to the difuranyl ketone **4**. Consequently, we report on a new Pd^{II}-catalyzed carbonylative dimerization of allenyl ketones as an efficient synthesis of difuranylketones[10] (Scheme 1).

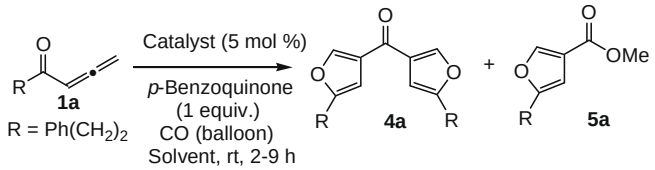
Initially, we selected **1a** as a standard substrate to optimize potential solvents and catalysts. The carbonylation of **1a** was performed under the same conditions as used in our previously reported Pd^{II}/*p*-benzoquinone catalytic system[7,8,11] (Scheme 2, Table 1). Briefly, the reaction of **1a** with $(CH_3CN)_2PdCl_2$ (5 mol %) in the presence of *p*-benzoquinone (1 equiv) in CH_3CN under a carbon monoxide atmosphere (balloon) generated the expected difuranylketone **4a** in 27% yield along with the known dimer **2a** (26%) (Table 1, entry 1). Whereas toluene was not suitable as a solvent for the reaction, the use of CH_2Cl_2 and MeOH did successfully improve the yield of **4a** (Table 1, entries 2–4). When the reaction was performed in MeOH, **4a** was precipitated from the reaction mixture. After collection by filtration, washing with cold MeOH, pure **4a** was afforded in 65% yield. A further amount of **4a** (4%) along with the furan carboxylate **5a** (13%) could be obtained from the fil-

* Corresponding authors. Fax: +81 474 721 825 (K.K.).
E-mail address: kkk@phar.toho-u.ac.jp (K. Kato).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.06.016



Scheme 1. Palladium catalyzed reaction of allenyl ketone and this work.



Scheme 2. Carbonylation of allenyl ketone **1a** with $(CH_3CN)_2PdCl_2$.

Table 1
Carbonylation of allenyl ketone **1a** with $(CH_3CN)_2PdCl_2$ (Scheme 2)

Entry	Solvent	Catalyst	Yield of **4a** (%)	Yield of **5a** (%)
1[a]	CH_3CN	$(CH_3CN)_2PdCl_2$	27	—
2	CH_2Cl_2	$(CH_3CN)_2PdCl_2$	49	—
3	Toluene	$(CH_3CN)_2PdCl_2$	Complex mixture	
4	MeOH	$(CH_3CN)_2PdCl_2$	69	13
5	MeOH	$(C_6H_5CN)_2PdCl_2$	64	19
6	MeOH	$Pd(TFA)_2$	52	24
7	MeOH	$(CH_3CN)_4Pd(BF_4)_2$	58	10
8	MeOH	$Pd(TFA)_2$/(*S*)-Phbox	68	3

[a] **2a** (R = $Ph(CH_2)_2$) was also obtained in 26% yield.

trate (Table 1, entry 4). Next, we investigated other catalysts such as $(C_6H_5CN)_2PdCl_2$, $Pd(TFA)_2$, and $(CH_3CN)_4Pd(BF_4)_2$; notably, these gave similar results as the initial catalyst (Table 1, entries 4–7). However, $Pd(OAc)_2$ and (2,2'-bipyridine)dichloropalladium(II) did not show catalytic activity, and $(Ph_3P)_2PdCl_2$ gave **5a** in poor yield (17%).[12] These results can be interpreted as a result of the decreasing electrophilicity of the palladium species.[7,8,13] Next, in order to enhance the π-philicity of Pd^{II} complexes,[7e,8] we investigated the use of the (*S*)-Phbox ligand (Table 1, entry 8). As expected, the products ratio (**4a**/**5a**) was increased, but the yield of **4a** was almost the same, and the total yield was decreased. Thus, we selected the $(CH_3CN)_2PdCl_2$ catalyst in a MeOH solvent as the optimized conditions.

We then examined the scope of this reaction, with the results summarized in Table 2 (Scheme 3). For substrates **1a**–**c** having hydrocarbon substituents, the reaction proceeded smoothly, affording the products **4a**–**c** in 63–74% yields along with a small amount of furan carboxylates **5a**–**c** (4–13%) (Table 2, entries 1–3). The structure of **4c** was determined by X-ray crystallographic analysis after recrystallization.[14]

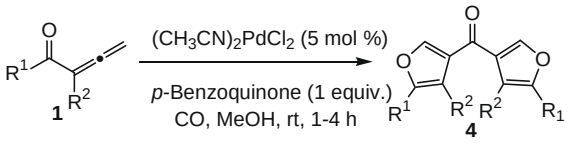
The benzoates **1d**–**g** having different carbon chain lengths gave almost the same results (Table 2, entries 4–7). Although the reaction of the TBDMS ether **1h** proceeded smoothly, partial desilylation was observed, and thus the product **4h** was isolated after re-silylation of the crude mixture (Table 2, entry 8). The phenyl-substituted **1i** and furanyl-substituted **1j** and **1k** gave 60–68% yields (Table 2, entries 9–11). While the product yields of substrates having unsubstituted allenyl ketones **(1a–k)** were moderate, this improved with the addition of an R^2 substituent into the substrates. For substrates **1l**–**n**, with a methyl or ethyl substituent at R^2, the reactions proceeded well, affording the products **4l**–**n** in 89–96% yields along with a small amount of furan carboxylates **5l**–**n** (3–9%) (Table 2, entries 12–14). In the case of the substrates **1o**–**t**, we failed to isolate the furan carboxylates **5o**–**t** in pure form, although the difuranylketones **4o**–**t** were obtained in good yield (Table 2, entries 15–20). The precise reason for this substituent effect is presently unclear, but may be related to stability of the compounds under the reaction condition. In the case of unsubstituted

Table 2
$(CH_3CN)_2PdCl_2$ catalyzed carbonylative dimerization of allenyl ketones **1**[a]

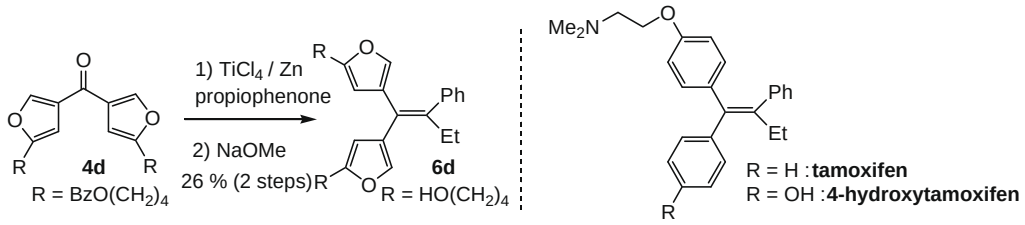
Entry	R^1	R^2	Yield of **4** (%)
1	$Ph(CH_2)_2$	H	**4a**:69
2	Nonyl	H	**4b**:63
3	Cyclohexyl	H	**4c**:74
4	$BzO(CH_2)_4$	H	**4d**:73
5	$BzO(CH_2)_3$	H	**4e**:61
6	$BzO(CH_2)_2$	H	**4f**:62
7	$BzOCH_2$	H	**4g**:59
8[b]	$TBSO(CH_2)_3$	H	**4h**:70
9	Ph	H	**4i**:68
10	2-Furanyl	H	**4j**:64
11	3-Furanyl	H	**4k**:60
12	$Ph(CH_2)_2$	Me	**4l**:89
13	$Ph(CH_2)_2$	Et	**4m**:90
14	$BzO(CH_2)_4$	Me	**4n**:96
15	$BzO(CH_2)_3$	Me	**4o**:93
16	$BzO(CH_2)_2$	Me	**4p**:85
17	2-Furanyl	Et	**4q**:87
18	3-Furanyl	Et	**4r**:82
19	Ph	Et	**4s**:85
20	2-Furanyl	Me	**4t**:83

[a] All reactions were performed with $(CH_3CN)_2PdCl_2$ (5 mol %) in MeOH. In most cases, furan carboxylate **5** was obtained as a by-product in low yield. See Supplementary data.

[b] Partial desilylation was observed during the carbonylation reaction. The product was isolated after re-silylation.



Scheme 3. $(CH_3CN)_2PdCl_2$ catalyzed carbonylative dimerization of allenyl ketones **1**.



Scheme 4. Synthetic approach to the new tamoxifen analogue.

allenyl ketones **1a–k**, some unidentified small spots were detected from the reaction mixture by thin-layer chromatography.

To investigate the utility of the present reaction, a preliminary study for the synthesis of a new tamoxifen analogue is shown in Scheme 4. Tamoxifen (Nolvadex®) is one of the most important chemotherapeutic agents for the treatment of breast cancer. Its primary metabolite, 4-hydroxytamoxifen has a greater affinity for the estrogen receptor than tamoxifen, and may contribute to the in vivo antitumour activity.[3] However, after a period of response, tamoxifen-resistant tumours eventually develop, creating the need for new potent non-toxic antiestrogens. Towards this aim, coupling of the difuranylketone **4d** with propiophenone using $TiCl_4$/Zn in THF[3e] followed by methanolysis afforded the tamoxifen analogue **6d** in 26% yield.

In conclusion, we have developed a new type of Pd^{II}-catalyzed carbonylative dimerization of allenyl ketones **1**. The difuranylketones **4** were obtained in moderate to good yields. The electrophilicity of the acylpalladium species **B** is considered to contribute to the oxypalladation of an additional molecule of **1**. We are currently investigating a new tandem reaction for the synthesis of other kinds of diheteroaromatic ketones based on the cyclization–carbonylation–cyclization strategy presented here while also trying to improve the synthetic efficiency of some tamoxifen analogues.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.016.

References and notes

1. Yang, Y.; Wong, H. N. C. *Tetrahedron* **1994**, *50*, 9583. and references cited therein.
2. Neumann, H.; Brennführer, A.; Beller, M. *Chem. Eur. J.* **2008**, *14*, 3645. and references cited therein.
3. (a) Nguyen, A.; Top, S.; Pigeon, P.; Vessières, A.; Hillard, E. A.; Plamont, M.-A.; Huché, M.; Rigamonti, C.; Jaouen, G. *Chem. Eur. J.* **2009**, *15*, 684; (b) Chao, E. Y. H.; Collins, J. L.; Gaillard, S.; Miller, A. B.; Wang, L.; Orband-Miller, L. A.; Nolte, R. T.; McDonnell, D. P.; Willson, T. M.; Zuercher, W. J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 821; (c) Pandey, R. K.; Wakharkar, R. D.; Kumar, P. *Synth. Commun.* **2005**, *35*, 2795; (d) Olier-Reuchet, C.; Aitken, D. J.; Bucourt, R.; Husson, H.-P. *Tetrahedron Lett.* **1995**, *36*, 8221; (e) Coe, P. L.; Scriven, C. E. *J. Chem. Soc., Perkin Trans. 1* **1986**, 475.
4. (a) Schmidt, F.; Stemmler, R. T.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev.* **2006**, *35*, 454; (b) Das, S. K.; Panda, G.; Chaturvedi, V.; Manju, Y. S.; Gaikwad, A. K.; Sinha, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5586; (c) Álvarez, C.; Álvarez, R.; Corchete, P.; López, J. L.; Pérez-Melero, C.; Peláez, R.; Medarde, M. *Bioorg. Med. Chem.* **2008**, *16*, 5952.
5. (a) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002; Vol. II, p 2309; For recent reviews, see: (b) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067; (c) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12; (d) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701; (e) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127; (f) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285; (g) Soderberg, B. C. G. *Coord. Chem. Rev.* **2004**, *248*, 1085; (h) Vizer, S. A.; Yerzhanov, K. B.; Quntar, A. A. A. A.; Dembitsky, V. M. *Tetrahedron* **2004**, *60*, 5499; (i) Muzart, J. *Tetrahedron* **2005**, *61*, 9423; (j) Asao, N. *Synlett* **2006**, 1645; (k) Zeni, G.; Rarock, R. C. *Chem. Rev.* **2006**, *106*, 4644.
6. (a) Marshall, J. A.; Robinson, E. D. *J. Org. Chem.* **1990**, *55*, 3450; (b) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966; (c) Hashmi, A. S. K. *Angew. Chem.* **1995**, *107*, 1749; . *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1581; (d) Hashmi, A. S. K.; Ruppert, T. L.; Knöfel, T.; Bats, J. W. *J. Org. Chem.* **1997**, *62*, 7295; (e) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem.* **2000**, *112*, 2382; . *Angew. Chem., Int. Ed.* **2000**, *39*, 2285; (f) Ma, S.; Li, L. *Org. Lett.* **2000**, *2*, 941; (g) Ma, S.; Zhang, J.; Lu, L. *Chem. Eur. J.* **2003**, *9*, 2447; (h) Ma, S.; Yu, Z. *Chem. Eur. J.* **2004**, *10*, 2078; (i) Ma, S.; Yu, Z.; Gu, Z. *Chem. Eur. J.* **2005**, *11*, 2351; (j) Deng, Y.; Li, J.; Ma, S. *Chem. Eur. J.* **2008**, *14*, 4263; (k) Alcaide, B.; Almendros, P.; Martínez del Campo, T. *Eur. J. Org. Chem.* **2007**, 2844.
7. Propargyl acetates: (a) Kato, K.; Nouchi, H.; Ishikura, K.; Takaishi, S.; Motodate, S.; Tanaka, H.; Okudaira, K.; Mochida, T.; Nishigaki, R.; Shigenobu, K.; Akita, H. *Tetrahedron* **2006**, *62*, 2545; 4-Alkynols: (b) Kato, K.; Matsuba, C.; Kusakabe, T.; Takayama, H.; Yamamura, S.; Mochida, T.; Akita, H.; Peganova, T. A.; Vologdin, N. V.; Gusev, O. V. *Tetrahedron* **2006**, *62*, 9988; 4-Alkynones: (c) Kusakabe, T.; Kato, K.; Takaishi, S.; Yamamura, S.; Mochida, T.; Akita, H.; Peganova, T. A.; Vologdin, N. V.; Gusev, O. V. *Tetrahedron* **2008**, *64*, 319; Propargyl ketols: (d) Kato, K.; Motodate, S.; Takaishi, S.; Kusakabe, T.; Akita, H. *Tetrahedron* **2008**, *64*, 4627; Intermolecular methoxycarbonylation: (e) Kato, K.; Motodate, S.; Mochida, T.; Kobayashi, T.; Akita, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 3326.
8. (a) Kato, K.; Teraguchi, R.; Yamamura, S.; Mochida, T.; Akita, H.; Peganova, T. A.; Vologdin, N. V.; Gusev, O. V. *Synlett* **2007**, 638; (b) Kato, K.; Teraguchi, R.; Motodate, S.; Uchida, A.; Mochida, T.; Peganova, T. A.; Vologdin, N. V.; Akita, H. *Chem. Commun.* **2008**, 3687; (c) Kato, K.; Akita, H. *J. Synth. Org. Chem. Jpn.* **2009**, *67*, 16.
9. $Fe(CO)_5$ catalyzed cyclization of 1,2-allenyl ketones with CO afforded lactones: Sigman, M. S.; Kerr, C. E.; Eaton, B. E. *J. Am. Chem. Soc.* **1993**, *115*, 7545.
10. Synthesis of difuranylketones amd arylfuranylketones: (a) Benassi, R.; Folli, U.; Larossi, D.; Schenetti, L.; Taddei, F.; Musatti, A.; Nardelli, M. *J. Chem. Soc., Perkin Trans. 2* **1989**, 1741; (b) Yang, Y.; Wong, H. N. C. *Tetrahedron* **1994**, *50*, 9583; (c) Okuro, K.; Furuune, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1992**, *57*, 4754.
11. Marshall, J. A.; Yanik, M. M. *Tetrahedron Lett.* **2000**, *41*, 4717.
12. In addition, the use of (−)-sparteine/$Pd(TFA)_2$ and (2,2'-bipyridine) dichloropalladium(II) resulted in no reaction and complex mixture, respectively.
13. Xu, Y.-H.; Lu, J.; Loh, T.-P. *J. Am. Chem. Soc* **2009**, *131*, 1372.
14. Crystallographic data (excluding structure factors) for the structure have been deposited with the Cambridge Crystallographic Data Center as supplementary publication No. 723226. See the Supplementary data of this article.