Journal of Organometallic Chemistry 838 (2017) 9–11

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

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

Communication

Palladium-catalyzed carbonylative synthesis of alkynones from aryl iodides and phenylpropiolic acid employing formic acid as the CO source

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ARTICLE INFO

Article history:
Received 20 January 2017
Received in revised form
27 February 2017
Accepted 12 March 2017
Available online 15 March 2017

Keywords:
Phenylpropiolic acid
Decarboxylation
Carbonylation
Palladium
Formic acid
Alkynones

ABSTRACT

A palladium-catalyzed procedure for the decarboxylative-carbonylation of phenylpropiolic acid with iodobenzenes to the corresponding alkynones with formic acid as carbon monoxide source has been developed. Various alkynones were produced in moderate to good yields.

Alkynones act as an important structural motif in many biological active products [1]. Additionally, alkynone and derivatives are versatile carbonyl functional groups in organic synthesis, especially for heterocyclic compounds construction, such as furans, pyrroles, pyrazoles, and quinoline derivatives [2]. Due to the high importance, various methods have been reported for their synthesis [3]. Among those methods, palladium-catalyzed Sonogashira-type carbonylation of aryl halides with terminal alkynes has been established and applied in the past decades [4]. This protocol has emerged as a straightforward and useful tool to prepare numerous alkynones in the presence of carbon monoxide or its surrogates. Notably, Lee and co-workers reported an interesting palladium-catalyzed decarboxylative carbonylation of aryl alkynyl carboxylic acids and aryl iodides in 2011 [5]. Under the pressure of carbon monoxide, various alkynones were prepared in good yields.

On the other hand, owing to the disadvantages (toxicity, flammable, odorless) of carbon monoxide, many procedures based on *ex/in situ* CO generation have been developed by various research groups [6]. Among them, we have explored the potential to apply formic acid as CO source in carbonylative coupling transformations. In 2015, we reported a palladium-catalyzed one-pot carbonylative Sonogashira reaction of terminal alkynes employing formic acid as the carbon monoxide source [7]. As our continual interests on this topic, herein, a palladium-catalyzed carbonylation of phenylpropiolic acid with iodobenzenes employing formic acid as the carbon monoxide source to prepare alkynones has been established. Various alkynones were produced in moderate to good yields.

Initially, we performed the reaction with iodobenzene (1.0 mmol) and phenylpropiolic acid (1.0 mmol) in the presence of $Pd(OAc)_2$ (3 mol%), PPh_3 (6 mol%), formic acid (2 mmol), Ac_2O (2 mmol) and Et_3N (triethylamine, 5 equiv.) as the base at 100 °C. To our disappointed, no desired product was detected (Table 1, entry 1). Attempts to reduce the reaction temperature were successful, and 2% yield of the desired product was formed at 80 °C (Table 1, entries 2–3). Then, several other phosphine ligands were tested (Table 1, entries 4–12). The yield of the product can be further improved to 27% by using DPPM as the ligand (Table 1, entry 12). Among the tested organic solvents, toluene was found to be superior to the others (Table 1, entry 18). Inspired by the work from Lee's group, we then tested $PdCl_2(PPh_3)_2$ (1 mol%) in toluene at

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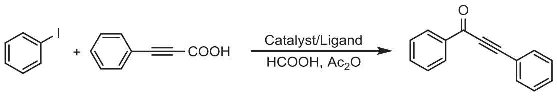
http://dx.doi.org/10.1016/j.jorganchem.2017.03.028

Table 1
Optimization of the reaction conditions.[a]



Entry	Catalyst	Ligand	Solvent	Temp.	Yield[b] (%)
1[c]	$Pd(OAc)_2$	PPh_3	DMF	100 °C	0
2[c]	$Pd(OAc)_2$	PPh_3	DMF	80 °C	2
3[c]	$Pd(OAc)_2$	PPh_3	DMF	70 °C	<1
4	$Pd(OAc)_2$	DPPF[g]	DMF	80 °C	14
5	$Pd(OAc)_2$	DPPE[g]	DMF	80 °C	27
6	$Pd(OAc)_2$	DPEphos[g]	DMF	80 °C	24
7	$Pd(OAc)_2$	DPPB[g]	DMF	80 °C	21
8	$Pd(OAc)_2$	DPPP[g]	DMF	80 °C	26
9	$Pd(OAc)_2$	DPPPE[g]	DMF	80 °C	7
10[c]	$Pd(OAc)_2$	BINAP	DMF	80 °C	24
11[c]	$Pd(OAc)_2$	PCy_3	DMF	80 °C	18
12	$Pd(OAc)_2$	DPPM[g]	DMF	80 °C	27
13	$Pd(OAc)_2$	DPPM	CH_3CN	80 °C	6
14	$Pd(OAc)_2$	DPPM	THF	80 °C	16
15	$Pd(OAc)_2$	DPPM	1,4-dioxane	80 °C	27
16	$Pd(OAc)_2$	DPPM	cyclohexane	80 °C	19
17	$Pd(OAc)_2$	DPPM	DMAc	80 °C	13
18	$Pd(OAc)_2$	DPPM	toluene	80 °C	33
19[d]	$PdCl_2(PPh_3)_2$	/	toluene	80 °C	62
20[e]	$PdCl_2$	/	toluene	80 °C	15
21[d]	$PdCl_2$(DPPF)		toluene	80 °C	70
22[d]	$PdCl_2$DPPE)		toluene	80 °C	65
23[d]	$PdCl_2$(DPPF)	DPPF[f]	toluene	80 °C	63

[a] Reaction conditions: iodobenzene (1.0 mmol), phenylpropiolic acid (1.0 mmol), catalyst (3 mol%), ligand (3 mol%), HCOOH (2.0 mmol), Ac_2O (2.0 mmol), Et_3N (5 equiv.), solvent (2 mL), 12 h.

[b] Determined by GC analysis of the reaction mixture using dodecane as an internal standard.

[c] Ligands (6 mol%).

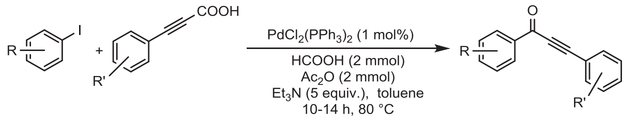
[d] Catalyst (1 mol%).

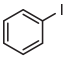
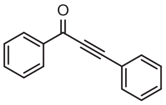
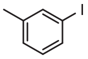
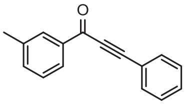
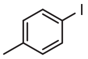
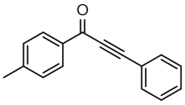
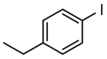
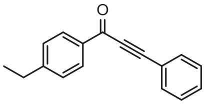
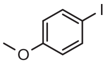
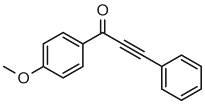
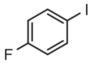
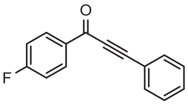
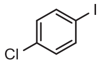
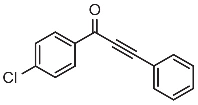
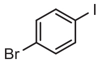
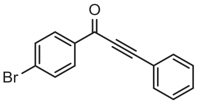
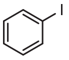
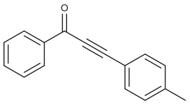
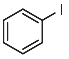
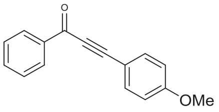
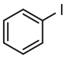
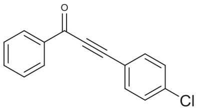
[e] $PdCl_2$ (2 mol%).

[f] 1 mol%.

[g] DPPF = 1,1′-Bis(diphenylphosphino)ferrocene; DPPE = 1,2-bis(diphenylphosphino)ethane; DPEphos = bis (2-diphenylphosphinophenyl)ether; DPPB = 1,4-bis(diphenylphosphino)butane; DPPP = 1,3-bis(diphenylphosphino)propane; DPPPE = 1,5-bis(diphenylphosphino)pentane; DPPM = bis (diphenylphosphino) methane.

Table 2
Synthesis of alkynones from iodobezenes and phenylpropiolic acid.[a]

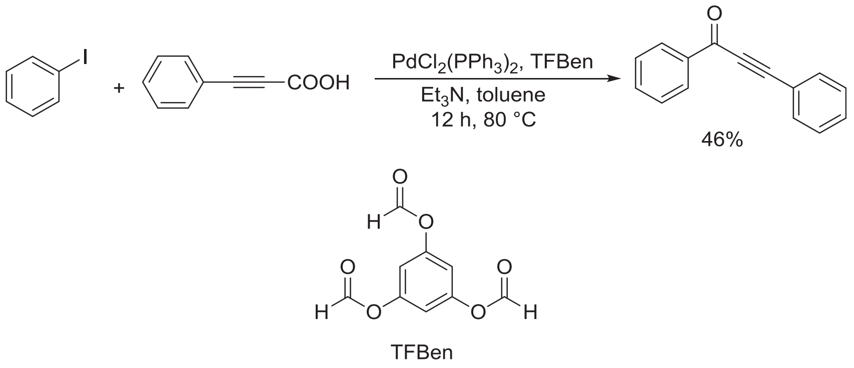


Entry	Substrate	Product	Yield (%)
1			59%
2			62%
3			65%
4			59%
5			58%
6			43%
7			45%
8			trace
9			60%
10			55%
11			63%

[a] Iodobenzenes (1.0 mmol), phenylpropiolic acid (1.0 mmol), $PdCl_2(PPh_3)_2$ (1 mol %), HCOOH (2 mmol), Ac_2O (2 mmol), Et_3N (5 equiv.), toluene (2 mL), 80 °C, 10–14 h, isolated yields.

80 °C, to our delight, 62% yield of the desired product can be formed (Table 1, entry 19). Then other palladium precursors were tested, improved yields could be obtained with $PdCl_2$(DPPF) or $PdCl_2$(DPPE) as the catalyst (Table 1, entries 21 and 22). The adding of additional amount of ligand could not further improve the reaction outcome (Table 1, entry 23). Additional variations on loadings of catalyst and CO could not further improve the outcomes. Due to the differences in catalysts' price, we decided to choose $PdCl_2(PPh_3)_2$ for the substrates testing. Notably, diphenyl acetylene as the decarboxylative Sonogashira reaction product could be detected during the optimization process.

With the optimal reaction conditions in hand, we started to examine the substrates scope of this method (Table 2). 3-Methyl, 4-methyl, 4-ethyl, and 4-methoxyl substituted iodobenzenes were reacted to form the corresponding alkynones in 58–65% (Table 2, entries 2–5). Furthermore, *p*-X (X = F, Cl) substituted iodobenzenes were also examined (Table 2, entries 6 and 7), moderate yields can be obtained without further optimizations. Unfortunately, 1-bromo-4-iodobenzene did not react under our conditions, and the starting material was reduced to bromobenzene (Table 2, entry 8). Due to the limited availability of alkynyl carboxylic acids, propiolic acid and cinnamic acid were tested with iodobenzene under our standard reaction conditions. But no desired products could be detected in these cases. Additionally, in oreder to prove the generality of this methodology, three arylpropiolic acids derivatives were prepared and applied under our conditions and moderate yields of the corresponding products were obtained successfully (Table 2, entries 9–11). Remarkably, the model reaction was



Scheme 1. Pd-catalyzed carbonylation with TFBen as the CO source.

performed at 5 mmol scale as well and 50% of the corresponding alkynone was obtained.

Moreover, our group firstly developed TFBen (benzene-1,3,5-triyl triformate) as an efficient, non-reacting carbon monoxide (C1) source in carbonylation reactions [8]. The possibility to apply TFBen as a new CO resource in this transformation has been studied as well. To our delight, 46% isolated yield of desired alkynone can be achieved (Scheme 1) [9].

In conclusion, a palladium-catalyzed carbonylative procedure for the transformation of phenylpropiolic acid with iodobenzenes to alkynones with formic acid as carbon monoxide source has been developed. Various alkynones were produced in moderate to good yields.

Acknowledgments

The authors thank the financial supports from NSFC (21472174, 21602201, 21602204) and Zhejiang Natural Science Fund for Distinguished Young Scholars (LR16B020002). X.—F. Wu appreciates the general support from Professor Matthias Beller in LIKAT.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jorganchem.2017.03.028.

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[9] Reaction condition: iodobenzene (1.0 mmol), phenylpropiolic acid (1.0 mmol), PdCl2(PPh3)2 (1 mol%), TFBen (2.0 mmol), Et3N (2 equiv.), toluene (2 mL), 80 oC, 12 h.