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Synthesis of Alkyl Alkynyl Ketones by Pd/Light-Induced Three-Component Coupling Reactions of Iodoalkanes, CO, and 1-Alkynes

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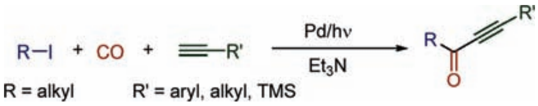
ABSTRACT



Under photoirradiation conditions using xenon light, in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ with triethylamine as a base, a three-component coupling reaction of iodoalkanes, carbon monoxide, and terminal alkynes proceeded to give alkyl alkynyl ketones in good yields.

Alkynyl ketones are contained in several biologically active molecules[1] and play a crucial role as key intermediates in the synthesis of natural compounds[2] and in heterocyclic systems.[3] Although the most common route for the synthesis of alkynyl ketones is the acylation reaction of alkynyl organometallic reagents with acid chlorides,[4] a three-component approach comprising organo halides, carbon monoxide, and terminal alkynes based on transition-metal-catalyzed carbonylation represents a more straightforward approach in terms of simplicity, which makes it possible to avoid the preparation of somewhat unstable acid chlorides.[5,6] For the past decade, significant efforts have been made to improve carbonylative approaches, and several mild reaction conditions have been found thus far. However, the system remains largely restricted to the use of aryl or vinyl halides; aliphatic halides are not necessarily applicable due to the

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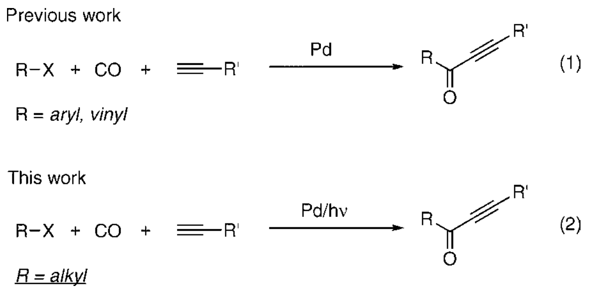
low reactivity of sp^3-carbon−halogen bonds toward oxidative addition with palladium.[7]

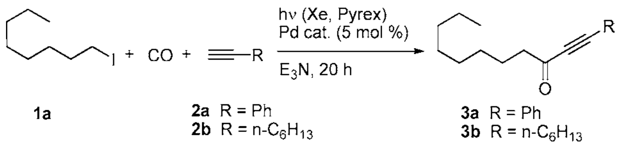
We recently reported that radical/metal hybrid reactions under photoirradiation conditions[8] accelerated the atom-transfer carbonylation of alkyl halides leading to carboxylic acid esters, amides, and related heterocycles.[9,10] In these reactions, it is assumed that the intervention of a free-radical mechanism will generate acylpalladium intermediates, thus representing a radical/metal collaboration system. Herein, we report that such a strategy was applied successfully to a carbonylative Sonogashira reaction using alkyl iodides, CO, and terminal alkynes, which gave good yields of alkyl alkynyl ketones (Scheme 1).

Scheme 1. Carbonylative Sonogashira Coupling Reaction Leading to Alkynyl Ketones



When 1-iodooctane (**1a**) and phenylacetylene (**2a**) were exposed to photocarbonylation conditions (irradiation with a 500 W xenon lamp through Pyrex under 45 atm of CO pressure) in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$, the desired alkynyl ketone **3a** was obtained in 19% yield (Table 1, entry 3). The use of $Pd(PPh_3)_4$ as a catalyst led to a slight decline in the yield of **3a** (entry 2), but the addition of water to the reaction system of $PdCl_2(PPh_3)_2$ improved the yield of **3a** to as high as 71% (entry 4).[11] Both the catalyst and photoirradiation conditions were indispensable for this reaction system. When a quartz linear or a weaker xenon lamp (300 W) was used, the yield of **3a** considerably decreased, suggesting that the conversion of **1a** to **3a** was extremely sensitive to the power of the light source as well as to the wavelength.

Table 1. Pd/Light-Induced, Three-Component Coupling Reaction of 1-Iodooctane (**1a**) with Phenylacetylene (**2a**) and 1-Octyne (**2b**)



entry	iodoalkane, alkyne	catalyst	solvent	product	yield[a] (%)
1	**1a, 2a**		$C_6H_6/H_2O(10/1)$	**3a**	<1
2	**1a, 2a**	$Pd(PPh_3)_4$	C_6H_6	**3a**	16
3	**1a, 2a**	$PdCl_2(PPh_3)_2$	C_6H_6	**3a**	19
4	**1a, 2a**	$PdCl_2(PPh_3)_2$	$C_6H_6/H_2O(10/1)$	**3a**	71[b]
5[c]	**1a, 2b**	$PdCl_2(PPh_3)_2$	$C_6H_6/H_2O(10/1)$	**3b**	40[b]
6[d]	**1a, 2a**	$PdCl_2(PPh_3)_2$	$C_6H_6/H_2O(10/1)$	**3b**	88[b]

[a] Yields were determined from ^1H NMR using tetrachloroethane as an internal standard. [b] Isolated yield by silica gel chromatogryaphy. [c] Nonanoic acid anhydride was formed as byproduct (22%). [d] Reaction was carried out using 5.2 equiv of **2b**.

In contrast with the above case of phenylacetylene (**2a**), under similar conditions, treatment of 1-octyne (**2b**) with 1-iodooctane (**1a**) resulted in the corresponding alkynyl ketone **3b** in 40% yield (entry 5). In this reaction, nonanoic acid anhydride (**4**) was also formed as a byproduct. However, the use of a large excess of 1-octyne (5.2 equiv relative to **1a**) resulted in a notable yield enhancement in which the corresponding alkynyl ketone **3b** was obtained in 88% yield (entry 6).

Primary alkyl iodides with various substituents or structures were applied to the present alkyl alkynyl ketone synthesis (Table 2). A variety of functional groups were tolerated in these reactions. Thus, when 1-chloro-8-iodooctane (**1b**) was used, the corresponding alkynyl ketone **3c** was obtained in good yield (entry 3). Similarly, alkyl iodides, which had methyl ester or TBS ether, also gave the desired coupling compounds (entries 4 and 5). Secondary and tertiary alkyl iodides reacted with phenylacetylene (**2a**) to give the corresponding alkynyl ketones in good yields (entries 6−10). The coupling reaction of aliphatic acetylene, such as 1-octyne (**2b**), with secondary and tertiary substrates also proceeded in good yields (entries 11 and 12), whereas trimethylsilylacetylene (**2c**) gave moderate yields of the desired products (entries 13−15).

We also examined radical cascade sequences accompanying ring-opening or ring-closing processes (Scheme 2). The reaction of cyclopropylmethyl iodide (**1j**) and **2a** afforded the alkynyl ketone **3p**, which possessed an olefin structure generated from the ring-opening of a cyclopropylcarbinyl

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[7] Eckhardt, M; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642. Also see the following reviews: (a) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674. (b) Netherton, M. R.; Fu, G. C. *Adv. Synth. Catal.* **2004**, *346*, 1525. (c) Rudolph, A.; Lautens, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 2656.

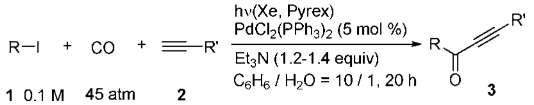
[8] For previous efforts on metal-catalyzed carbonylation under photoirradiation conditions, see: (a) Kondo, T.; Sone, Y.; Tsuji, Y.; Watanabe, Y. *J. Organomet. Chem.* **1994**, *473*, 163. (b) Ishiyama, T.; Murata, M; Suzuki, A.; Miyaura, N. *J. Chem. Soc., Chem. Commun.* **1995**, 295.

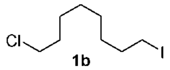
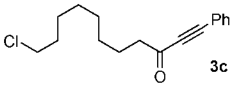
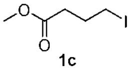
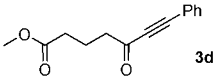
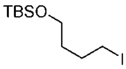
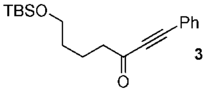
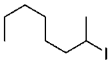
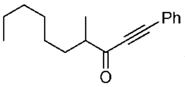
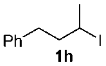
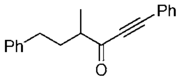
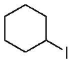
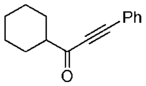
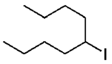
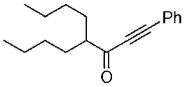
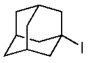
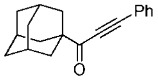
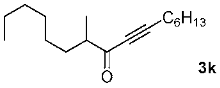
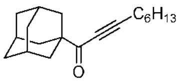
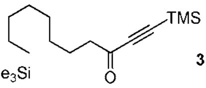
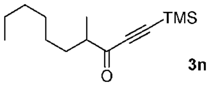
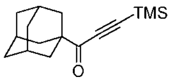
[9] For atom transfer carbonylation reactions, see: (a) Ryu, I.; Nagahara, K.; Kambe, N.; Sonoda, N.; Kreimerman, S.; Komatsu, M. *Chem. Commun.* **1998**, 1953. (b) Nagahara, K.; Ryu, I.; Komatsu, M.; Sonoda, N. *J. Am. Chem. Soc.* **1997**, *119*, 5465. (c) Kreimerman, S.; Ryu, I.; Minakata, S.; Komatsu, M. *Org. Lett.* **2000**, *2*, 389. Also see a review: (d) Ryu, I. *Chem. Soc. Rev.* **2001**, *30*, 16.

[10] For radical/metal hybrid reactions, see: (a) Ryu, I.; Kreimerman, S.; Araki, F.; Nishitani, S.; Oderaotoshi, S.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **2002**, *124*, 3812. (b) Fukuyama, T.; Nishitani, S.; Inouye, T.; Morimoto, K.; Ryu, I. *Org. Lett.* **2006**, *8*, 1383. (c) Fukuyama, T.; Inouye, T.; Ryu, I. *J. Organomet. Chem.* **2007**, *692*, 685. Also see a review: (d) Ryu, I. *Chem. Rec.* **2002**, *2*, 249.

[11] Acceleration by water may be concerned with the fact that in the absence of water the reaction mixture became a suspension due to the gradually formed amine-HI salt, which is supposed to prevent effective photoirradiation. In the presence of water, we observed that a clear solution was maintained during the photoirradiation reaction.

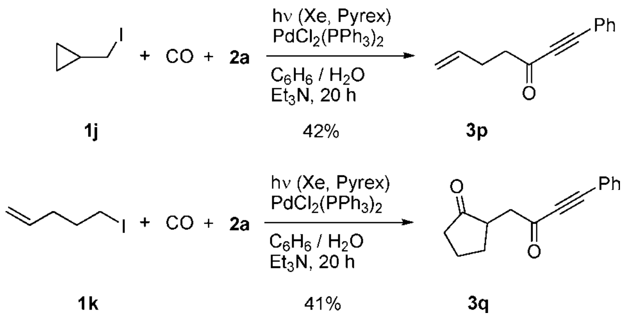
Table 2. Synthesis of Acetylenic Ketones by a Three-Component Coupling Reaction[a]



entry	R-I **1**	alkynes **2**	ketones **3**	yield (%)[b]
1	**1a**	**2a** R' = Ph	**3a** R' = Ph	71%
2	**1a**	**2b** R' = n-C_6H_{13}	**3b** R' = n-C_6H_{13}	88%
3	 **1b**	**2a**	 **3c**	70%
4	 **1c**	**2a**	 **3d**	63%
5	 **1d**	**2a**	 **3e**	53%
6	 **1g**	**2a**	 **3f**	65%
7	 **1h**	**2a**	 **3g**	65%
8	 **1i**	**2a**	 **3h**	57%
9	 **1j**	**2a**	 **3i**	74%
10	 **1k**	**2a**	 **3j**	70%
11[c]	**1e**	**2b**	 **3k**	70%
12[c]	**1i**	**2b**	 **3l**	76%
13[c]	**1a**	**2c** R' = Me_3Si	 **3m**	58%
14[c]	**1e**	**2c**	 **3n**	40%
15[c]	**1i**	**2c**	 **3o**	44%

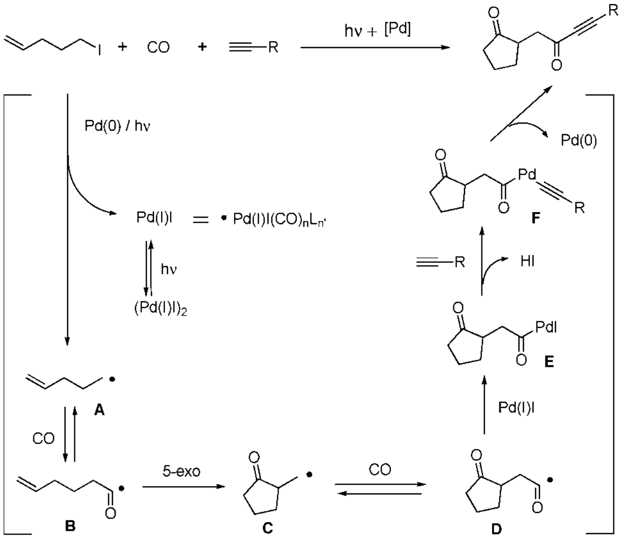
[a] Conditions: **1** (0.5 mmol); **2** (1.2−1.3 equiv); catalyst, $PdCl_2(PPh_3)_2$ (5 mol %); base, NEt_3 (1.2−1.4 equiv); benzene (5 mL); H_2O (0.5 mL); CO (45 atm); light (500 W xenon lamp, Pyrex). [b] Isolated yield by silica gel chromatography. [c] Acetylene (5 equiv) was used.

Scheme 2. Cascade Radical Carbonylation Reactions



radical.[12] When the reaction of 5-iodo-1-pentene (**1k**) and **2a** was carried out, alkynyl ketone **3q** bearing a cyclopentanone scaffold was formed through a carbonylation−cyclization−carbonylation−alkynylation sequence. These results show that Pd/light-assisted carbonylation reactions can combine well with radical cascade pathways.

Scheme 3. Possible Reaction Mechanism



The proposed mechanism for Pd/light-assisted carbonylation is shown in Scheme 3, using **1k** to **3q** as an example. In the first step, alkyl iodide reacts with Pd(0) under irradiation to afford alkyl radical **A** and Pd(I)I via a one-electron transfer.[13] The resulting alkyl radical **A** traps CO to form acyl radical **B** and then affords alkyl radical **C** through 5-exo cyclization of acyl radical **B**. The acyl radical

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[12] (a) Bowry, V. W.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5699. (b) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151.

[13] For precedents of electron transfer from low-valent palladium and platinum complexes, see: (a) Kramer, A. V.; Osborn, J. A. *J. Am. Chem. Soc.* **1974**, *96*, 7832. (b) Kramer, A. V.; Labinger, J. A.; Bradley, J. S.; Osborn, J. A. *J. Am. Chem. Soc.* **1974**, *96*, 7145. Miyaura and co-workers also proposed an electron transfer from Pd(0) to alkyl iodides to afford a radical pair (Pd(I)I + alkylradical); see ref 8b.

species **D** generated from CO and alkyl radical **C** couples with Pd(I)I to lead to acylpalladium intermediate **E** and gives the alkynyl ketone through an intermediate **F**. In this reaction mechanism, a rather unfamiliar Pd(I)I-type species is postulated. This may exist in an equilibrium with PdI dimer[14] under photoirradiation conditions.[15]

In summary, we have demonstrated a three-component coupling reaction of alkyl iodides, CO, and alkynes leading to alkynyl ketones that was affected by a Pd/light combined system. This protocol employs readily available alkyl iodides and terminal alkynes and could become a standard method for alkynyl ketone synthesis.

Acknowledgment. T.F. and I.R. thank JSPS and MEXT Japan for funding. We thank Prof. Armido Studer for stimulating discussions on the mechanism involving persistent radicals.

Supporting Information Available: Experimental procedure and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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[14] For photogeneration of Pd radical from Pd dimer complex, see: Lemke, F. R.; Kubiak, C. P. *J. Organomet. Chem.* **1989**, *373*, 391.

[15] It would be also possible to assume that $^{\bullet}$C(O)Pd(II)I might exist as a persistent radical. For the persistent radical effect, see the following reviews: (a) Fischer, H. *Chem. Rev.* **2001**, *101*, 3581. (b) Studer, A. *Chem.—Eur. J.* **2001**, *7*, 1159. (c) Studer, A. *Chem. Soc. Rev.* **2004**, *33*, 267. (d) Studer, A.; Schulte, T. *Chem. Rec* **2005**, *5*, 27. Also see: (e) Focsaneanu, K. S.; Aliaga, C.; Scaiano, J. C. *Org. Lett.* **2005**, *7*, 4979.