ORGANIC LETTERS

2002
Vol. 4, No. 17
2849−2851

Carbon Monoxide Free Aminocarbonylation of Aryl and Alkenyl Iodides Using DMF as an Amide Source

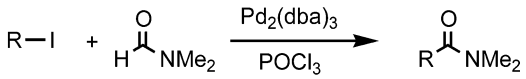
Kazushi Hosoi,[†] Kyoko Nozaki,*[†,‡,1] and Tamejiro Hiyama*[,†]

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan, and PRESTO, JST, Honcho, 4-1-8, Kawaguchi, Saitama 332-0012, Japan

nozaki@chembio.t.u-tokyo.ac.jp

Received May 23, 2002

ABSTRACT

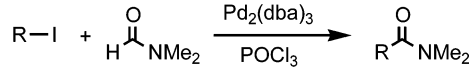


R = aryl or alkenyl

Palladium-catalyzed coupling reaction of *N,N*-dimethylformamide with aryl or alkenyl halides successfully proceeded in the presence of phosphoryl chloride to afford the corresponding tertiary amides in good yields.

In 1974, Heck reported the synthesis of amides from aryl, heterocyclic, and alkenyl halides by the reaction with primary or secondary amines and carbon monoxide catalyzed by Pd species.[2−5] Later, Yamamoto et al. found the double carbonylation of aryl halides afforded α-keto amides and studied comprehensively the mechanistic aspects of both single- and double-carbonylative amide formations.[6,7] Recently, Indolese et al. have reported that formamides are employable as the amine source in the palladium-catalyzed aminocarbonylation to give primary amides.[8] All the precedents utilized carbon monoxide as the carbonyl source, and the reactions were carried out under a CO atmosphere. Here, we report the first example of CO-free aminocarbonylation of aryl and alkenyl halides. In the presence of Pd catalyst, the coupling reaction of aryl and alkenyl iodides with *N,N*-dimethylformamide (DMF) produces the corresponding aromatic amides in one step (Scheme 1). The use of phosphoryl chloride ($POCl_3$) as an additive is the key for the success.

Scheme 1. Aminocarbonylation of Aryl and Alkenyl Iodide with *N,N*-Dimethylformamide



1 **2**

R = aryl or alkenyl

In the presence of $Pd_2(dba)_3$, 4-iodobenzotrifluoride (**1a**) was heated with 2 mol of $POCl_3$ in DMF for 24 h to give *N,N*-dimethyl-(4-trifluoromethyl)benzamide (**2a**). In the absence of $POCl_3$, homocoupling product **3a** was obtained in 12% yield, and most of **1a** remained unchanged. When aryl iodide **1a** was treated with $POCl_3$ in the absence of Pd catalyst, no reaction took place. The use of 1 equiv of $POCl_3$

[†] Kyoto University.
[‡] JST.

(1) Present Address: Department of Chemistry and Biotechnology, Graduate School of Engineering, The University of Tokyo, Hongo, Bunkyo-ku 113-8656 Japan.

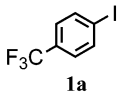
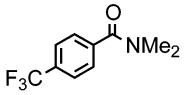
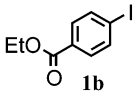
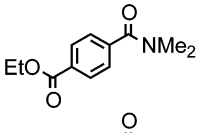
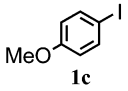
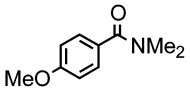
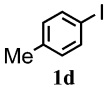
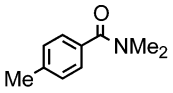
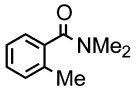
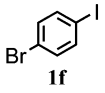
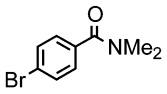
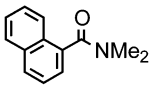
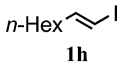
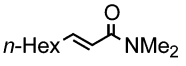
(2) Heck, R. F. In *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985; p 352.
(3) Tsuji, J. In *Palladium Reagents and Catalysts*; John Wiley and Sons Ltd: Chichester, 1995; p 188.
(4) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327.
(5) Aryl chlorides are also applicable to the amide formation: Perry, R. J.; Wilson, B. D. *J. Org. Chem.* **1996**, *61*, 7482.
(6) (a) Ozawa, F.; Yamamoto, A. *Chem. Lett.* **1982**, 865. (b) Ozawa, F.; Soyama, H.; Yamamoto, T.; Yamamoto, A. *Tetrahedron Lett.* **1982**, *23*, 3383. (c) Ozawa, F.; Soyama, H.; Yanagihara, I.; Aoyama, H.; Takino, K.; Izawa, T.; Yamamoto, T.; Yamamoto, A. *J. Am. Chem. Soc.* **1985**, *107*, 3235. (d) Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 433.
(7) Kobayashi, T.; Tanaka, M. *J. Organomet. Chem.* **1982**, *233*, C64.
(8) Schnyder, A.; Beller, M.; Mehltretter, G. Nsenda, T.; Studer, M.; Indolese, A. F. *J. Org. Chem.* **2001**, *66*, 4311.

10.1021/ol026236k CCC: $22.00
Published on Web 07/24/2002

with **1a** retarded the reaction. Both reaction at lower temperatures and use of other Lewis acids such as $BF_3{\cdot}OEt_2$, $SnCl_4$, or $TiCl_4$ were futile. The reaction is specific for DMF, and no coupling product was obtained with *N*,*N*-dimethylacetamide, *N*-methylformamide, formamide, benzaldehyde, or butyl formate.

Various aryl iodides are applicable to the reaction. The results are summarized in Table 1.[9] The aminocarbonylation proceeded smoothly for iodobenzenes bearing either an electron-withdrawing or an electron-donating group at the para position (entries 2−4). The substituent at the ortho position does not affect the reaction (entry 5). Aryl bromides are inert against the current aminocarbonylation, and thus, iodide can be converted to an amide group, selectively (entry 6). 1-Iodonaphthalene (**1g**) and alkenyl iodide **1h** also gave the corresponding amides (entries 7 and 8).

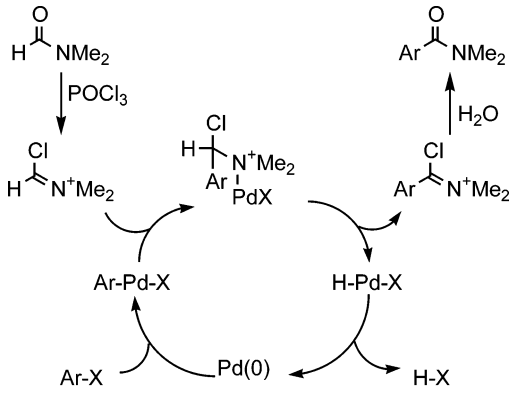
Table 1. Aminocarbonylation of Organic Halides in DMF Using Phosphoryl Chloride[a]

entry	organic halide	time (h)	product	isolated yield (%)
1	 **1a**	24		92[b]
2	 **1b**	10		72
3	 **1c**	20		87
4	 **1d**	20		92
5	 **1e**	24		89
6	 **1f**	36		84
7	 **1g**	20		90
8	 **1h**	36		66[c]

[a] The reactions were performed using **1** (0.3 mmol), $Pd_2(dba)_3$ (2.5 mol %), $POCl_3$ (0.6 mmol), and DMF (3 mL) at 120 °C, unless otherwise stated. [b] The reaction was carried out using 0.1 mmol of **1a**. [c] Including 13% of isomers (determined by GCMS).

An admixture of DMF and $POCl_3$ is known to produce imminium salt $[Me_2N^+{=}CHCl]{\cdot}[Cl_2P(=O)O^-]$ (Vilsmeier reagent).[10] Also, oxidative addition of aryl halide to Pd(0) is likely to take place affording arylpalladium halide under the reaction conditions.[11] Thus, we consider the reaction proceeds via the Heck-type addition of aryl halides to an imminium species as shown in Scheme 2. Recently, Ishiyama and Hartwig reported the Rh-catalyzed Heck-type addition of aryl halides to *N*-pyrazylaldimines.[12] They describe that the existence of the neighboring nitrogen atom[13] is essential for the carbon−nitrogen double bond to insert into the aryl−rhodium bond. Unlike their studies, the Heck-type addition of aryl−palladium, to an imminium in our case, did not require the neighboring effect. This may be attributed to the higher electrophilicity of an imminium than an imine.

Scheme 2. Probable Mechanism for the Aminocarbonylation: Heck-Type Addition of Aryl Halide to C−N Double Bond and β-Hydride Elimination



Two other possible mechanisms are drawn in Scheme 3. One is the neucleophilic addition of an arylpalladium halide to a Lewis acid activated DMF to form a palladium alkoxide followed by β-hydride elimination.[14] Another one is the oxidative addition of a C−H bond of DMF[15] followed by exchange process yielding $Ar{-}Pd{-}CONMe_2$, which provides the product amide via reductive elimination. Instead of the exchange, insertion of Ar−X to $Ar{-}Pd{-}CONMe_2$ to afford Pd(IV) might be an alternative precursor for the

(9) **Representative Procedure.** A typical procedure for the aminocarbonylation is as follows. To a mixture of ethyl 4-iodobenzoate (**1b**, 82.8 mg, 0.30 mmol) and $Pd_2(dba)_3$ (6.9 mg, 15 mmol of Pd) in DMF (3 mL) was added $POCl_3$ (92.0 mg, 0.60 mmol), and the mixture was heated at 120 °C for 10 h. After aqueous workup, the crude mixture was purified by silica gel column chromatography (hexane/AcOEt = 3/1) to obtain *N*,*N*-dimethyl-(4-ethoxycarbonyl)benzamide (**2b**) in 72% yield.

(10) (a) Vilsmeier, A.; Haack, A. *Chem. Ber.* **1927**, *60*, 119. (b) James, P. N. In *Organic Syntheses*; Wiley and Sons: New York, 1963; Collect. Vol. IV, p 539.

(11) Examples of oxidative addition of Ar−I to Pd(0): a) Fitton, B. P.; Johnson, M. P.; McKeon, J. E. *J. Chem. Soc., Chem. Commun.* **1968**, 6. See also ref 2.

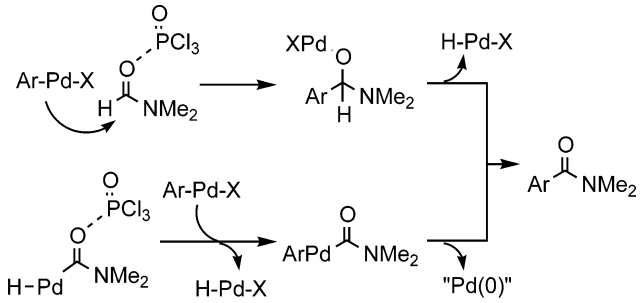
(12) Ishiyama, T.; Hartwig, J. *J. Am. Chem. Soc.* **2000**, *122*, 12043.

(13) Jun, C.-H.; Hong, J.-B. *Org. Lett.* **1999**, *1*, 887.

(14) (a) Quan, L. G.; Lamrani, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*. 4827. (b) Quan, L. G.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3545. (c) Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4089.

(15) (a) Tatsumi, T.; Tominaga, H.; Hidai, M.; Uchida, Y. *J. Organomet. Chem.* **1981**, *215*, 67. (b) Tsuji, Y.; Yoshii, S.; Ohsumi, T.; Kondo, T.; Watanabe, Y. *J. Organomet. Chem.* **1987**, *331*, 379.

Scheme 3. Two Other Possible Mechanisms: (i) Nucleophilic Addition of Arylpalladium to a Carbonyl Activated by a Lewis Acid and (ii) Oxidative Addition of Formyl C−H Followed by an Exchange Process



reductive elimination of amide.[16,17] Here, if the reaction involved a nucleophilic addition of arylpalladium, the more electrophilic aldehyde would be more reactive. Meanwhile, if the C−H activation of the formyl group of DMF were the key reaction, butyl formate, which has similar formyl group, would have given the product. The fact that no reaction was observed either with benzaldehyde or butyl formate may suggest that the formation of highly electrophilic species, the Vilsmeier reagent in this case, is essential for the reaction to take place. It should be noted that, in all the three mechanisms mentioned above, conventional examples require the existence of base to regenerate Pd(0) species from H−Pd−X, although the conditions we employed do not contain any base.

In conclusion, here we have reported the efficient single-step synthesis of arylcarboxamides from aryl halides and DMF. The reaction proceeds in the absence of carbon monoxide unlike the precedent aminocarbonylation reactions.

Acknowledgment. We acknowledge financial support from the Ministry of Education, Science, Sports and Culture, Japan. T.H. is thankful for a Grant-in-Aid for COE Research on Elements Science, No. 12CE2005.

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

OL026236K

(16) (a) Meegalla, S. K.; Taylor, N. J.; Rodrigo, R. *J. Org. Chem.* **1992**, *57*, 2422. (b) Larock, R. C.; Doty, M. J. *J. Org. Chem.* **1993**, *58*, 4579.

(17) Satoh, T.; Itaya, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1996**, 823.