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

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ABSTRACT

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 \(\alpha\)-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).

Scheme 1. Aminocarbonylation of Aryl and Alkenyl Iodide with \(N,N\)-Dimethylformamide

In the presence of \(Pd(dba)_3\), 4-iodobenzotrifluoride (1a) was heated with 2 mol of POCl₃ in DMF for 24 h to give \(N,N\)-dimethyl-(4-trifluoromethyl)benzamide (2a). In the absence of POCl₃, homocoupling product 3a was obtained in 12% yield, and most of 1a remained unchanged. When aryl iodide 1a was treated with POCl₃ in the absence of Pd catalyst, no reaction took place. The use of 1 equiv of POCl₃...
with 1a retarded the reaction. Both reaction at lower temperatures and use of other Lewis acids such as BF$_3$·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 of iodobenzenes bearing either an electron-withdrawing or an electron-donating group at the para position (entries 2 and 4) proceeded smoothly for iodobenzenes bearing either an electron-withdrawing or an electron-donating group at the ortho position (entry 5). Aryl bromides are inert against the current aminocarbonylation, and thus, position does not affect the reaction (entry 5). Aryl bromides such as SnCl$_4$, or TiCl$_4$ were futile. The reaction is specific for DMF, temperatures and use of other Lewis acids such as BF$_3$·OEt$_2$.

Probable Mechanism for the Aminocarbonylation:

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

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 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 halides to an imminium species as shown in Scheme 2. Recently, Ishiyama

| Table 1. Aminocarbonylation of Organic Halides in DMF Using Phosphoryl Chloride$^*$ |
|---|---|---|---|---|
| entry | organic halide | time (h) | product | isolated yield (%) |
| 1 | F$_3$C-I | 24 | F$_3$C-C=N-Me$_2$ | 92$^b$ |
| 2 | OEt-O | 10 | OEt-C=N-Me$_2$ | 72 |
| 3 | MeO-O | 20 | MeO-C=N-Me$_2$ | 87 |
| 4 | Me | 20 | Me-C=N-Me$_2$ | 92 |
| 5 | Ie | 24 | Ie-C=N-Me$_2$ | 89 |
| 6 | Br-I | 36 | Br-C=N-Me$_2$ | 84 |
| 7 | Ig | 20 | Ig-C=N-Me$_2$ | 90 |
| 8 | n-Hex-I | 36 | n-Hex-C=N-Me$_2$ | 66$^c$ |

$^*$ 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).

(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/acetone = 3/1) to obtain N,N-dimethyl-(4-ethoxycarbonyl)benzamide (2b) in 72% yield.


reductive elimination of amide. 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.


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