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Dimethylformamide as a Carbon Monoxide Source in Fast Palladium-Catalyzed Aminocarbonylations of Aryl Bromides

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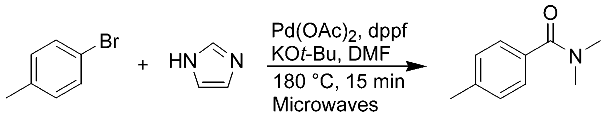
Received May 24, 2002

Abstract: Dimethylformamide (DMF) acts as an efficient source of carbon monoxide and dimethylamine in the palladium-catalyzed aminocarbonylation (Heck carbonylation) of *p*-tolyl bromide to provide the dimethylamide. Addition of amines to the reaction mixture in excess delivers the corresponding aryl amides in good yields. The amines employed, benzylamine, morpholine, and aniline, all constitute good reaction partners. The reaction proceeds smoothly with bromobenzene and more electron-rich aryl bromides, but electron-deficient aryl bromides fail to undergo aminocarbonylation. The reactions are conducted at 180−190 °C for 15−20 min with microwave heating in a reaction mixture containing imidazole and potassium *tert*-butoxide: the latter is required to promote decomposition of the DMF solvent at a suitable rate. The beneficial effects of controlled microwave irradiation as an energy source for the rapid heating of the carbonylation reaction mixture are demonstrated. The carbonylation procedure reported herein, which relies on the in situ generation of carbon monoxide, serves as a convenient alternative to other carbonylation methods and is particularly applicable to small-scale reactions where short reaction times are desired and the direct use of carbon monoxide gas is impractical.

Palladium-catalyzed aminocarbonylation (Heck carbonylation) is a selective and useful method for the direct synthesis of aryl amides from aryl halides.[1] Carbon monoxide gas is the most commonly employed source of the carbonyl group in these transformations.[1c−e] The recent interest in new high-throughput chemistry techniques has redirected focus toward the automated handling of liquids and solids rather than the development of special gas delivery systems that, in theory, also could make the direct use of reactive gases feasible for providing reactants in fast reactions. Today, the somewhat troublesome gas handling procedure and the toxicity of carbon monoxide limit the use of carbonylation reactions for the small-scale synthesis of compound libraries.[2]

SCHEME 1



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More than three decades ago, Corey and Hegedus reported the use of several equivalents of the hazardous $Ni(CO)_4$ as a combined C−X activator and liquid carbon monoxide source[3] for efficient aminocarbonylation reactions with vinyl bromides. Recently, our laboratory reported that the less harmful $Mo(CO)_6$ acts as a solid carbon monoxide releasing reagent[4] in microwave-assisted palladium-catalyzed[5] carbonylation reactions. This technique of in situ delivery of carbon monoxide is very suitable for high-throughput organic synthesis. However, it is obvious that the concept of in situ liberation would be even more appealing if inexpensive organic materials, preferably the solvent itself, could serve as the source of carbon monoxide. In fact, the common solvent dimethylformamide (DMF) has previously been utilized as a liquid carbon monoxide source but only for preparation of inorganic metal−carbonyl complexes.[6]

We herein report that dimethylformamide is an excellent carbon monoxide precursor in fast palladium-catalyzed aminocarbonylations of aryl bromides. In the presence of potassium *tert*-butoxide (KO*t*-Bu), imidazole, and various amines, the corresponding aryl amides were isolated in moderate to high yields after reaction times of 15−20 min at 180−190 °C.

In an ongoing medicinal chemistry program,[7] we wished to synthesize *N*-arylated imidazoles, which we planned to prepare by Buchwald−Hartwig aminations using a strong base.[8] In a model reaction, we employed imidazole and 4-bromotoluene as reactants with DMF as solvent but were surprised to find that the dimethylamide **1**, rather than the aryl imidazole, was the predominant product, formed in good yield by controlled microwave heating at 180 °C for 15 min (Scheme 1). This finding encouraged us to study the scope and limitations of DMF as a potential carbon monoxide precursor for carbonylation reactions in more detail.

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10.1021/jo025965a CCC: $22.00

SCHEME 2

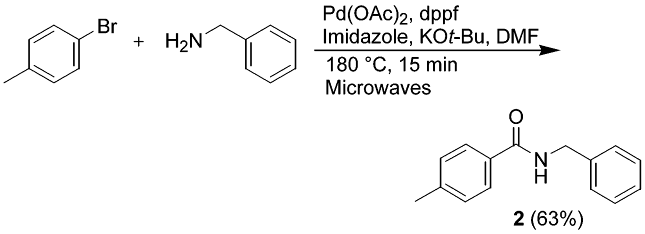

TABLE 1. Palladium-Catalyzed Aminocarbonylation of 4-Bromotoluene under Different Reaction Conditions

entry[a]	solvent	precatalyst	ligand	additive	base	isolated yield of **2** (%)
1	DMF	Pd(OAc)$_2$	dppf	imidazole	KO*t*-Bu	63
2	DMF	Pd(OAc)$_2$	dppp	imidazole	KO*t*-Bu	37
3	DMF	Pd(OAc)$_2$	binap	imidazole	KO*t*-Bu	49
4	DMF	Pd(OAc)$_2$	PPh$_3$	imidazole	KO*t*-Bu	0
5	DMF	Pd(OAc)$_2$	P(*o*-Tol)$_3$	imidazole	KO*t*-Bu	0
6	DMF	Pd(OAc)$_2$		imidazole	KO*t*-Bu	*b*
7	DMF	Pd(OAc)$_2$	dppf	*N*-Me-imidazole	KO*t*-Bu	0[c]
8	DMF	Pd(OAc)$_2$	dppf	DMAP	KO*t*-Bu	0[c]
9	DMF	Pd(OAc)$_2$	dppf		KO*t*-Bu	0[c]
10	DMF		dppf	imidazole	KO*t*-Bu	0[d]
11	DMF	Pd(OAc)$_2$	dppf	imidazole	K$_2$CO$_3$	0[d]
12	DMAc	Pd(OAc)$_2$	dppf	imidazole	KO*t*-Bu	0[c]

[a] Reaction conditions: 4-bromotoluene (0.75 mmol), benzylamine (3.0 mmol), additive (0.75 mmol), KO*t*-Bu (0.75 mmol), palladium acetate/ligand (0.038 mmol/0.038 mmol), solvent (1 mL), and microwave heating (180 °C, 15 min). [b] Vial eruption. [c] *N*-Benzyl-4-methylaniline was the major product. [d] *N*-Benzylformamide was the major product.

First, we decided to employ benzylamine as an external amine to assess whether aryl amides other than aryl dimethylamides were accessible. Thus, 4-bromotoluene (0.75 mmol), benzylamine (3.0 mmol), imidazole (0.75 mmol), KO*t*-Bu (0.75 mmol), and palladium acetate/dppf (0.038 mmol/0.038 mmol) were warmed with a microwave synthesizer in sealed Pyrex vessels to 180 °C in DMF. The aryl benzylamide **2** could be isolated in 63% yield after a reaction time of 15 min (Scheme 2).

A series of combinations of reagents were screened, and the results are presented in Table 1. Only bidentate ligands delivered products, while monodentate ligands resulted in no desired product **2** (cf. entries 1–5).

Attempts to conduct the reaction with palladium acetate in the absence of ligand caused an uncontrollably high pressure in the reaction vessel and in some cases also an eruption of the contents from the reaction vessel (entry 6). The cause of the high pressure may be attributed to deposition of metallic palladium on the Pyrex wall and subsequent failure of the temperature–microwave feedback control. Furthermore, neither employing *N*-methylimidazole or DMAP (4-(dimethylamino)pyridine) instead of imidazole nor the absence of imidazole provided **2** (<1% by GC/MS, entries 7–9).

Omitting the palladium catalyst or employing potassium carbonate as base resulted in the predominant formylation of the benzylamine and recovery of the starting material (entries 10, 11). It also became clear that a reaction conducted in dimethyl acetamide (DMAc) did not render **2** with the Buchwald–Hartwig amination as the predominant reaction (entry 12). The reactions in Table 1 were conducted with 1.0 equiv of KO*t*-Bu at 180 °C. By increasing the amount of base to 1.5 equiv, the yield of **2** was improved to 73%, while 2.0 equiv resulted in somewhat lower isolated yields. A considerable amount of starting material was recovered after shortening the reaction time to 10 min (53% yield) or after performing the reaction at 150 °C for 15 min (3% yield), but a minor improvement was achieved (76% yield) by performing the reaction at 190 °C for 15 min.[9]

The preparative results obtained with various aryl bromides and different amines are shown in Table 2. As apparent from Table 2, benzylamine, aniline, and the secondary amine morpholine were all suitable amines for the aminocarbonylation reaction with 4-bromotoluene, producing isolated yields of the amides **2**–**4**, ranging from 76% to 78% with high selectivities (<5% of **1**). The yield of **1**, which relies on the liberation of dimethylamine from the solvent, was slightly lower (59%, entry 1). In addition, electron-rich and sterically hindered aryl bromides also afforded high yields of **5**–**7** (70–94%), while no trace of the desired aryl amide was observed in reactions with electron-deficient 4-bromobenzonitrile or 4-bromobenzotrifluoride. Instead, 4-benzylaminobenzonitrile and 4-benzylaminobenzotrifluoride, derived from competing Buchwald–Hartwig aminations,[8] were isolated as the major products. In the absence of any aryl bromide, transamidation occurred and *N*-formylbenzylamine was isolated in 67% yield.

We postulate that the aminocarbonylation reactions proceed as outlined in Scheme 3. It is well established that DMF decarbonylates under heating to yield carbon monoxide and dimethylamine in the presence of base.[10] However, the present methodology is, to the best of our knowledge, the first example where the carbon monoxide is both liberated from the solvent and thereafter utilized in an efficient organic carbonylation procedure.[6b]

As apparent from the pressure graphs, that we anticipate to reflect the liberation of these gases, KO*t*-Bu, not imidazole or the palladium catalyst,[6b,11] seems to promote this decomposition upon heating to 180 °C (Figure 1A). Both of the two components formed by the DMF decarbonylation reaction participate in the aminocarbonylation reaction to give **1**, and the pressure in the reaction vessel during the aminocarbonylation is found to be relatively low (Figure 1B).

The lower pressure monitored is accounted for by the consumption of carbon monoxide and dimethylamine in the reaction process. The arylpalladium oxidative addition complex (**8**), initially created from palladium(0) and the aryl bromide, coordinates the carbon monoxide, and subsequently, an aroylpalladium compound (**9**) is generated.[1c–e] The nucleophilic catalyst imidazole reacts with the aroylpalladium species, delivering a reactive aroylimidazole (**10**), anticipated to be attacked smoothly by the amine to provide the amide **1**.[12] Since substitution of imidazole for *N*-methylimidazole is deleterious to the reaction, it seems that the formation of the aroylimidazole species is crucial for the reaction to occur.

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[9] Corresponding experiment with classical oil-bath heating of 130 °C for 10 h furnished a 25% yield of compound **2**.

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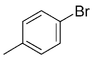
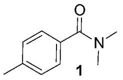
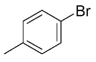
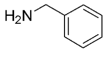
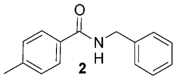
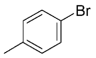
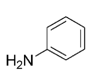
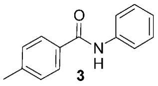
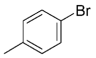
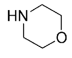
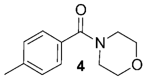
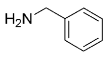
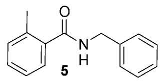
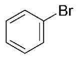
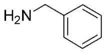
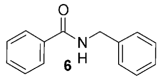
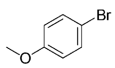
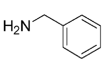
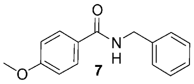
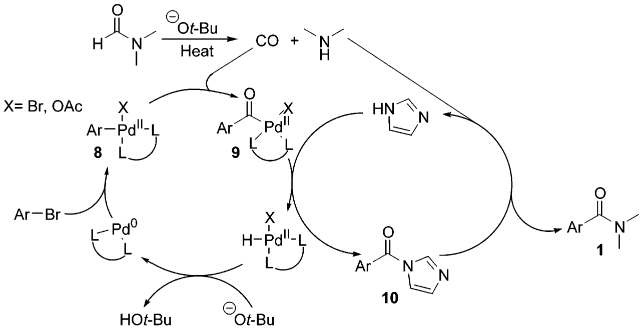
TABLE 2. Palladium-Catalyzed Aminocarbonylation of Aryl Bromides with DMF as Carbon Monoxide Source

Entry[a]	Aryl Bromide	Amine	Product	Time (min)	Temp (°C)	Isolated Yield (%)
1		-	 **1**	15	180	59
2			 **2**	15	190	76
3			 **3**	20	190	77
4			 **4**	20	190	78
5			 **5**	20	190	94
6			 **6**	15	190	82
7			 **7**	20	190	70

[a] Reaction conditions: aryl bromide (0.75 mmol), amine (3.0 mmol), imidazole (0.75 mmol), KO*t*-Bu (1.13 mmol), palladium acetate/dppf (0.038 mmol/0.038 mmol), DMF (1 mL), microwave heating. Less than 5% of **1** was formed in entries 2−7.

SCHEME 3



The activation of carboxylic acids by conversion to the corresponding carbonylimidazoles is a common strategy in peptide synthesis.[13] In entries 2−7 in Table 2, large excesses (4 equiv) of benzylamine, aniline, or morpholine were added to the reaction mixture to enable favorable competition with dimethylamine. The KO*t*-Bu, which is consumed in the regeneration of the palladium, is added in excess to ensure the continuous liberation of carbon monoxide and the dimethylamine. The use of dppf and binap effected efficient generation of product **2**, while reactions with the monodentate ligands failed (Table 1). This corroborates well with the fact that bidentate ligands are known to inhibit the agglomeration of Pd atoms and the formation of less-active palladium−carbonyl complexes.[14]

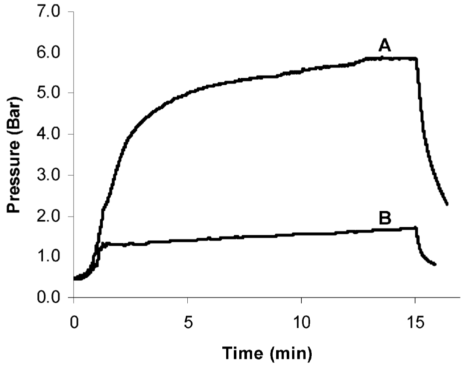


FIGURE 1. Pressure curves recorded from microwave heating of sealed vessels at 180 °C (15 min): (A) DMF, KO*t*-Bu; (B) DMF, imidazole, 4-bromotoluene, Pd(OAc)$_2$, dppf, KO*t*-Bu (Table 2, entry 1).

The fact that the electron-deficient aryl bromides do not deliver aryl amides is accounted for, at least in part, by a nonfavored insertion of carbon monoxide to afford the aroylpalladium complex from the arylpalladium−carbonyl complex. This assumption is supported by the previous observation that electron-poor aroylpalladium halides are considerably more prone to undergoing decarbonylation than their electron-rich counterparts.[15] Hence, with the electron-deficient aryl bromides, the competing Buchwald−Hartwig amination was strongly favored.

Recently, Schnyder et al. reported on formamide as an ammonia synthon and efficiently synthesized, under carbon monoxide pressure, a series of primary aromatic

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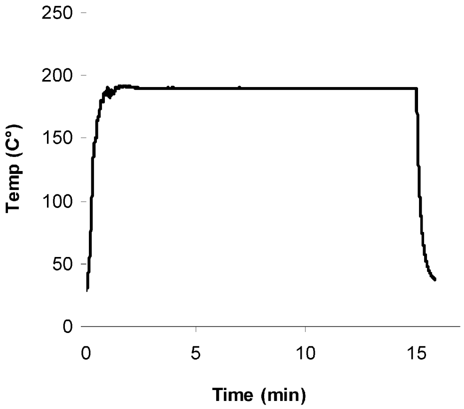

FIGURE 2. Temperature curve recorded from microwave synthesizer heating of a typical reaction mixture (Table 2, entry 2).

amides in high yields by aminocarbonylation of aryl halides.[12] These reactions required a palladium catalyst in combination with a nucleophilic Lewis base such as imidazole or DMAP. In one example given, an aryl dimethylamide was prepared in 89% yield. Imidazole was utilized here as the base and DMF as both the solvent and the dimethylamine source. The reaction proceeded for 18 h at a carbon monoxide pressure of 5 bar. Importantly, the inlet of carbon monoxide gas into the reaction flask was a prerequisite for amide formation. This is sharply different from our observations under the more basic conditions depicted in Scheme 1 and Table 2.

The fast heating of the reaction mixture achieved by controlled microwave irradiation is demonstrated in Figure 2. A temperature of 190 °C is reached after only 2 min by the high power and specific internal heating of the polar reaction mixture, and the temperature drops rapidly, by active air-cooling, after the switch off of the microwave power. Wall effects and seed formation are suppressed by this methodology, and superheating can be achieved both conveniently and rapidly.[16]

In summary, the solvent DMF has been shown to be an excellent source of carbon monoxide and dimethylamine, with both gases serving as building blocks in the palladium-catalyzed aryl amide synthesis, provided that a strong base, such as KO*t*-Bu and imidazole, is used as a coreactant. An excess of amine in the reaction medium affords the corresponding aryl amide in good isolated yield. The in situ carbon monoxide generation methodology works efficiently with bromobenzene and more electron-rich aryl bromides, but aminocarbonylation of electron-deficient aromatic systems fails. Although only a limited number of examples are presented herein, we believe the method will attract attention due to the experimental simplicity and the fact that no external carbon monoxide gas needs to be added. It should serve as a convenient alternative to other existing methodologies for the aminocarbonylation of aromatics: in particular for small-scale reactions where short reaction times are desired.

Experimental Section

General Considerations. ^1H and ^{13}C NMR spectra were recorded at 270.2 and 67.9 MHz, respectively. Chemical shifts are given as δ values (ppm) downfield from tetramethylsilane. Flash column chromatography was performed on silica gel 60 (0.04−0.063 mm). Thin-layer chromatography was performed on precoated silica gel F-254 plates (0.25 mm) and was visualized with UV light or ninhydrin in ethanol. All chemicals were purchased from commercial suppliers and used directly without further purification.

All microwave reactions were carried out in 2-mL vials. The microwave heating was performed in a single mode cavity, producing controlled irradiation at 2450 MHz. **It is recommended to perform these pressurized high-temperature reactions in a dedicated and safe microwave reactor.** GC-MS was performed with an electron impact (70 eV) mass selective detector and a capillary column using a 70−305 °C temperature gradient. The isolated compounds **1**,[17] **2**,[18] **3**,[19] **5**,[18a,20] **6**,[21] **7**,[22] and *N*-formylbenzylamine[23] have previously been characterized and corresponded satisfactorily with NMR literature data. The isolated compound **4**[24] has previously been characterized and corresponded satisfactorily with boiling point data; NMR data are provided in the Supporting Information.

General Procedure for Synthesis of Amides 2−7. A vial was charged with aryl bromide (0.75 mmol), amine (3 mmol), $Pd(OAc)_2$ (0.038 mmol), dppf (0.038 mmol), imidazole (0.75 mmol), potassium *tert*-butoxide (1.13 mmol), and DMF (1 mL). The reaction mixture was flushed with nitrogen, and the cap was tightened thoroughly. The vessel was exposed to microwave irradiation for 15−20 min. The reaction tube was thereafter cooled to room temperature, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine and dried over potassium carbonate, and the solvent was removed under reduced pressure. The products were purified on silica gel.

Acknowledgment. We gratefully acknowledge Dr. Kristofer Olofsson for creative discussions. We also acknowledge the financial support from the Swedish Research Council and from the Knut and Alice Wallenbergs Foundation. We thank Personal Chemistry for providing the microwave synthesizers.

Supporting Information Available: ^1H and ^{13}C NMR data and purification details for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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