JOURNAL OF combinatorial CHEMISTRY



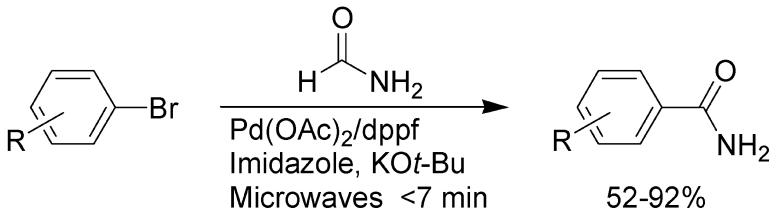
Report

# Formamide as a Combined Ammonia Synthon and Carbon Monoxide Source in Fast Palladium-Catalyzed Aminocarbonylations of Aryl Halides

Yiqian Wan, Mathias Alterman, Mats Larhed, and Anders Hallberg

*J. Comb. Chem.*, **2003**, 5 (2), 82-84• DOI: 10.1021/cc0200843 • Publication Date (Web): 25 January 2003






## More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML



Journal of Combinatorial Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

# Formamide as a Combined Ammonia Synthon and Carbon Monoxide Source in Fast Palladium-Catalyzed Aminocarbonylations of Aryl Halides

Yiqian Wan, Mathias Alterman,* Mats Larhed, and Anders Hallberg

*Department of Organic Pharmaceutical Chemistry, BMC, Uppsala University, P.O. Box 574, SE-751 23, Uppsala, Sweden*

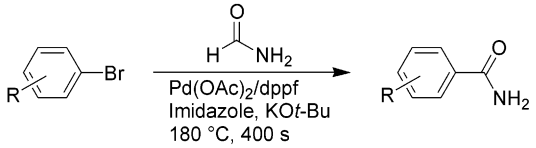
*Received September 19, 2002*

**Introduction.** The palladium-catalyzed carbonylation of aryl halides in the presence of carbon monoxide gas and amines constitutes a versatile methodology for selective, direct synthesis of secondary and tertiary benzamide derivatives.[1] Unfortunately, the synthesis of primary amides is recognized as considerably more difficult, which is attributable to both the lower nucleophilicity of ammonia and difficulties associated with the handling of gaseous ammonia. In 1998, Morera and Ortar[2] addressed this issue and exploited hexamethyldisilazane (HMDS), which had been employed successfully as a synthon for ammonia in other reactions.[3] Good to excellent yields of primary benzylamides could now be achieved with palladium-catalyzed aminocarbonylation reactions after acidic work up.[2] Ueda et al. utilized a titanium−nitrogen complex as an ammonia source, which also delivered the primary benzamides, although in more modest yields.[4] The synthesis of primary aromatic amides by aminocarbonylation of aryl halides using formamide as an ammonia synthon, recently reported by Schnyder et al. represents a major milestone.[5] The reported procedure is efficient and provides high yields of the primary benzamides under a carbon monoxide pressure of 5 bar in an autoclave. Furthermore, this methodology avoids the use of either expensive or difficult to handle reagents, such as HMDS and ammonia.[5]

We believed that the procedure of Schnyder et al. would be even more attractive if the handling of toxic carbon monoxide gas also could be avoided,[6] in particular for applications to small scale reactions in the context of high-throughput library generation.[7] We herein report the aminocarbonylation of aryl halides where formamide is used not only as a solvent, but additionally serves as a source of ammonia and carbon monoxide. Consequently, no cumbersome handling of gases is needed, and good yields of primary benzamides are obtained after reaction times of <7 min.

**Results.** A series of diverse aryl bromides (and one aryl iodide) in formamide were heated in sealed Pyrex vessels for 400 s at 180 °C with microwave irradiation.[8] Because the catalytic system $Pd(OAc)_2$/dppf (5 mol %, 1:1) was employed, imidazole was utilized as the nucleophilic catalyst, and KO*t*-Bu, necessary for efficient formamide decomposition, was used as the base[9] (Scheme 1). The energy transfer from the magnetron to the sealed reaction system is very rapid as a result of the high loss tangent of formamide (tan $\delta = 0.56$),[10] the high power, and the focused irradiation.[11] The reaction temperature of 180 °C is thus reached after only 30 s. The preparative results are summarized in Table 1. Good isolated yields were obtained with all aryl halides tested, demonstrating that electron-withdrawing and electron-donating groups, in addition to ortho substituents, are well-tolerated. In the initial experiments, longer reaction times, 900 s, were employed, but these reactions were accompanied by significant dehydration to the corresponding nitriles (up to 20% aryl nitriles, as deduced from GC/MS analyses). By shortening the reaction times, this problem was circumvented, and nitrile formation was suppressed considerably while retaining complete aryl halide conversion.[12] Note that to ensure that high yields were obtained, we found it important to commence heating shortly after mixing the reagents (within 10 min).

**Scheme 1**



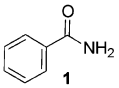
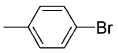
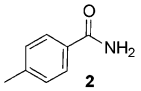
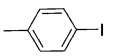
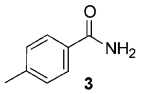
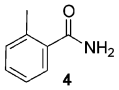
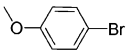
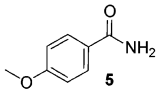
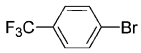
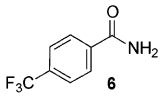
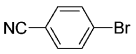
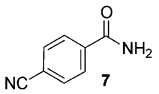
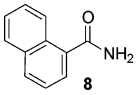

**Discussion.** The conditions used are essentially identical to those we reported recently for the preparation of various secondary and tertiary benzamides.[9] These reactions were performed in the presence of a variety of amines and dimethylformamide (DMF), acting here as a carbon monoxide source.[9] Prior to this study, DMF had been utilized as a liquid carbon monoxide source for the preparation of inorganic metal carbonyl complexes.[13] Like DMF, formamide is known to thermally decompose.[14] Although formamide has been reported to serve as an ammonia synthon,[5] we are, to the best of our knowledge, not aware of any examples in which it has been exploited both as a surrogate for ammonia and as a source of carbon monoxide in the same reaction. It is demonstrated by the pressure graphs that the pressure increases significantly in the sealed vessels, but only after addition of KO*t*-Bu (Figure 1, curves A and D). Therefore, we postulate that the strong base facilitates the decomposition of formamide at high temperatures.

We believe that the aminocarbonylation reaction proceeds as outlined in Scheme 2. Both of the gaseous components formed by the formamide decarbonylation process are consumed in the amide formation, and the pressure in the vessel is therefore reduced during the progress of the reaction (Figure 1, curve C). The arylpalladium oxidative addition complex, initially generated from palladium(0) and the aryl bromide, captures the liberated carbon monoxide, and subsequently an aroylpalladium species is generated,[1] which reacts with the nucleophilic catalyst, imidazole. In the

* To whom correspondence should be addressed. mathias.alterman@orgfarm.uu.se.

10.1021/cc0200843 CCC: $25.00 
Published on Web 01/25/2003

**Table 1.** Palladium-Catalyzed Aminocarbonylation of Aryl Halides with Formamide as Ammonia and Carbon Monoxide Source

| Entry[a] | Aryl Halide | Product | Isolated Yield (%) |
|---|---|---|---|
| 1 |  |  **1** | 83 |
| 2 |  |  **2** | 81 |
| 3 |  |  **3** | 79 |
| 4 |  |  **4** | 86 |
| 5 |  |  **5** | 74 |
| 6 |  |  **6** | 84 |
| 7 |  |  **7** | 52 |
| 8 |  |  **8** | 92 |

[a] Aryl halide (0.75 mmol), imidazole (0.75 mmol), KO*t*-Bu (1.13 mmol), $Pd(OAc)_2$/dppf (0.038 mmol/ 0.038 mmol) and formamide (1 mL), microvave heating (400 s, 180 °C).

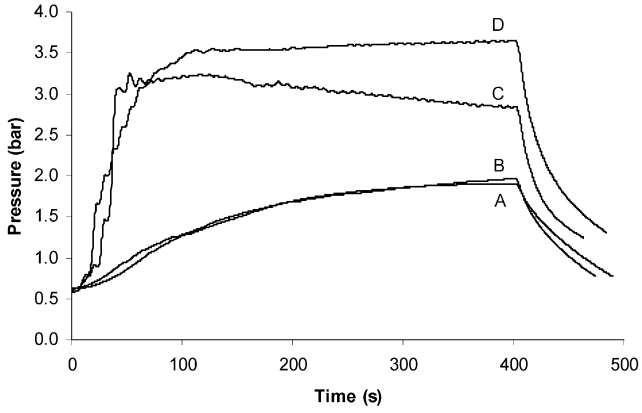
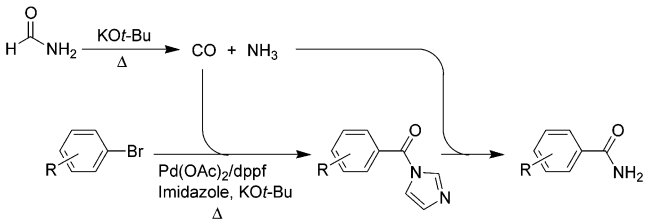



**Figure 1.** Pressure curves recorded from microwave heating of sealed vessels at 180 °C (400 s): (A) formamide (1 mL); (B) formamide (1 mL), imidazole (0.75 mmol); (C) formamide, KO*t*-Bu, imidazole, $Pd(OAc)_2$, dppf, 4-bromotoluene (Table 1, entry 2); and (D) formamide (1 mL), KO*t*-Bu (1.13 mmol).

absence of the imidazole, no benzamides are formed, and it is therefore believed that the aroylimidazole intermediate plays a key role and is attacked by ammonia to afford the aryl amide products.[5,9] Activation of carboxylic acids by conversion to carbonyl imidazoles is a common strategy for peptide bond formation.[15] It is notable that only traces of

**Scheme 2**




products derived from a competing Buchwald−Hartwig amination was encountered, reflecting the lower nucleophilicity of ammonia as compared to primary and secondary amines.[16,17] Instead, dehydration to form nitriles constituted the major side-reaction.[12]

**Conclusion.** In summary, the solvent formamide has been shown both to be an excellent source of carbon monoxide and in parallel to serve as an ammonia synthon, provided that a strong base, such as KO*t*-Bu, is used as additive. The in situ carbon monoxide generation/carbonylation methodology works efficiently with all aryl halides tested. Although the examples presented herein are limited, we believe the method will attract attention because of the short reaction times, the experimental simplicity, and the fact that no external carbon monoxide or ammonia surrogates need to be added. It should constitute a convenient alternative to other existing procedures for the preparation of primary benzamides from aryl halides, particularly applicable to small-scale reactions for which short reaction times are desired.

**Acknowledgment.** We acknowledge the financial support from the Swedish Research Council and from the Knut and Alice Wallenbergs Foundation. We thank Personal Chemistry for providing the Smith microwave synthesizers.

**Supporting Information Available.** Experimental details, including general considerations and the general procedure for the synthesis of amides **1**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

## References and Notes

(1) (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318−3326. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327−3331. (c) Beller, M.; Cornils, B.; Frohning, C. D.; Kohlpaintner, C. W. *J. Mol. Catal. A: Chem.* **1995**, *104*, 17−85. (d) Soderberg, B. C. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 12, pp 241−291. (e) Yamamoto, A.; Kayaki, Y.; Nagayama, K.; Shimizu, I. *Synlett* **2000**, 925−937.

(2) Morera, E.; Ortar, G. *Tetrahedron Lett.* **1998**, *39*, 2835−2838.

(3) (a) King, F. D.; Walton, D. R. M. *J. Chem. Soc., Chem. Commun.* **1974**, 256−257. (b) Pellegata, R.; Italia, A.; Villa, M.; Palmisano, G.; Lesma, G. *Synthesis* **1985**, 517−519. (c) Bruning, J. *Tetrahedron Lett.* **1997**, *38*, 3187−3188.

(4) Ueda, K.; Sato, Y.; Mori, M. *J. Am. Chem. Soc.* **2000**, *122*, 10722−10723.

(5) Schnyder, A.; Beller, M.; Mehltretter, G.; Nsenda, T.; Studer, M.; Indolese, A. F. *J. Org. Chem.* **2001**, *66*, 4311−4315.

(6) Kaiser, N.-F. K.; Hallberg, A.; Larhed, M. *J. Comb. Chem.* **2002**, *4*, 109−111.

(7) (a) Larhed, M.; Hallberg, A. *Drug Discov. Today* **2001**, *6*, 406−416. (b) Everett, J.; Gardner, M.; Pullen, F.; Smith, G. F.; Snarey, M.; Terrett, N. *Drug Discov. Today* **2001**, *6*, 779−785. (c) Goodnow, R. A. *J. Cell. Biochem.* **2001**, 13-21. (d) Hunter, D. *J. Cell. Biochem.* **2001**, 22−27.

(8) (a) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717−727. (b) Alterman, M.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 7984−7989. (c) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582−9584.

(9) Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 6232−6235.

(10) The dissipation factor (tan $\delta$) expresses the ability of a material to transform electromagnetic energy into thermal energy at a given temperature and frequency. A higher value for the tan $\delta$ indicates a higher susceptibility to microwave energy. Gabriel, C.; Gabriel, S.; Grant, E. H.; Halstead, B. S. J.; Mingos, D. M. P. *Chem. Soc. Rev.* **1998**, *27*, 213−224.

(11) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283.

(12) For microwave-promoted synthesis of nitriles from primary amides, see: Bose, D. S.; Jayalakshmi, B. *J. Org. Chem.* **1999**, *64*, 1713−1714.

(13) (a) Rusina, A.; Vlcek, A. A. *Nature* **1965**, *206*, 295−296. (b) Serp, P.; Hernandez, M.; Richard, B.; Kalck, P. *Eur. J. Inorg. Chem.* **2001**, 2327−2336. Formic acid has successfully been utilized as a CO source in hydroxycarbonylation reaction with an iridium catalyst: (c) Simonato, J. P.; Walter, T.; Metivier, P. *J. Mol. Catal. A: Chem* **2001**, *171*, 91−94.

(14) (a) Harada, K. *Nature* **1967**, *214*, 479−480. (b) Kakumoto, T.; Saito, K.; Imamura, A. *J. Phys. Chem.* **1985**, *89*, 2286−2291. (c) Parmeter, J. E.; Weinberg, W. H. *J. Am. Chem. Soc.* **1988**, *110*, 7583−7590.

(15) Sauve, G.; Le Berre, N.; Zacharie, B. *J. Org. Chem.* **1990**, *55*, 3002−3004.

(16) (a) Hartwig, J. F. *Modern Amination Methods*; Wiley-VCH: Weinheim, 2000. (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146.

(17) Anilines were the major side-products in the carbonylation reactions with DMF as solvent; see ref 9.

(18) Friedeburg, L. H. *Justus Liebigs Ann. Chem.* **1871**, *158*, 19−33.

(19) Reed, K. L.; Gupton, J. T.; Solarz, T. L. *Synth. Commun.* **1990**, *20*, 563−571.

(20) Wiley, J. C.; Linn, C. B. *J. Org. Chem.* **1970**, *35*, 2104−2105.

(21) Becke, F.; Gnad, J. *Justus Liebigs Ann. Chem.* **1968**, *713*, 212−214.

(22) O'Connor, C. J.; Martin, R. W.; Calvert, D. J. *Aust. J. Chem.* **1981**, *34*, 2297−2305.

(23) (a) Lichtenberger, J.; Weiss, F. *Bull. Chim. Soc. France* **1962**, 915−619. (b) De Rosa, M.; Brown, K.; McCoy, M.; Ong, K.; Sanford, K. *J. Chem. Soc., Perkin Trans. 2* **1993**, 1787−1790.

(24) (a) Berther, C. *Chem. Ber.* **1959**, *92*, 2616−2621. (b) Chou, W.; Pomerantz, M.; Witzcak, M. K. *J. Org. Chem.* **1990**, *55*, 716−721.

(25) Chakraborty, D. P.; Mandal, A. K.; Roy, S. K. *Synthesis* **1981**, 977−979.

CC0200843