Palladium-catalyzed carboxylative synthesis of N-cyanobenzamides from aryl iodides/bromides and cyanamide

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N-Cyanobenzamides, also known as N-acylcyanamides or N-cyanocarboxamides, and their derivatives exhibit a diverse range of biological activities. They have been reported to show excellent herbicidal and fungicidal properties and have also been utilized as prodrugs of cyanamide. N-Cyanocarboxamides (pKa ~2–4) are known carboxylic acid bioisosteres and have been employed as the key acidic function in complex hepatitis C virus NS3 protease inhibitors. Although some N-acylcyanamide derivatives can undergo intermolecular decomposition, N-cyanobenzamides are found to be stable. The valuable two-nitrogen, one-carbon skeleton of cyanamide and N-acylcyanamides, makes them versatile building blocks that can undergo various reactions such as addition at the cyano group forming acyl ureas and acyl guanidines, cycloaddition to give acyl tetrazoles, cyclotrimerization, reduction to primary amines, and metal complex formation. N-Cyanobenzamides have been employed as versatile synthetic intermediates in radical cascade reactions for the synthesis of lutonin A, guanidines, quinazolinones, and acylguanidine and precursors for chloromethylsilane-mediated synthesis of mono-N-acylcyanamides.

Typically, N-acylcyanamides are synthesized by reacting an acid chloride (or equivalent) with sodium cyanamide in an inert solvent (Scheme 1, path a). Several additional methods have also been developed, such as N-cyanation of an amine followed by acylation (path b) or direct N-cyanation of amides to form N-cyanobenzamides (path c), and derivatives and ring-opening rearrangement of 8-methylimidazo[1,5-d][1,2,4]triazin-1(2H)-one (path d). These methods possess a number of drawbacks including the use of toxic reagents, low functional group tolerance, complex starting material preparation, and very strict reaction conditions. Because of their importance, there exists a continuing interest in the development of new and selective methodologies for the preparation of N-cyanobenzamides.

Since Heck reported the first palladium(0)-catalyzed carboxylation reaction employing aryl or vinyl halides (or a halide surrogate), a variety of carboxylation methodologies have been reported for the synthesis of amides, esters, and ketones. The majority of carboxylation reactions require the use of gaseous CO, a highly toxic, invisible, flammable, odorless, and tasteless substance. To overcome this problem, Skrydstrup and co-workers developed and explored a connected two chamber system for the Pd-catalyzed aminocarbonylation of aryl halides using ex situ generation of CO gas from a CO-releasing source. As a part of our continuing efforts in this area, we have previously reported a palladium(0)-catalyzed aminocarbonylation of aryl halides using Mo(CO)₆ as a solid CO-releasing reagent in a bridged two-vial system (Fig. 1) for the synthesis of benzamides with primary/secondary amines, sluggish anilines, and nitro group carrying substrates. This approach was subsequently employed for the novel synthesis of acyl sulfonimidamides. We reasoned that the use of cyanamide as a nucleophile could provide an

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efficient method for the preparation of N-cyanobenzamides from readily available aryl halides. Although aryl cyanamides are reported, to the best of our knowledge, the synthesis of N-cyanobenzamides via an aminocarbonylation approach using cyanamide is unknown in the literature. Herein, we disclose the first palladium(0)-catalyzed aminocarbonylation protocol for the synthesis of these valuable compounds utilizing both Mo(CO)₆₆ as a solid source of CO in a bridged two-vial system and gaseous CO.

Initially, we examined the reaction protocol previously developed by us using tetraakis(triphenylphosphine)-palladium(0) as the catalyst and Et₃N as the base in 1,4-dioxane. Vial C1 was charged with 0.5 equiv of Mo(CO)₆ and vial C2 with 5% Pd[PPh₃]₄, 1 equiv of 4-iodoanisole, 2 equiv of cyanamide, 2 equiv of Et₃N as the base, and finally DBU was added through the septum into C1. Heating at 65 °C for 15 h resulted in incomplete conversion of the aryl iodide, however a promising 68% isolated yield of N-cyano-4-methoxybenzamide (1) was obtained (Table 1, entry 1). No significant increase in conversion was found when 1 equiv of Mo(CO)₆ was used (70%, entry 2). When 3 equiv of cyanamide was used, a slight increase in yield was observed (76%, entry 3) and finally, extending the reaction time from 15 h to 20 h led to full conversion of the aryl iodide and the corresponding product was isolated in 83% yield.

After the identification of productive reaction conditions (Table 1, entry 4), we next set about exploring the scope and limitations of the protocol using various aryl iodides (Table 2). In general meta- and para-substituted aryl iodides afforded good to excellent yields of the corresponding N-cyanobenzamides. Iodobenzene and 4-iodobiphenyl performed well affording the desired products in excellent yields (88% and 84%, respectively). Notably, meta-nitriodobenzene was coupled effectively to yield 80% of N-cyano-3-nitrobenzamide (4), without traces of the corresponding aniline product. The presence of an ortho- substituent resulted in a slightly lower yield, presumably due to adverse steric effects (7, 58%). A double aminocarbonylation could also be performed, producing N,N-dicyanoterthaphtalamide (8) in 78% yield. In addition, heterocyclic N-cyanothiophene-3-carboxamide (9) was obtained in good yield (81%). For the para-nitriodobenzene, the desired product 10 was obtained in moderate yield (54%) due to competitive hydrolysis to the corresponding primary acyl urea. Finally, the diacidic, 4-(cyanocarbamoyl) benzoic acid 11 was prepared in moderate yield (64%) from 4-iodobenzoic acid. Single vial reactions were also performed to examine whether the two-vial system was essential for the process. These reactions gave low isolated yields and complex product mixtures were observed, most likely due to Mo-complexes being formed during the reaction (Table 2). In accordance with previous studies with amino nucleophiles, the use of nitro group containing substrates yielded <10% of the desired product utilizing the single-vial protocol. These results further demonstrate the advantages of the bridged two-vial system in Mo(CO)₆-mediated carboxylation.

Having demonstrated a wide scope for the direct preparation of N-cyanobenzamides using a range of aryl iodides, we turned our attention to the analogous aryl bromides. Thus, aryl bromides and cyanamide were reacted under conditions similar to those outlined in Table 2. It was found that the optimized conditions employed for the aryl iodides were also applicable for aryl bromides, although a higher temperature (85 °C) was required. Using these conditions, the majority of the aryl bromides provided moderate to good yields of the desired products. However, less reactive 4-bromoanisole produced only a moderate yield (46%). Rewardingly, by changing the Pd catalyst to Pd(dppf)Cl₂, the corresponding product was isolated in an improved 68% yield. For other substrates such as ortho- or meta-nitro, 1,4-dibromo and heteroaryl, the desired N-cyanobenzamides were obtained in comparable yields using the two catalysts. In analogy to the results using aryl iodides, aryl bromides bearing a nitro group at ortho- or para-positions produced lower yields. Heteroaryl bromides such as 3-bromo thiophene and 3-bromobenzo[b] thiophene also furnished good yields.

After demonstrating the effective use of Mo(CO)₆ as a solid CO source for the synthesis of N-cyanobenzamides, we decided to explore the aminocarbonylation by employing CO gas (molybdenum-free), with a focus on identifying conditions suitable for larger scale applications, using a pressurized reactor. With the optimized conditions defined, carbonylative coupling reactions using various aryl iodides and aryl bromides produced the corresponding N-cyanobenzamides in moderate to good yields as shown in Table 3. Notably, 4-chloro-N-cyanobenzamide (14) was isolated chemoselectively in 78% yield. Furthermore, 4-iodoanisole, iodobenzene and 1,4-diiodobenzene were coupled effectively with cyanamide, on a 5 mmol scale, without affecting the reaction outcome.

In summary, we have developed a novel gas-free method for the synthesis of N-cyanobenzamides via the palladium-catalyzed aminocarbonylation of aryl halides and cyanamide. This Mo(CO)₆-promoted method displays a broad substrate scope and affords moderate to excellent yields of the N-cyanobenzamides. In
Applications of this methodology for the synthesis of 13C-labeled N-cyanobenzenemides for PET studies are currently underway in our laboratory and will be reported in due course.

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**Supplementary data**

Supplementary data associated with this article can be found, in the online version, at [http://dx.doi.org/10.1016/j.tetlet.2013.10.040](http://dx.doi.org/10.1016/j.tetlet.2013.10.040).

**References and notes**

20. General procedure for the aminocarbonylation using Mo(CO)6 in a two-vial system (see Fig. 1): Vial (C2) was loaded with aryl iodide/bromide (0.5 mmol), Pd(PPh3)4 (29 mg, 5 mol %), Et3N (139 μL, 1 mmol) and cyanamide (63 mg, 1.5 mmol). To vial (C1) was added Mo(CO)6 (138 mg, 0.5 mmol) and thereafter 1,4-dioxane (3+3 mL) was added to C1 and C2. The two vials were capped with a gas-tight cap and DBU (224 μL, 1.5 mmol) was added to C1. The sealed double vial was heated in a heat-block (65 °C for iodides and 85 °C for bromides) for 20 h with vigorous stirring. General procedure for the aminocarbonylation using CO gas: Aryl iodide/bromide (0.5 mmol), cyanamide (3.0 equiv), Pd(PPh3)4 (5 mol %) and Et3N (1 mmol) were taken up in 1,4-dioxane (10 mL) and the reaction mixture was placed inside a high pressure reactor. The reactor was pressurized with CO (2 atm) and heated for 18 h at 65 °C for iodides and 85 °C for bromides. General work-up procedure: After careful evacuation of excess CO, the crude reaction mixture from C2 was evaporated to dryness and 10% HCl was added. The residue was extracted with EtOAc (3 × 10 mL) and concentrated. Purification by flash column chromatography eluting with CHCl3/MeOH (9.5/0.5) gave the desired products.