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Palladium-catalyzed carbonylative synthesis of *N*-cyanobenzamides from aryl iodides/bromides and cyanamide ☆

Rajendra S. Mane, Patrik Nordeman, Luke R. Odell, Mats Larhed *

Organic Pharmaceutical Chemistry, Department of Medicinal Chemistry, Uppsala Biomedical Center, Uppsala University, PO Box 574, SE-751 23 Uppsala, Sweden

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ABSTRACT

A novel and convenient protocol for the synthesis of *N*-cyanobenzamides starting from readily available aryl halides and cyanamide via palladium-catalyzed aminocarbonylation has been developed. The protocol utilizes $Mo(CO)_6$ as the CO source or CO(gas) and affords the desired *N*-cyanobenzamides in moderate to good yields.

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[1] and fungicidal[2,3] properties and have also been utilized as prodrugs of cyanamide.[4] *N*-Acylcyanamides (pK_a ~2–4) are known carboxylic acid bioisosteres[5] and have been employed as the key acidic function in complex hepatitis C virus NS3 protease inhibitors.[6] Although some *N*-acylcyanamide derivatives can undergo intermolecular decomposition, *N*-cyanobenzamides are found to be stable.[7] 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.[8] *N*-Cyanobenzamides have been employed as versatile synthetic intermediates in radical cascade reactions[9] for the synthesis of luotonin A, guanidines, quinazolinones, and acylguanidine and precursors for chloromethylsilane-mediated synthesis of mono-*N*-acylguanidines.[10]

Typically, *N*-acylcyanamides are synthesized by reacting an acid chloride (or equivalent) with sodium cyanamide in an inert solvent (Scheme 1, path a).[4,11] Several additional methods have also been developed, such as N-cyanation of an amine followed by acylation (path b)[9a] or direct N-cyanation of amides to form *N*-cyanobenzamides (path c),[9a] and derivatives[12] and ring-opening rearrangement of 8-methylimidazo[1,5-*d*][1,2,4]triazin-1(2*H*)-one (path d).[3b] 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 carbonylation reaction employing aryl or vinyl halides (or a halide surrogate),[13] a variety of carbonylation methodologies have been reported for the synthesis of amides, esters, and ketones.[14] The majority of carbonylation reactions require the use of gaseous CO, a highly toxic, invisible, flammable, odorless, and tasteless substance. To overcome this problem, Skrydstrup and co-workers[15] 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,[16] 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)[17] 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.[18] We reasoned that the use of cyanamide as a nucleophile (Scheme 1), could provide an

* Corresponding author. Tel.: +46 18 471467; fax: +46 18 4714474.
E-mail address: mats.larhed@orgfam.uu.se (M. Larhed).

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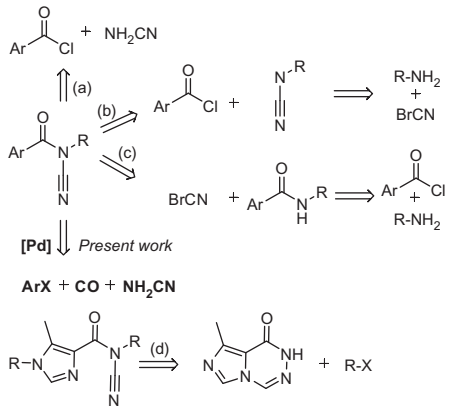


Scheme 1. Synthetic methods for *N*-cyanobenzamides.

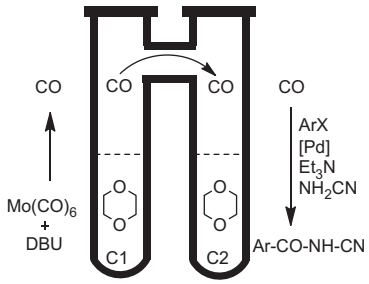


Figure 1. Schematic representation of the two-vial system.

efficient method for the preparation of *N*-cyanobenzamides from readily available aryl halides. Although aryl cyanamides[19] 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 $Mo(CO)_6$ as a solid source of CO in a bridged two-vial system and gaseous CO.

Initially, we examined the reaction protocol[20] previously developed by us[17] using tetrakis(triphenylphosphine)-palladium(0) as the catalyst and Et_3N as the base in 1,4-dioxane. Vial C1 was charged with 0.5 equiv of $Mo(CO)_6$ and vial C2 with 5% $Pd(PPh_3)_4$, 1 equiv of 4-iodoanisole, 2 equiv of cyanamide, 2 equiv of Et_3N as the base, and finally DBU[21] 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.

Table 1
Optimization of the two-vial aminocarbonylation

Entry	Time (h)	$Pd(PPh_3)_4$ (mol %)	$Mo(CO)_6$ (equiv)	NH_2CN (equiv)	Yield[a] (%)
1	15	5	0.5	2	68
2	15	5	1	2	70
3	15	5	1	3	76
4	20	5	1	3	83

[a] Reaction conditions: Vial C1 was loaded with $Mo(CO)_6$. Vial C2 was loaded with 4-iodoanisole (0.5 mmol) and $Pd(PPh_3)_4$. 1,4-Dioxane (6 mL, 3 mL in each vial) was added to vial C1 and to vial C2 were added Et_3N (1 mmol) and cyanamide. After capping, DBU (1.5 mmol) was added to vial C1 which was then sealed and the double vial was heated at 65 °C for 15–20 h.

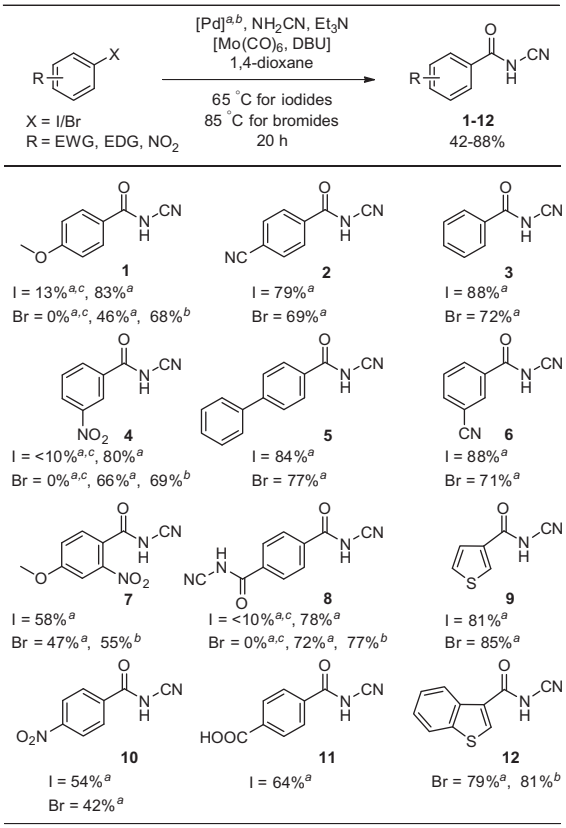
After the identification of productive reaction conditions (Table 1, entry 4), we next set about exploring the scope and limitations of the protocol using various aryl iodides (Table 2). In general *meta*- and *para*-substituted aryl iodides afforded good to excellent yields of the corresponding *N*-cyanobenzamides. Iodobenzene and 4-iodobiphenyl performed well affording the desired products in excellent yields (88% and 84%, respectively). Notably, *meta*-nitroiodobenzene was coupled effectively to yield 80% of *N*-cyano-3-nitrobenzamide (**4**), without traces of the corresponding aniline product.[17] 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*-dicyanoterephthalamide (**8**) in 78% yield. In addition, heterocyclic *N*-cyanothiophene-3-carboxamide (**9**) was obtained in good yield (81%). For the *para*-nitroiodobenzene, the desired product **10** was obtained in moderate yield (54%) due to competitive hydrolysis to the corresponding primary acyl urea.[22] 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,[17] 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 carbonylations.

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 $Pd(dppf)Cl_2$, 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-bromothiophene 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.

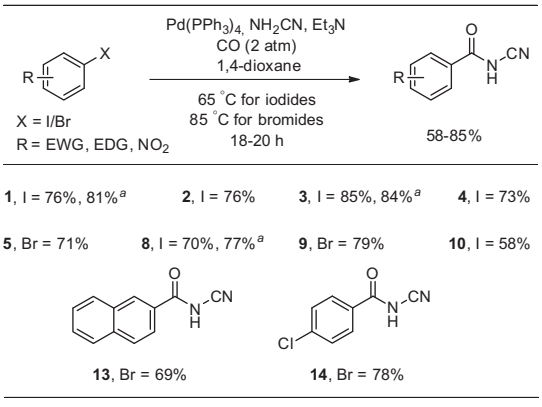
In summary, we have developed a novel gas-free method for the synthesis of *N*-cyanobenzamides via the palladium-catalyzed aminocarbonylation of aryl halides and cyanamide. This $Mo(CO)_6$-promoted method displays a broad substrate scope and affords moderate to excellent yields of the *N*-cyanobenzamides. In

Table 2
Synthesis of *N*-cyanobenzamides from aryl iodides and aryl bromides using $Mo(CO)_6$



Reaction conditions: vial C1 was loaded with $Mo(CO)_6$ (1.0 equiv). The vial C2 was loaded with aryl halide (0.5 mmol) and [Pd] (5 mol %). 1,4-Dioxane (6 mL, 3 mL in each vial) was added and to vial C2 were added Et_3N (1 mmol) and cyanamide (3.0 equiv). After capping, DBU (1.5 mmol) was added to vial C1 and sealed and the double vial was heated at 65/85 °C for 20 h.
[a] $Pd(PPh_3)_4$.
[b] $Pd(dppf)Cl_2$.
[c] All reagents were placed in a single vial.
All yields are isolated yields.

Table 3
Synthesis of *N*-cyanobenzamides from aryl iodides and aryl bromides using CO gas



Reaction conditions: aryl halide (0.5 mmol), cyanamide (3.0 equiv), $Pd(PPh_3)_4$ (5 mol %), Et_3N (1 mmol) and CO (2 atm) were reacted in 1,4-dioxane at 65/85 °C for 18–20 h.
[a] Reaction conducted on 5 mmol scale.
All yields are isolated yields.

addition, we have also shown its applicability by using CO gas up to a 5 mmol scale. To the best of our knowledge, this is the first reported aminocarbonylative synthesis of *N*-cyanobenzamides. Applications of this methodology for the synthesis of ^{11}C-labeled *N*-cyanobenzamides 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.

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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), $Pd(PPh_3)_4$ (29 mg, 5 mol %), Et_3N (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), $Pd(PPh_3)_4$ (5 mol %) and Et_3N (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 $CHCl_3$/MeOH (9.5/0.5) gave the desired products.
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