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Molybdenum-Mediated Carbonylation of Aryl Halides with Nucleophiles Using Microwave Irradiation

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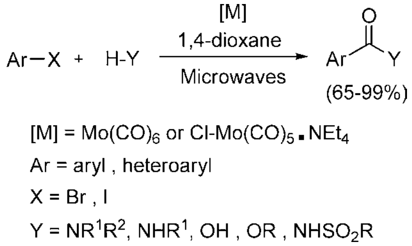
ABSTRACT



A new, efficient, and practical molybdenum-mediated carbonylation of aryl and heteroaryl halides with a variety of nucleophiles is described using microwave irradiation. A range of reactions illustrating the wide scope of this chemistry were carried out and proceeded in good to excellent yields.

Heck and co-workers first reported the palladium-catalyzed reaction of carbon monoxide, aryl halides, and alcohols or amines to give the respective benzoate and benzamide products.[1] Since then, the scope of this reaction has been developed such that a wide range of nucleophiles can be used, enabling the efficient synthesis of numerous carbonyl compounds.[2] In recent years, a number of CO gas-free palladium-catalyzed carbonylative conditions have been reported using formamides or solid metal carbonyls as CO sources.[3] The palladium-catalyzed carbonylative coupling of aryl and heteroaryl halides with a variety of nucleophiles using Mo(CO)$_6$ as the CO source is also well established.[4] It is also known that some metal carbonyls such as Ni(CO)$_4$ can be used stoichiometrically to carbonylate aryl iodides and alkenyl halides in the presence of alcohols, metal alkoxides, or amines to give carboxylic acids, esters, and amides.[5] Here, we report molybdenum-mediated carbonylation of aryl halides with a variety of nucleophiles in the absence of palladium using microwave irradiation in sealed vials.[6]

We began by examining the reaction shown in Table 1; using iodobenzene and benzylamine with 1,4-dioxane as solvent, we screened a range of group VI metal carbonyl complexes. Reactions were carried out with a 1:1:2 ratio of metal carbonyl complex, iodobenzene, and benzylamine and

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(1) (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327.

(2) (a) Martinelli, J. R.; Watson, D. A.; Freckmann, D. M. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7102, and references cited within. For a general review on carbonylation reactions, see: Barnard, C. F. J. *Organometallics* **2008**, 5402.

(3) (a) Morimoto, T.; Kakiuchi, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 5580. (b) Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 6232. (c) Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Comb. Chem.* **2003**, *5*, 82.

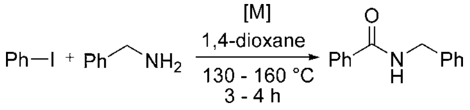
(4) For selected examples, see: (a) Lagerlund, O.; Larhed, M. *J. Comb. Chem.* **2006**, *8*, 4. (b) Wu, X.; Wannberg, J.; Larhed, M. *Tetrahedron* **2006**, *62*, 4665, and references cited within.

(5) (a) Bauld, N. L. *Tetrahedron Lett.* **1963**, 1841. (b) Nakayama, M.; Mizoroki, T. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 508. (c) Corey, E. J.; Hegedus, L. S. *J. Am. Chem. Soc.* **1969**, *91*, 1233.

(6) All reactions were performed in a CEM Discover single-mode microwave reactor equipped with a 300 W source set to 50 W. Each of the reactions were performed in a CEM 10 mL microwave reaction vial. All temperature measurements were performed with an infrared probe. *Caution*: Mo(CO)$_6$ and its derivatives are toxic, and these pressurized reactions should only be carried out using specialized microwave equipment.

10.1021/ol1016965

Table 1. Reaction of Metal Carbonyl Complexes [M] with Iodobenzene and Benzylamine[a]



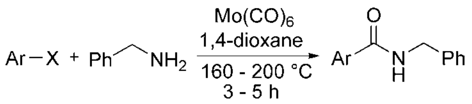
entry	[M]	time (h)	temp (°C)	yield[b] (%)
1	$Cr(CO)_6$	3	160	trace
2	$Cr(CO)_5Cl.NEt_4$	4	130	trace
3	$Mo(CO)_6$	3	160	84
4	$Mo(CO)_5Cl.NEt_4$	4	130	95
5	$W(CO)_6$	3	160	10
6	$W(CO)_5Cl.NEt_4$	4	130	29

[a] Iodobenzene (1 mmol), benzylamine (2 mmol), and metal carbonyl complex (1 mmol) mixed in 1,4-dioxane (1 mL) and microwave heated in a sealed vial. [b] Isolated and purified.

optimized in the microwave with respect to time and temperature. The molybdenum carbonyl complexes gave the best conversions and excellent isolated yields (Table 1, entries 3 and 4). Interestingly, entry 4 provided a slightly higher isolated yield of product at a lower temperature. At first, we suspected palladium contamination. These two exciting results were repeated using sublimed and reagent-grade molybdenum hexacarbonyl[7] and new magnetic stirrer bars,[8] and the reaction mixtures were subjected to palladium analysis before and after reaction. Identical results were obtained, and gratifyingly, no detectable levels of palladium (limit of quantification <2 ppm) were found.[9]

Further examination of the $Mo(CO)_6$-mediated carbamoylation using benzylamine was then performed with a range of aryl and heteroaryl halides. The reactions were carried out with a 1:1:2 ratio of $Mo(CO)_6$, aryl halide, and benzylamine. Aryl iodides required a temperature of 160 °C and a time of 3 h, whereas aryl bromides required a temperature of 200 °C and a time of 5 h for complete conversion (Table 2). A wide range of ortho-, meta-, and para-electron-deficient and -electron-rich aryl halides all gave excellent yields (Table 2, entries 3−10). Alkenyl bromide and heteroaryl halides also performed well in the reaction (Table 2, entries 12−16). It is worth noting that a subsequent optimization of brombenzene with benzylamine was repeated, and a temperature of 150 °C for 5 h gave 87% yield of benzamide (Table 2, entry 2), indicating that our initial optimization temperatures for aryl bromides are higher than required for complete conversion. While amines performed well in this reaction, other nucleophiles gave poor results using these conditions.

Table 2. $Mo(CO)_6$-Mediated Carbamoylation of Aryl Halides with Benzylamine[a]



entry	aryl halide	yield[b] (%)
1	C_6H_5I	84
2	C_6H_5Br	92 (87)[c]
3	2-MeC_6H_4I	93
4	2-MeC_6H_4Br	98
5	3-ClC_6H_4I	99
6	3-ClC_6H_4Br	92
7	4-$MeOC_6H_4I$	84
8	4-$MeOC_6H_4Br$	87
9	4-$Et_2NC(O)C_6H_4I$	72
10	4-$Me_2NC(O)C_6H_4Br$	77
11	2-naphthyl-Br	97
12	$C_6H_5CH{=}CHBr$	89
13	3-thienyl-I	98
14	3-thienyl-Br	95
15	3-pyridyl-I	84
16	3-pyridyl-Br	92

[a] Aryl halide (1 mmol), benzylamine (2 mmol), and molybdenum hexacarbonyl (1 mmol) mixed in 1,4-dioxane (1 mL) and microwave heated in a sealed vial. Aryl iodides 160 °C for 3 h. Aryl bromides 200 °C for 5 h. [b] Isolated and purified. [c] 150 °C for 5 h.

While this work was in progress, we noted a related recent publication by Ren and Yamane[10] where they reported palladium-free carbamoylation of aryl halides using molybdenum and tungsten amine pentacarbonyl complexes. This method is efficient but is limited to amide formation and requires the synthesis and isolation of the individual amine complexes to obtain products with amide variation. Inspired by this report and our previous result of using $Mo(CO)_5Cl{\bullet}NEt_4$ (Table 1, entry 4), we envisaged a one-pot procedure where $Mo(CO)_5Cl{\bullet}NEt_4$ could be formed in situ from $Mo(CO)_6$ in the presence of a nucleophile (Nu) to give a complex of type $Mo(CO)_5{\bullet}Nu$, which would then react with aryl halides to give a range of carbonylated products. Initial attempts combining iodobenzene, $Mo(CO)_6$, tetraethylammonium chloride, and benzylamine in 1,4-dioxane with microwave heating at 130 °C for 4 h gave the required benzamide product in an encouraging 62% yield. However, microwave heating $Mo(CO)_6$ and tetraethylammonium chloride in 1,4-dioxane at 140 °C for 2 min (formation of $Mo(CO)_5Cl{\bullet}NEt_4$ was confirmed by comparison with an authentic isolated sample by ^1H NMR) and then adding iodobenzene and benzylamine, followed by further microwave heating for 4 h at 130 °C, gave the required benzamide in 95% yield (Table 3, entry 1).

Application of this one-pot method using benzylamine was then performed with a range of aryl and heteroaryl halides. Aryl iodides required a temperature of 130 °C and a reaction time of 4 h, whereas aryl bromides required a temperature

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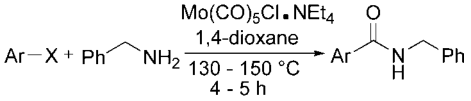
(7) Sublimed $Mo(CO)_6$ (purity 99+%) and reagent grade $Mo(CO)_6$ (purity 98%) were purchased from Adrich Chemicals, and $ClMo(CO)_5{\bullet}NEt_4$ was synthesized from sublimed and reagent-grade $Mo(CO)_6$ by the method of: Abel, E. W.; Butler, I. S.; Reid, J. G. *J. Chem. Soc.* **1963**, 2068.

(8) Rare earth Teflon-coated magnetic stirrer bars.

(9) ICP analysis of all independent reagents and reaction mixtures before and after the reaction were analyzed, and at a limit of detection of 2 ppm, no palladium was observed. Full information, ICP, and corroborating XRF spectra for a pre-reaction mixture are provided in the Supporting Information.

(10) Ren, W.; Yamane, M. *J. Org. Chem.* **2010**, *75*, 3017.

Table 3. In Situ $Mo(CO)_5Cl{\cdot}NEt_4$-Mediated Carbonylation of Aryl Halides with Benzylamine[a]



entry	aryl halide	yield[b] (%)
1	C_6H_5I	95
2	C_6H_5Br	91
3	$2\text{-}MeC_6H_4I$	98
4	$2\text{-}MeC_6H_4Br$	79
5	$3\text{-}ClC_6H_4I$	98
6	$3\text{-}ClC_6H_4Br$	96
7	$4\text{-}MeOC_6H_4I$	90
8	$4\text{-}MeOC_6H_4Br$	81
9	$4\text{-}Et_2NC(O)C_6H_4I$	99
10	$4\text{-}Me_2NC(O)C_6H_4Br$	80
11	2-naphthyl-Br	75
12	$C_6H_5CH{=}CHBr$	85
13	3-thienyl-I	97
14	3-thienyl-Br	91
15	3-pyridyl-I	95
16	3-pyridyl-Br	87

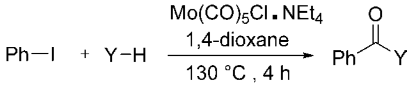
[a] $Mo(CO)_6$ (1 mmol) and $NEt_4{\cdot}Cl$ (1 mmol) in 1,4-dioxane (1 mL) were microwave heated in a sealed vial to 140 °C for 2 min and then allowed to cool, aryl halide (1 mmol); benzylamine (2 mmol) added; mixture microwave heated in a sealed vial. Aryl iodides 130 °C for 4 h. Aryl bromides 150 °C for 5 h. [b] Isolated and purified.

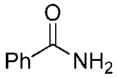
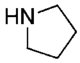
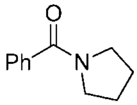
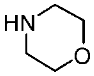
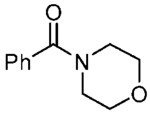
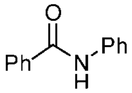
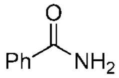
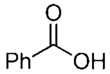
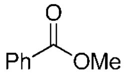
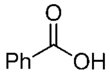
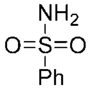
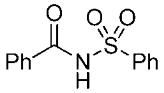
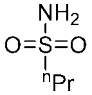
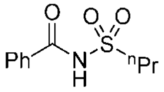
of 150 °C and a reaction time of 5 h for complete conversion (Table 3). Gratifyingly, all the previous halide classes described in Table 2 performed equally well in the reaction under these conditions.

Having established a good scope with this one-step protocol using benzylamine, we investigated other nucleophiles (Table 4). Aqueous ammonia, cyclic secondary amines, and the less nucleophilic aniline all performed well in the reaction (Table 4, entries 1−4). Using *tert*-butyl carbamate and *tert*-butyl alcohol, the corresponding primary amide and carboxylic acid were formed, presumably by thermolytic cleavage of the *tert*-butyl groups[11] (Table 4, entries 5 and 6). Methanol and water gave the corresponding carboxylic ester and acid (Table 4, entries 7 and 8). Aryl and alkyl sulfonamides also performed well in the reaction (Table 4, entries 9 and 10). This easy variation in the nucleophile and broad scope represents a significant advantage over previously reported work.

The mechanism for these reactions is unclear at present, but one can speculate on possible pathways (Scheme 1).[12] In their work with amine molybdenum complexes (**B**), Ren and Yamane[10] suggested two possibile pathways: (i) Formation of acyl metal intermediate (**E**). This would be generated by oxidative addition of aryl halide to molybdenum complex (**C**) followed by CO insertion to the phenyl-molybdenum bond. (ii) Formation of carbamoyl metal intermediate (**G**). This would be generated from aryl metal halide (**D**) or from carbamoyl intermediate (**F**) by oxidative addition of aryl halide. To gain some insight to the $Mo(CO)_6$-mediated carbamoylation, benzylamine, $Mo(CO)_6$, and 1,4-dioxane were heated in a 1:1 ratio in the microwave at 160 °C for 30 min; formation of $Mo(CO)_5\text{-}NH_2Bn$ (**B**) was confirmed by ^1H NMR comparison with an authentic sample synthesized from $Mo(CO)_5Cl{\cdot}NEt_4$ and benzylamine.[13] For the in situ $Mo(CO)_5Cl{\cdot}NEt_4$-mediated

Table 4. In Situ $Mo(CO)_5Cl{\cdot}NEt_4$-Mediated Carbonylation of Iodobenzene with a Range of Nucleophiles[a]



entry	nucleophile	product	yield (%)[c]
1	NH_3 (aq)		75
2			96
3			95
4	Ph-NH_2		99
5	Boc−NH_2		51
6	^{t}Bu−OH		75[b]
7	Me−OH		65[b]
8	H_2O		95[b]
9			71
10			93

[a] $Mo(CO)_6$ (1 mmol) and $NEt_4{\cdot}Cl$ (1 mmol) in 1,4-dioxane (0.8 mL) microwave heated in a sealed vial to 140 °C for 2 min and then allowed to cool; iodobenzene (1 mmol); nucleophile (2 mmol) added and mixture microwave heated to 130 °C for 4 h. [b] Nucleophile (0.2 mL) was used. [c] Isolated and purified.

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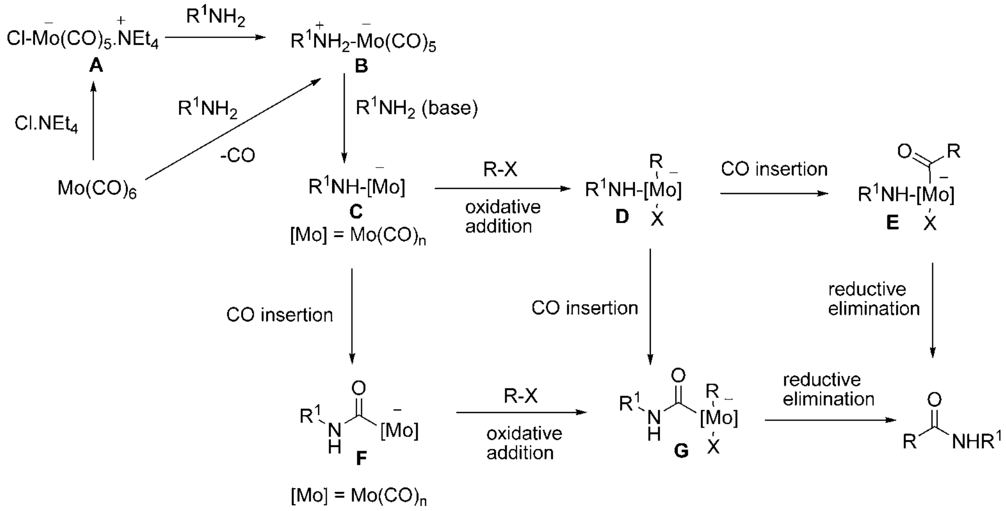
[11] Choy, J.; Jaime-Figueroa, S.; Lara-Jaime, T. *Tetrahedron Lett.* **2010**, *51*, 2244, and references cited within.

[12] For related mechanisms and oxidative addition of aryl halides to group VI metal(0) complexes, see: (a) Sangu, K.; Watanabe, T.; Takaya, J.; Iwasawa, N. *Synlett* **2007**, *6*, 929. (b) Sangu, K.; Takaya, J.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 7090. (c) Pan, Y. H.; Ridge, D. P. *J. Am. Chem. Soc.* **1992**, *114*, 2773. (d) Looman, S. D.; Richmond, T. G. *Inorg. Chim. Acta* **1995**, *240*, 479. (e) McCusker, J. E.; Main, A. D.; Johnson, K. S.; Grasso, C. A.; McElwee-White, L. *J. Org. Chem.* **2000**, *65*, 5216.

Scheme 1. Speculative Mechanisms for the $Mo(CO)_6$ and the in Situ $Mo(CO)_5Cl{\bullet}NEt_4$-Mediated Carbonylation of Aryl Halides with Amines (R^1 = Benzyl)



carbonylation we have confirmed formation of $Mo(CO)_5Cl{\bullet}NEt_4$ from $Mo(CO)_6$, and we know this readily reacts with amines to give the amine−molybdenum complex. Thus, we suggest that the $Mo(CO)_6$-mediated carbamoylation and the in situ $Mo(CO)_5Cl{\bullet}NEt_4$-mediated carbonylation both proceed through amine−molybdenum complexes (**C**) via one of the suggested pathways. More work to clarify further steps in the mechanism is underway.

In summary, we have developed a $Mo(CO)_6$-mediated carbamoylative coupling and an in situ $Mo(CO)_5Cl{\bullet}NEt_4$-mediated carbonylation with a range of nucleophiles from $Mo(CO)_6$. These methods allow access to a wide range of carbonyl compounds in excellent yield without the need for gaseous CO and palladium catalysts. The methods are ideally suited for parallel synthesis and automation often required in modern drug discovery. Further development of nonstoichiometric and catalytic versions of the reactions are in progress.

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Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra and HRMS analysis for all compounds. Characterization (^1H and ^{13}C NMR data) for all new compounds. ICP palladium analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Schenk, W. A. *J. Organomet. Chem.* **1979**, *179*, 253.