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Microwave-Assisted Synthesis of Weinreb and MAP Aryl Amides via Pd-Catalyzed Heck Aminocarbonylation Using $Mo(CO)_6$ or $W(CO)_6$

Anna Więckowska, Rebecca Fransson, Luke R. Odell,* and Mats Larhed

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

luke.odell@orgfarm.uu.se

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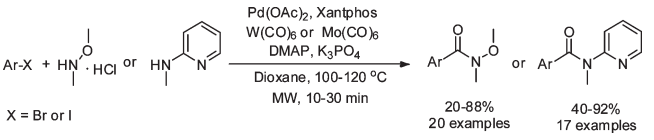

A simple and expedient process for the Heck aminocarbonylative synthesis of Weinreb and MAP amide acylating agents, from aryl halides, is reported. This methodology utilizes solid sources of CO making it readily accessible to chemists working in small-scale laboratory applications.

Since their discovery in 1981 by Nahm and Weinreb,[1] the *N*-methoxy-*N*-methylamides (i.e., Weinreb amides, see Figure 1) have, over the past 20 years, been extensively developed and utilized as acylating agents.[2−5] Their clean interaction with both Grignard and organolithium reagents to generate ketones and with metalhydrides to form aldehydes, without overaddition, makes them extremely useful in the preparation of carbonyl containing compounds. Recently, ylids were reported to generate ketones and aldehydes from Weinreb amides, offering even milder reaction conditions in comparison to the organometallic reagents.[6,7]

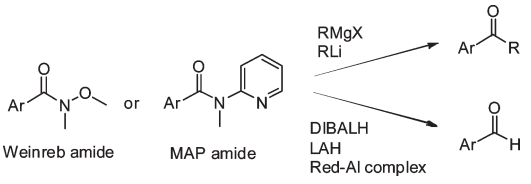

FIGURE 1. General structures of Weinreb and MAP aryl amides and their application as acylating agents.

Almost at the same time as the Weinreb amides were discovered, Meyers and Comins reported the use of *N*-methylamino pyridyl amides (MAPA) as acylating agents.[8,9] In contrast to the Weinreb amides, which form a stable metal-chelated intermediate preventing a second nucleophilic addition, the MAP amides can be more sensitive toward further alkylation and the reaction outcome depends largely on the organometallic reagent used. Nonetheless, the MAP agents can be useful in the synthesis of aldehydes, ketones, alcohols, amides and esters.[9−11]

Traditionally, Weinreb amides have been prepared from carboxylic acids[5,12,13] and their derivatives, for example, acid chlorides,[1] esters,[14] lactones, amides and anhydrides.[5] More recent methods have focused on transition metal-catalysis and include the cross-coupling of *N*-methoxy-*N*-methylcarbamoyl chloride with vinyl and aryl stannanes[15] or boronic acids[16] and the Heck aminocarbonylation[17−21] of *N*,*O*-dimethylhydroxylamine (**1**) with aryl bromides,[22] aryl and vinyl iodides,[23] and lactam/lactone-derived triflates,[24] under a carbon monoxide (CO) atmosphere.

Our interest in the Heck carbonylation reaction lies in the development of CO-gas free methods, which are suitable for small scale laboratory applications and parallel synthesis. The benefits of these protocols are well established and include their low cost, preparative ease (reactions do not need to be carried out under an inert atmosphere) and, more importantly, the *in situ* generation of toxic CO-gas. We[25−32]

*Fax: + 46 18 4714474.

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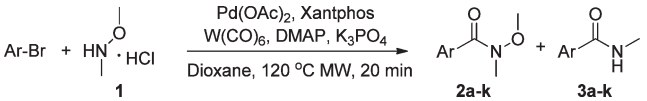
and others[33−36] have previously reported on various palladium-catalyzed $Mo(CO)_6$-mediated carbonylative couplings under classical heating[37] and microwave-assisted conditions.[38−40]

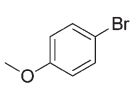
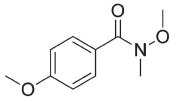
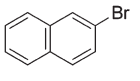
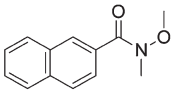
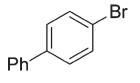
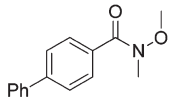
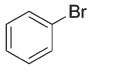
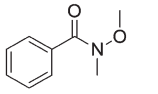
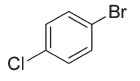
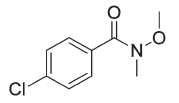
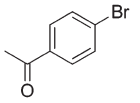
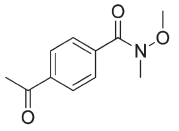
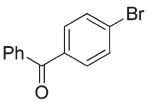
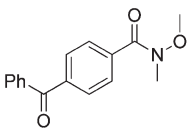
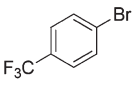
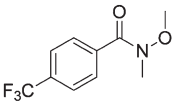
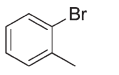
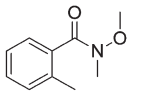
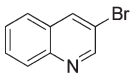
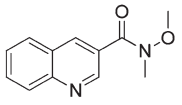
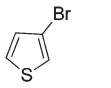
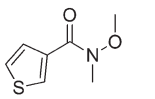
To the best of our knowledge, the synthesis of Weinreb amides via a CO-gas free Heck carbonylation approach is unknown in the literature. Furthermore, the direct carbonylative synthesis of MAP amides, from (hetero)aryl halide precursors, is previously unreported. Herein we disclose the first microwave-assisted palladium(0)-catalyzed protocol for the synthesis of these valuable synthetic intermediates utilizing $Mo(CO)_6$ or $W(CO)_6$ as solid CO sources.

Our initial investigations focused on the preparation of Weinreb amides and utilized 4-bromo-1,1′-biphenyl as the model substrate, microwave irradiation as the energy source and catalytic conditions similar to those previously reported by the Buchwald group.[22] Thus, $Pd(OAc)_2$ was used as the palladium source, Xantphos as the ligand, K_3PO_4 as the base and toluene as the solvent. Unfortunately, when employing $Mo(CO)_6$ as the CO source, these conditions provided only trace amounts of the desired product (**3c**) after 20 min of microwave irradiation at 120 °C. Furthermore, a screening of ligands previously shown to promote $Mo(CO)_6$ mediated aminocarbonylations failed to provide an improved reaction outcome.[41] Due to the high propensity of aryl bromides to undergo oxidative addition and CO insertion, we suspected that the failure of the reaction was due to the sluggish attack of the acylpalladium intermediate by **1**.[22,23] Encouraged by our previous success of using *N*,*N*-dimethylaminopyridine (DMAP) to facilitate the aminocarbonylation of hindered and poorly nucleophilic amines,[32] we decided to investigate the effect of DMAP on this transformation. Gratifyingly, the addition of 2 equiv of DMAP to the original reaction mixture resulted in greater conversion of the starting material however, the reaction mixture consisted of the desired Weinreb amide product **2c** and the corresponding *N*-methylamide **3c** (**2c**:**3c** = 40:60 according to GC/MS analysis). The formation of **3c** is most probably a result of N−O bond cleavage under the $Mo(CO)_6$ mediated reaction conditions, a transformation with considerable literature precedent.[42−45]

In order to ascertain whether **1** or the Weinreb amide product was being reduced, purified **2c** was subjected to the carbonylative reaction conditions. Interestingly, only intact **2c** was recovered after this reaction suggesting that **1** is reduced to methylamine, which in turn undergoes an aminocarbonylation to generate **3c**. To overcome this problem we turned to the use of alternative, and less reactive, solid CO sources.[29] To our delight, when the reaction was performed with 1 equiv. $W(CO)_6$ the amount of **3c** was reduced considerably (**2c:3c** = 70:30) and, after fine-tuning of the reaction parameters, **2c** could be isolated in 88% yield (**2c:3c** = 93:7, 0.33 equiv. $W(CO)_6$ see

TABLE 1. Preparation of Weinreb Aryl Amides by Aminocarbonylation of Aryl Bromides[a]



entry	ArBr	Product		Yield %[b] (**2:3**)[c]
1			**2a**	57 (78:22)
2			**2b**	87 (99:1)
3			**2c**	88 (93:7) 94[d] 77[e]
4			**2d**	70 (81:19)
5			**2e**	76 (99:1)
6			**2f**	70 (97:3)
7			**2g**	54 (64:36)
8			**2h**	37 (48:52)
9			**2i**	20[f] (17:83)
10			**2j**	84 (98:2)
11			**2k**	79 (94:6)

[a]Aryl bromide (0.25 mmol), 0.75 mmol **1**, 7.5 mol % $Pd(OAc)_2$, 15 mol % Xantphos, 0.08 mmol $W(CO)_6$, 0.50 mmol DMAP, 1.5 mmol K_3PO_4, 1,4-dioxane (2 mL), 120 °C, 20 min, MW. [b]Isolated yields. [c]Determined by GC/MS analysis. [d]Reaction conducted on 1 mmol scale. [e]Reaction conducted in an oil bath. [f]Reaction time 40 min.

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TABLE 2. Preparation of Weinreb Aryl Amides by Aminocarbonylation of Aryl Iodides[a]

entry	ArI	product	yield (%)[b] (**2:3**)[c]
1	4-$MeOC_6H_4I$	**2a**	82 (99:1)
2	2-naphthyl-I	**2b**	84 (99:1)
3	4-PhC_6H_4I	**2c**	81 (93:3)
4	C_6H_5I	**2d**	80 (99:1)
5	4-$MeCOC_6H_4I$	**2f**	74 (96:4)
6	4-$PhCOC_6H_4I$	**2g**	64 (71:29)
7	4-$CF_3C_6H_4I$	**2h**	39 (73:27)
8	2-MeC_6H_4I	**2i**	69 (91:9)
9	3-thienyl-I	**2k**	77 (99:1)

[a]Aryl iodide (0.25 mmol), 0.75 mmol **1**, 5 mol % $Pd(OAc)_2$, 10 mol % Xantphos, 0.08 mmol $Mo(CO)_6$, 0.50 mmol DMAP, 1.5 mmol K_3PO_4, 1,4-dioxane (2 mL), 110 °C, 10 min. MW. [b]Isolated yields. [c]Determined by GC/MS analysis.

Table 1 for details). Despite this success the formation of **3c** could never be completely suppressed and varying amounts of this byproduct were always detected along with the desired Weinreb amide (see Table 1 for details). This procedure was then further evaluated for its scope and general applicability.

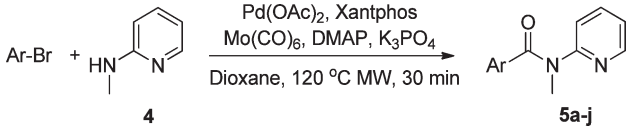
The identified reaction conditions were applied to a series of aryl and heteroaryl bromides and the preparative results are outlined in Table 1. Generally, the reaction performed well with electron-rich (entries 1−3), neutral (entry 4) and electron-poor (entries 5−7) bromides. Importantly, full chemoselectivity was observed for the aminocarbonylation of 4-bromochlorobenzene (entry 5) and no products arising from the activation of the aryl chlorine bond were detected by GC/MS analysis. Lower yields were obtained for the highly electron deficient 4-trifluoromethylphenylbromide (entry 8) and the sterically hindered 2-bromotoluene (entry 9). Moreover, both of these substrates afforded the corresponding methylamides as the major reaction product. This could be explained by a reduced reactivity rate for these electron-deficient or hindered substrates,[27] leading to increased concentrations of methylamine, at the expense of **1**, that can subsequently undergo aminocarbonylation. The heterocyclic bromides 3-bromoquinoline (entry 10) and 3-bromothiophene (entry 11) were also cleanly transformed into the corresponding Weinreb amides under these conditions. Finally, the reaction was successfully conducted under conventional heating conditions and on a 1 mmol scale affording **2c** in 77% and 94% yield, respectively.

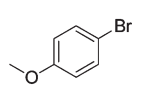
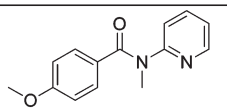
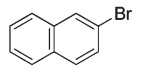
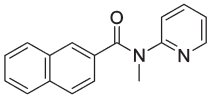
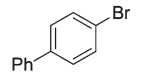
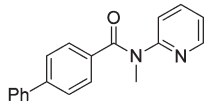
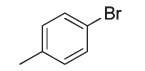
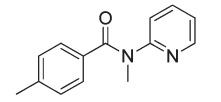
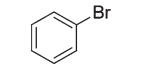
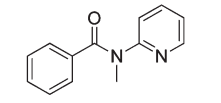
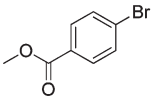
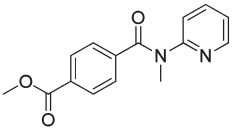
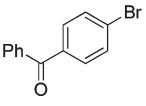
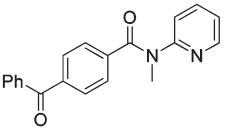
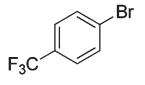
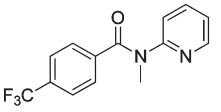
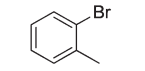
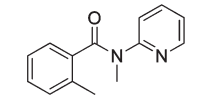
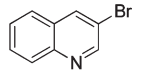
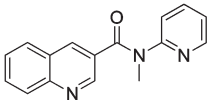
Next, to further explore the scope of this transformation we sought to apply the conditions to a range of aryl and heteroaryl iodides. Surprisingly, these conditions failed to provide more than trace amounts of the desired Weinreb amide products. After considerable experimentation, it was found that the reaction functioned well with $Mo(CO)_6$ and, after reoptimization, a suitable method was identified (10 min, 110 °C, 0.33 equiv. $Mo(CO)_6$, see Table 2). The success of $Mo(CO)_6$ in this reaction can be attributed to the lower reaction temperature and the increased reactivity of the iodide substrates and we believe that the carbonylation occurs faster than the reduction of **1**, resulting in the preferential formation of the desired products. These $Mo(CO)_6$ mediated conditions were then applied to various aryl and heteroaryl iodides and the results are presented in Table 2.

As can be seen from Table 2 good isolated yields were obtained with range of electron-rich (entries 1−3), neutral (entry 4) and moderately electron-poor substrates (entries 5 and 6). Again, the highly electron deficient 4-trifluoromethylphenyl system performed poorly, presumably due to competing reduction of the Ar−I bond (entry 7). The presence of an *ortho* substituent was also well tolerated (entry 8), indicating that the increased reactivity of the iodide outweighs the negative steric effects of the *ortho* methyl group (cf. entry 9, Table 1).

Having demonstrated a wide scope for the direct preparation of Weinreb amides, we turned our attention to the synthesis of MAP amides. Thus, 4-bromo-1,1′-biphenyl and 2-methylaminopyridine (**4**) were reacted under conditions similar to those outlined in Table 2. This resulted in the

TABLE 3. Preparation of MAP Aryl Amides by Aminocarbonylation of Aryl Bromides[a]



entry	ArBr	Product		Yield (%)[b]
1			**5a**	61
2			**5b**	93
3			**5c**	92
4			**5d**	80
5			**5e**	79
6			**5f**	92
7			**5g**	91
8			**5h**	59
9			**5i**	41
10			**5j**	85

[a]**4** (0.25 mmol), 1.25 mmol aryl bromide, 5 mol % $Pd(OAc)_2$, 10 mol % Xantphos, 0.25 mmol $Mo(CO)_6$, 0.50 mmol DMAP, 0.75 mmol K_3PO_4, 1,4-dioxane (2 mL), 120 °C, 30 min, MW. [b]Isolated yields.

TABLE 4. Preparation of MAP aryl amides by aminocarbonylation of aryl iodides[a]

entry	ArI	product	yield (%)[b]
1	4-$MeOC_6H_4I$	**5a**	59
2	1-naphthyl-I	**5k**	66[c]
			69
3	C_6H_5I	**5e**	63
4	4-$MeCOC_6H_4I$	**5l**	40
5	4-$PhCOC_6H_4I$	**5g**	50
6	4-$CF_3C_6H_4I$	**5h**	57
7	2-MeC_6H_4I	**5i**	62

[a]Aryl iodide (0.25 mmol), 0.75 mmol **4**, 10 mol % $Pd(OAc)_2$, 20 mol % Xantphos, 0.12 mmol $Mo(CO)_6$, 0.75 mmol K_3PO_4, 1,4-dioxane (2.5 mL), 100 °C, 20 min, MW. [b]Isolated yields. [c]$Mo(CO)_6$ (0.25 mmol).

modest consumption of the starting materials and the desired product (**5c**) was isolated in only 35% yield. Subsequent attempts to optimize this procedure (time, solvent, temperature, catalyst and ligand) were unsuccessful and full conversion of the starting material was never achieved. Initially, we believed that this was due to the electron-poor and sluggish nature of nucleophile; however, the addition of a large excess of the nucleophile (5−10 equiv) completely inhibited the reaction. This suggests that **4** may in fact coordinate to palladium, forming inactive Pd-pyridine complexes and thus, poisoning the catalyst. To overcome this problem we decided to conduct the reaction using an excess of the aryl bromide, with respect to **4**, and these results are shown in Table 3.

It is evident from Table 3 that this strategy was successful and the reaction performed well with a variety of electronically diverse aryl bromides. Electron-withdrawing (entries 6−8) and electron-donating (entries 1−4) groups were well tolerated as was the presence of a heterocyclic ring (entry 10). Interestingly, the methylester group remained intact despite the high reaction temperature and basic conditions (entry 6).

Finally, we decided to explore the synthesis of MAP amides from aryl iodides. To begin with, we applied the conditions from Table 3 and, with 1-naphthyliodide, this furnished the desired MAP aryl amide product **5k** in 77% yield. To increase the applicability of the method, we were interested in exploring whether the reaction could be conducted with the aryl iodide as the limiting reagent. We believed that the increased propensity of aryl iodides to undergo oxidative addition could counteract the catalyst poisoning effects of **4**. Pleasingly, the reaction proceeded well, and after screening of various reaction conditions, the desired product **5k** was obtained in 69% yield. The optimized method requires a palladium loading of 10 mol %, a relatively high value for an aryl iodide substrate in a palladium-catalyzed coupling. This is consistent with reduced catalytic activity due to coordination of **4** to palladium. This method was then applied to a small range of aryl iodide substrates. As illustrated in Table 4, aryl iodides bearing electron-donating (entries 1 and 2), electron-withdrawing (entries 4−6) and *ortho* substituents (entries 2 and 7) afforded the corresponding products in moderate to good yields.

In conclusion, we have developed various palladium(0)-catalyzed methods for the direct synthesis of Weinreb amide and MAP amide acylating agents from (hetero)aryl bromides and iodides. The reactions tolerate a range of different functional groups and the desired products were obtained in good yields with short reaction times. More importantly, these methods utilize solid sources of CO making them readily accessible to preparative chemists working in small-scale laboratory applications.

Experimental Section

Representative Procedure for the Synthesis of Weinreb Amides from Aryl Bromides. 4-Acetyl-*N*-methoxy-*N*-methylbenzamide (2f). A 2−5 mL process vial was charged with 1-(4-bromophenyl)ethanone (49.7 mg, 0.250 mmol), $W(CO)_6$ (29.0 mg, 0.082 mmol), $Pd(OAc)_2$ (4.2 mg, 0.018 mmol, 7.5 mol %), Xantphos (21.6 mg, 0.037 mmol, 15 mol %), DMAP (61.0 mg, 0.500 mmol), K_3PO_4 (318.0 mg, 1.500 mmol), *O*,*N*-dimethylhydroxylamine hydrochloride (72.0 mg, 0.750 mmol) and 1,4-dioxane (2.0 mL). The vessel was sealed under air and exposed to microwave heating for 20 min at 120 °C. The resulting mixture was cooled to room temperature, filtered through a cotton pad (eluting with dichloromethane), and concentrated under reduced pressure. The crude product was thereafter purified by flash column chromatography on silica gel (EtOAc/*i*-Hexane 2:1) to provide the title compound as a colorless solid (36 mg, 70%): mp 51−53 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.94 (m, 2H), 7.76−7.70 (m, 2H), 3.52 (s, 3H), 3.35 (s, 3H), 2.61 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 169.1, 138.6, 138.5, 128.5, 128.1, 61.4, 33.6, 26.9. HRMS calcd for $C_{11}H_{14}NO_3$ [M + H$^+$] 208.0974, found 208.0968.

Caution! Pressurized reactions should not be conducted in sealed vessels without an appropriate pressure release device due as this could result in an explosion. Therefore the use of dedicated instrumentation is recommended for these procedures.

Acknowledgment. We gratefully acknowledge the financial support from the Swedish Research Council and Knut and Alice Wallenberg's Foundation.

Supporting Information Available: All experimental procedures and analytical data for newly synthesized compounds, as well as copies of ^{1}H and ^{13}CNMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.