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Microwave-Enhanced Aminocarbonylations in Water

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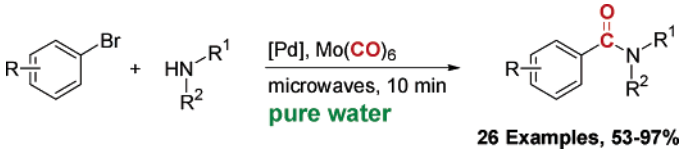
ABSTRACT



Aryl bromides can be rapidly converted to the corresponding secondary and tertiary benzamides in water. By using $Mo(CO)_6$ as the source of carbon monoxide, aminocarbonylations were conducted under air after only 10 min of high-density microwave heating.

The development of metal-catalyzed organic transformations in water[1,2] has become an important research area just as microwave-enhanced procedures have proved to possess a high utility due to great reaction control and high reaction rates.[3−5] Among the different solvent alternatives in organic chemistry, water is extremely cheap and nontoxic.[6] In addition to these two general advantages, several benefits for the reaction are expected when using water as reaction medium for microwave-superheated protocols. First, water is rapidly heated by microwave irradiation to high reaction temperatures, enabling water to act as a less polar pseudo-organic solvent.[7] Second, precise control of the reaction temperature is easily achieved because of the very high heat capacity of water. Third, the lack of flammable properties makes the use of water safe also with pressurized exothermic reactions.[7]

In addition, there is a need to implement more sustainable methods, not only for large-scale production but also for lab-scale medicinal chemistry research.[8] Although the aim of developing novel pharmaceutical drugs is commendable, large amounts of organic solvents are consumed in both lead generation and lead optimization work.[9] Thus, there is a definite request for aqueous methods.

Palladium(0)-catalyzed coupling reactions utilizing aryl halides as arylmetal precursors are among the most important methods in modern organic synthesis.[10] Such transformations include cross-coupling reactions, Heck reactions, Buchwald−Hartwig couplings, Sonogashira couplings, carbonylation reactions, and many others.[10] Today, most of these reaction types have been carried out both in aqueous media[11] and under controlled microwave irradiation.[12]

An increasing number of palladium-catalyzed protocols have also been performed in microwave-heated water.[13−15]

Palladium-catalyzed carbonylation of aryl halides affords different benzoic acid derivatives.[16,17] Depending on the nucleophile employed, aromatic acids, amides, esters, or

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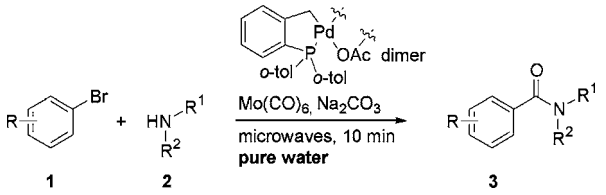
Scheme 1. $Mo(CO)_6$-Mediated Aminocarbonylation in Water



aldehydes are smoothly obtained. Noteworthy, all disclosed aqueous carbonylations of aryl halides have up to now provided only the hydroxycarbonylation product (the benzoic acid).[18−21] As an effort in the development of complementary carbonylation reactions in pure water, we examined the potential of carrying out aminocarbonylations with high efficiency. We now wish to report the first protocol for aminocarbonylation of aryl bromides in water. All presented examples were performed after only 10 min of microwave heating and with $Mo(CO)_6$ alone as the CO source.[22,23]

We started our development of an aqueous amidation protocol by examining the reported conditions for microwave-promoted aminocarbonylations using $Mo(CO)_6$ and palladium catalysis.[24] Aiming for a thermostable catalytic system and mild reaction conditions, Herrmann's palladacycle[25] was selected as a suitable Pd(0) source and Na_2CO_3 was chosen as a weak base (Scheme 1). The reactions were in all cases executed on a 1.0-mmol scale and heated in sealed vessels under an atmosphere of air. As shown in Table 1, 1-naphthyl bromide (**1g**) was reacted in different ratios with *n*-butylamine (**2a**) at 170 °C, delivering the expected amide product **3g**, accompanied by different amounts of the competing hydroxycarbonylation product 1-naphthoic acid (**4g**). The outcome of the reaction depended, as expected, on the varied **1g**/**2a** stoichiometry, and in the complete absence of **2a**, the aromatic acid was the only isolated product (Table 1). Increasing the amount of **1g** afforded higher and higher yields of **3g** (from 62% up to 81%), although competing hydroxycarbonylation also profited. To conclude the chemical optimization, the conditions utilizing a 2:1 ratio of **1g**/**2a** were selected as our standard protocol despite the fact that a higher aryl bromide concentration afforded sligthly improved yields of amide **3g**.

Table 1. Selective Formation of Aromatic Amide or Acid by Fast Carbonylation Reactions in Water[a]

1-naphthyl bromide (**1g**)	*n*-butyl-amine (**2a**)	isolated yield of amide (**3g**)	isolated yield of acid (**4g**)
1.0 mmol	0		67%
1.0 mmol	2.0 mmol	62%	10%
1.0 mmol	5.0 mmol	67%	10%
1.2 mmol	1.0 mmol	63%[b]	0.12 mmol
2.0 mmol	1.0 mmol	**79%**[b]	0.29 mmol[c]
5.0 mmol	1.0 mmol	81%[b]	0.38 mmol[c]

[a] **1g**, **2a**, 0.5 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % palladacycle, 2.0 mL of H_2O, microwave irradiated at 170 °C for 10 min. Yield based on **1g**. [b] Yield based on **2a**. [c] Noncomplete conversion of **1g**.

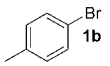
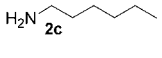
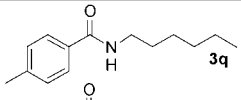
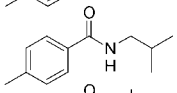
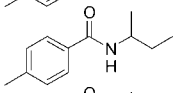
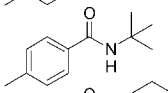
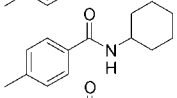
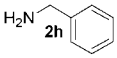
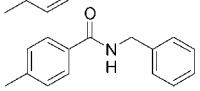
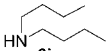
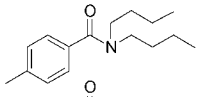
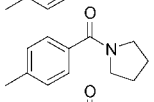
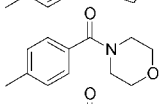
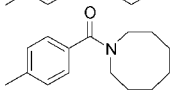
Table 2. Fast Aminocarbonylation of Aryl Bromides with *n*-Butylamine or Piperidine in Water[a]

ArBr	amine	product and isolated yield (%)[a]		
1a	**2a**	**3a**	75	
1b		**3b**	86	
1c		**3c**	74	
1d		**3d**	78	
1e		**3e**	63	
1f		**3f**	83	
1g		**3g**	79	
1h		**3h**	43 54[b]	
1a	**2b**	**3i**	84	
1b		**3j**	88	
1c		**3k**	70	
1d		**3l**	87	
1e		**3m**	80	
1f		**3n**	74	
1g		**3o**	78	
1h		**3p**	76	

[a] 1.0 mmol **2**, 2.0 of equiv **1a**−**h**, 0.5 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % palladacycle, 2.0 mL of H_2O, microwave irradiated under air at 170 °C for 10 min; >95% purity by GC−MS. [b] 180 °C for 10 min.

We next decided to investigate the scope of the aqueous protocol with different aryl bromides, using both a primary amine and a secondary amine (Table 2). *n*-Butylamine (**2a**) and piperidine (**2b**) were selected as the model amines. Good yields were obtained in most cases with **2a** and formation of piperidine products **3i**−**p** demonstrated that secondary

Table 3. Fast Aminocarbonylation of *p*-Tolyl Bromide with Miscellaneous Amines in Water[a]

ArBr	amine	product and isolated yield (%)[a]	
 **1b**	 **2c**		**3q** 97
	 **2d**		**3r** 82
	 **2e**		**3s** 74
	 **2f**		**3t** 60
	 **2g**		**3u** 78
	 **2h**		**3v** 81
	 **2i**		**3w** 53
	 **2j**		**3x** 92
	 **2k**		**3y** 73
	 **2l**		**3z** 70

[a] 1.0 mmol **2c**−**l**, 2.0 equiv of **1b**, 0.5 equiv of $Mo(CO)_6$, 3.0 equiv of Na_2CO_3, 5 mol % palladacycle, 2.0 mL of H_2O, microwave irradiated under air at 170 °C for 10 min; >95% purity by GC−MS.

amines also served as productive nucleophiles in water (Table 2). We were further able to achieve amidation of aryl bromides carrying electron-donating as well as electron-withdrawing functionalities. Aminocarbonylations leading to formation of ortho-substituted benzamides **3c**, **3g**, **3k**, and **3o** also worked satisfactorily. Disappointingly, the reaction between 3-thienyl bromide (**1h**) and *n*-butylamine did not proceed as smoothly as the corresponding reaction with piperidine. However, on raising the temperature to 180 °C, this aminocarbonylation furnished 54% isolated yield of **3h** (Table 2).

To further investigate the limits of compatibility, various nucleophilic amines were tested for their respective reactivity with aryl bromide **1b** using the identical water-based protocol. From Table 3, it can be concluded that the reaction is general although the noncyclic secondary amine **2i** afforded a reduced yield (53%). In contrast, unhindered primary amines benzylamine and pyrrolidine provided excellent productivity after only 10 min of irradiation. Even the sterically congested *tert*-butylamine competed favorably with water and the accompanying hydroxycarbonylation, affording a useful 60% yield of secondary **3t**.

To conclude, in the presence of $Mo(CO)_6$ and a palladium catalyst, aryl bromides were rapidly transformed into benzamides under microwave conditions. Despite the use of water as solvent, aminocarbonylation strongly dominated over hydroxycarbonylation, providing good yields of both secondary and tertiary model benzamides. This air-tolerant aqueous aminocarbonylation protocol provides operational convenience and increased safety for small-scale high-speed synthesis.

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Supporting Information Available: Experimental procedures and spectroscopic and purity data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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