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ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 2339–2343

Microwave assisted, palladium catalyzed aminocarbonylations of heteroaromatic bromides using solid $Mo(CO)_6$ as the carbon monoxide source

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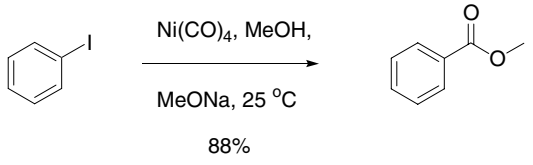
Received 19 December 2006; revised 16 January 2007; accepted 25 January 2007
Available online 30 January 2007

Abstract—The direct conversion of a variety of heteroaromatic bromides into heteroaromatic amides is described. This reaction utilizes $Mo(CO)_6$ as the carbon monoxide source and is performed using microwave heating allowing for very short reaction times. This convenient methodology allows for the preparation of a variety of heteroaromatic amides useful in medicinal chemistry applications.

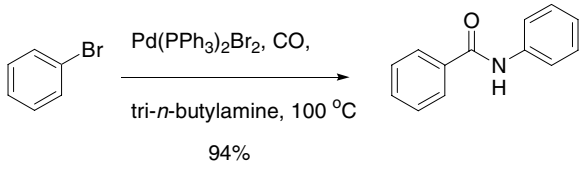
It has been known for quite some time that aryl and vinyl halides are useful intermediates for the preparation of acids, esters and amides. One common way to convert an aryl halide to an acid is by lithium halogen exchange followed by reaction with carbon dioxide. One of the variety of coupling reactions will then provide access to esters or amides. While these reactions work, direct methods for the synthesis of amides and esters from aryl halides are preferable in many cases. These include examples where the aryl lithium intermediate formed from the reaction of an aryl halide with an alkyl lithium is unstable. In addition, many times the carboxylic acids formed upon reaction with CO_2 can be difficult to handle or to isolate, particularly if basic amine functionalities are present in the molecule as is the case in many medicinal chemistry applications.

Many research groups have pursued the direct formation of aryl acids, esters, and amides from aryl halides. For example, nearly 40 years ago Corey and Hegedus[1] demonstrated that nickel tetracarbonyl in the presence of a sodium or potassium alkoxide reacts with iodobenzene to form methyl benzoate.

The palladium catalyzed formation of *n*-butyl benzoate from bromobenzene was later demonstrated by Heck and co-workers.[2] The Heck group also showed that



bromobenzene could be converted to *N*-phenyl benzamide in the presence of one atmosphere of carbon monoxide and 15 mol% $Pd(PPh_3)_2Br_2$.[3]



Most of the aminocarbonylation reactions that have been reported use carbon monoxide gas as the CO source.[4] Use of this toxic gas is rather inconvenient, particularly in the context of medicinal chemistry where parallel synthesis methods are preferred whenever possible. More recent operational advances in the conversion of aryl halides to amides have included using solid $Mo(CO)_6$ as the carbon monoxide source and the use of microwave reactors to facilitate these transformations (Scheme 1).[5–8] The use of solid $Mo(CO)_6$ is much more convenient than the use of carbon monoxide gas and performing the reaction in a microwave provides

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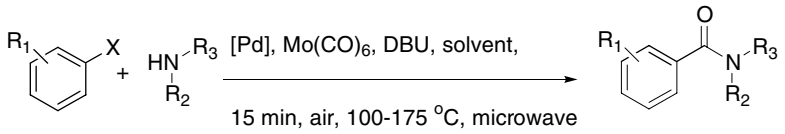
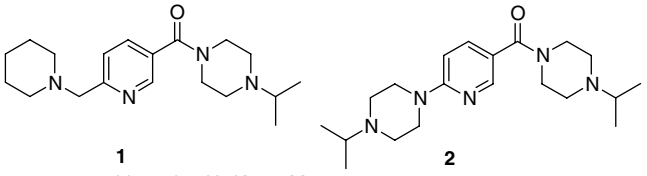
doi:10.1016/j.tetlet.2007.01.133



Scheme 1. Aminocarbonylation reactions of aryl halides.

semi-automated conditions desirable for medicinal chemistry.[9] These studies have also demonstrated that the reactions can be done in THF or water,[10] providing an alternative to organic solvents. The reaction conditions appear to be quite general, allowing for the preparation of a variety of benzamides.

Benzamide intermediates are quite useful for a variety of applications, however, many medicinal chemistry applications also require the preparation of heteroaromatic amide intermediates. We were particularly interested in heterocycle amides related to the potent histamine H_3 antagonists **1** and **2**.[11] Notably, very few heteroaromatic amides have been prepared using this type of aminocarbonylation methodology. There are a few examples of bromothiophenes[7,8,10] participating in these reactions and there are examples of heteroaromatic halides participating in aminocarbonylation reactions using carbon monoxide as a CO source,[12,13] however, we have not found other examples of microwave assisted aminocarbonylations of heteroaromatic halides using the more convenient $Mo(CO)_6$ as a CO source.



1 histamine H_3 K_i=1 nM

2 histamine H_3 K_i=4 nM

For our purposes, we required a quick, simple, and general method for the conversion of heteroaromatic bromides to amides. Preliminary studies in our group indicated that aminocarbonylations using microwave irradiation might provide a viable alternative to either the two step process of preparing the heteroaromatic acids and coupling with amines or the alternative aminocarbonylation using carbon monoxide. We now report the aminocarbonylation of a variety of commercially available heteroaromatic bromides in order to demonstrate the utility of this reaction.

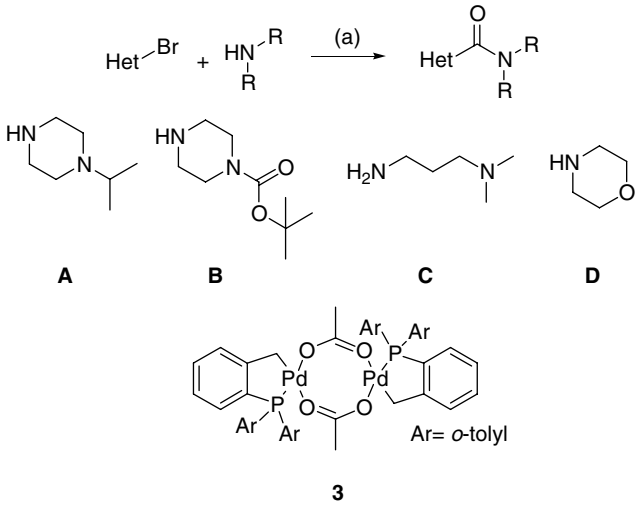
The general reaction is shown in Scheme 2. The reactions were typically done at 125 °C with microwave heating for 6 min. The palladium source for these reactions was *trans*-di-μ-acetatobis[2-(di-*o*-tolylphosphino)benzyl]dipalladium(II) (**3**). In all cases tri-*tert*-butylphosphonium tetrafluoroborate was used as a preligand and DBU as a base. Typically, the reactions were concentrated and chromatographed on silica gel without further workup.[14]

During the course of optimization of this procedure, the reaction of 5-bromo-2-methoxypyridine with 1-isopropyl-piperazine (Table 1, entry 3) was also conducted at 100 °C, with or without added DBU (Scheme 3). Not surprisingly, the reaction did not proceed in the absence of DBU. Under the standard conditions at 100 °C, 58% of the coupling product was obtained and at higher temperature (150 °C) the yield was 76%, indicating that 125 °C is near optimal for this reaction.

Table 1 shows the aryl bromides and amines used to prepare entries 1–16. Yields ranged from 34% to 97%. The reaction 1-isopropylpiperazine worked well with 2- and 5-bromopyridines (entries 1, 3 and 5), and 5-bromopyrimidines (entries 2, 4 and 6). It is interesting to note that in contrast to the reaction of 2-bromopyridine (entry 1) which gave the amide, 2-bromopyrimidine reacted with 1-isopropylpiperazine to give the aminopyrimidine (52%, entry 10) indicating that the 2-bromopyrimidine reacts with the amine prior to palladium insertion. No products of carbonyl insertion were isolated from this reaction.

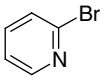
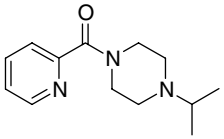
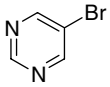
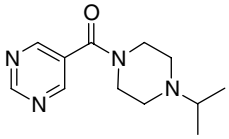
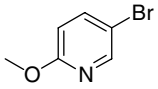
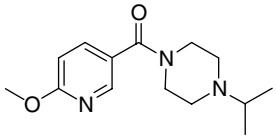
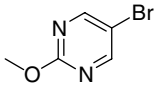
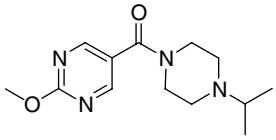
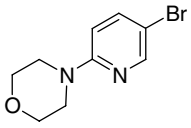
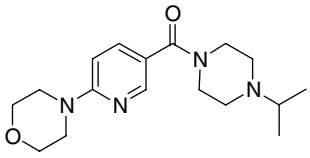
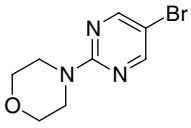
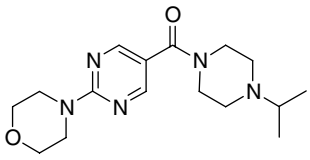
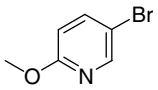
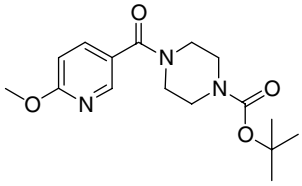
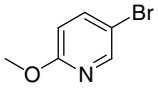
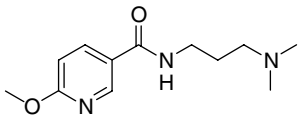
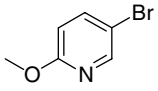
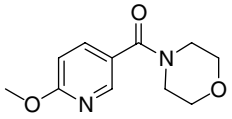
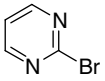
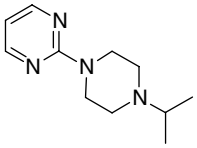
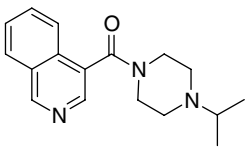
Other heterocycles that gave moderate yields of heterocyclic amides include 3-bromoisoquinoline (entry 11) and 4-bromoindole (entry 13). The yield for the latter reaction was low, however, palladium catalyzed coupling reactions of unprotected indoles are not widely reported, likely due to unwanted side reactions under normal coupling conditions.

Advances in this area include a recent report on the aminocarbonylation of unprotected indoles in the presence of palladium, a bidentate ligand and carbon mon-



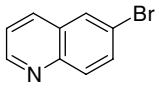
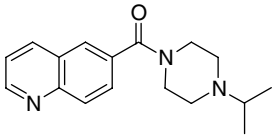
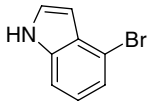
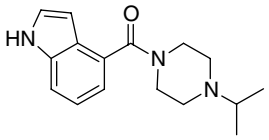
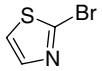
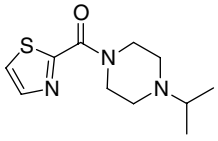
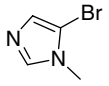
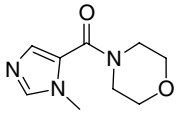
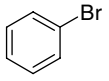
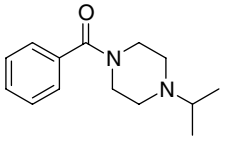
Scheme 2. Aminocarbonylation reactions. Reagents and conditions: (a) **3**, *t*-Bu_3PHBF_4, DBU, **A–D**, $Mo(CO)_6$, THF, microwave, 125 °C, 6 min.

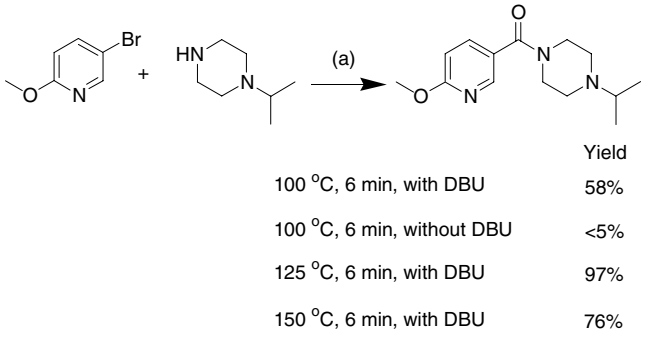
Table 1. Heteroaromatic amides formed via the reaction shown in Scheme 2[14]

Entry	Aryl bromide	Amine	Product	Yield (%)
1		A		60
2		A		51
3		A		97
4		A		88
5		A		69
6		A		70
7		B		78
8		C		89
9		D		82
10		A		52
11		A		43

(*continued on next page*)

Table 1 (*continued*)

Entry	Aryl bromide	Amine	Product	Yield (%)
12		A		74
13		A		34
14		A		52
15		D		61
16		A		80



Scheme 3. Reaction of 5-bromo-2-methoxypyridine with 1-isopropylpiperazine. Reagents and conditions: (a) **3**, *t*-Bu_3PHBF_4, $Mo(CO)_6$, THF, microwave.

oxide gas.[15] These reactions allowed access to CNS active indole amides. Our initial results indicate that the reactions of indoles can also be done using $Mo(CO)_6$ as the CO source, eliminating the need to use carbon monoxide and long reaction times (12–20 h) under normal conditions.

The reaction was also successful with the five-membered heteroaromatics 2-bromothiazole and 5-bromo-1-methyl-1*H*-imidazole (entries 14 and 15). In addition, these aminocarbonylation reactions proceed smoothly with primary amines (entry 8), with piperazine-1-carboxylic acid *tert*-butyl ester (entry 7), and with morpholine (entries 9 and 15) allowing access to a wide variety of useful intermediates for parallel synthesis.

No amide product was isolated upon reaction of 2-chloro-3-methylpyridine with 1-isopropylpiperazine under the same conditions (data not shown), however, others have reported success with aryl chlorides using certain palladium catalysts and carbon monoxide as the CO source.[12] Additional studies with alternative palladium sources and preligands will be needed in order to determine whether these reactions can be conducted using heteroaryl chlorides in the presence of $Mo(CO)_6$ as has been demonstrated for aryl chlorides.[8]

In order to compare our reaction conditions to those earlier reported for bromobenzene, we conducted the reaction of bromobenzene with 1-isopropylpiperazine (entry 16). Our results were similar to the data reported previously for the reaction of bromobenzene with piperidine.[16]

In conclusion, we have demonstrated the utility of microwave assisted aminocarbonylations of numerous heteroaromatic bromides using solid $Mo(CO)_6$ as the source of carbon monoxide. These reactions are simple to perform, proceed quickly, and give good to moderate yields of amides. The reactions work in the presence of Boc-protected amines and are suitable for the preparation of morpholine amides, adding to the versatility of the products obtained from the reaction. Since the reactions are done under microwave conditions, reaction times are less than 10 min allowing for rapid, semi-automated synthesis of small libraries of compounds. The heteroaromatic amides obtained from this reaction

allow easy access to numerous intermediates useful for the preparation of directed libraries for lead development. While our studies were conducted on relatively simple commercially available bromides, one can also envision the utility of the conversion of more structurally complex heteroaromatic bromides to amides via this methodology.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.133.

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14. *Typical experimental conditions for the preparation of entry 3*: 5-Bromo-2-methoxy-pyridine (260 μL, 2.01 mmol) was added to a 5 mL microwave vial containing a magnetic stir bar and THF (4 mL). 1-Isopropylpiperazine (400 μL, 2.80 mmol), 1,8-diazabicyclo(5.4.0)undec-7-ene (200 μL, 1.34 mmol), *trans*-di-μ-acetatobis[2-(di-*o*-tolyl-phosphino)-benzyl]di-palladium(II) (22.6 mg, 0.024 mmol), tri-*tert*-butylphos-phonium tetrafluoroborate (16.9 mg, 0.058 mmol) and molybdenum hexacarbonyl (251.5 mg, 0.957 mmol) were then sequentially added to the vial. The vial was sealed and heated to 125 °C in a microwave reactor for 6 min. The reaction was allowed to cool to room temperature and was concentrated on a rotary evaporator. The resulting oil was applied directly to a silica gel column and was chromatographed using a mixture of dichloromethane and 10% methanol containing 0.1% ammonium hydroxide as eluent to give (4-isopropyl-piperazin-1-yl)-(6-methoxy-pyridin-3-yl)-methanone (515.8 mg, 97%) as a clear oil. Products were characterized by ^{1}H NMR, MS, and HPLC and all gave satisfactory results.
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16. See Ref. 7. For the reaction of bromobenzene with piperidine the authors report 87% yield of phenyl-piperidin-1-yl-methanone under similar conditions upon heating in the microwave at 170 °C for 10 min. We obtained a 63% yield of phenyl-piperidin-1-yl-methanone using the conditions described in Scheme 2.