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Synthesis of primary amides by aminocarbonylation of aryl/hetero halides using non-gaseous NH_3 and CO sources

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ABSTRACT

A practically simple method for the synthesis of primary amides via the palladium-catalysed aminocarbonylation of aromatic halides by using solid sources of gaseous ammonia and carbon monoxide is described. The system tolerated a wide variety of hindered and functionalized aryl/hetero halides and afforded good to excellent yields (69–94%) of the amide. Pharmacologically active Exalamide and Pyrazinecarboxamide were synthesised in high yields to demonstrate the effectiveness of this method.

Ever since the first work of Heck and co-workers in 1974 on three component coupling reaction,[1] the transformation of aromatic halides to a wide variety of aromatic carbonyl derivatives has been frequently undertaken in organic synthesis. As a result, an impressive amount of approach has been put forward to effect this transformation in high yield and short reaction time.[2] Among all the palladium mediated carbonylations, synthesis of amides by aminocarbonylation is very useful in organic synthesis and pharmaceutical chemistry as they form a central part of many biologically active molecules.[3] An in-depth analysis of the Comprehensive Medicinal Chemistry database revealed that the amide group appears in more than 25% of known drugs.[4] This can be expected, since amides are neutral, stable and have both hydrogen-bond accepting and donating properties.[5] Also the primary amides serve as useful intermediates for the synthesis of nitriles by dehydration,[6] benzoxazoles by transition metal mediated coupling reaction,[7] and benzyl amines by reduction.[8]

A variety of strategies has been developed for the selective formation of primary amides. Frequently the carboxylic acids (by coupling reagents) or acid derivatives (e.g., esters, acid chlorides, anhydrides) are used to synthesise this class of compounds.[9] Among all the methods, the aminocarbonylation of aryl halides with ammonia is attractive.[10] However, the reaction protocols require high pressure equipments. Also, there may be difficulty in handling very toxic, flammable or corrosive carbon monoxide and ammonia gases in one reaction vessel. To overcome this, alternate sources of gaseous ammonia like hexamethyldisilazane,[11] *tert*-butylamine,[12] benzyl amine,[13] allyl amine[14] or ammoniumcarbamate[15] were developed. But, these methods require carbonylation and de-protection reaction sequence or selective cleavage by workup to get the desired primary amides. Also these reactions use an excess amount of CO gas and initial evacuation of the reaction vessel is required. Recently aqueous NH_3 was also used in the synthesis of primary amides from aryl iodides in good yields in the presence of $Pd(OAc)_2$/CYTOP®292, 100 psi of CO gas at 130 °C. But, aryl bromides cannot be used for the synthesis of primary amides by this method. Lately, Larhed and his group developed a new protocol to synthesise primary amides by the decomposition of hydroxylamine to ammonia at higher temperature, strong base and excess of $Mo(CO)_6$ under microwave irradiation.[16] Nielsen et al. used ammonium carbamate as ammonia source and 9-methyl-9*H*-fluorene-9-carbonyl chloride (COgen) as CO source to synthesise aromatic primary amides by a two-chamber system.[17] These methods are attractive as both the NH_3 and CO sources can easily be handled. However, the reactions are performed either at high temperatures and/or pressures for the decomposition of the corresponding solid sources to release ammonia/carbon monoxide or special reaction setups are required. Thus, there was scope for improvement and development over the existing methods.

Recently, we reported that the dicobalt octacarbonyl can be used as a solid alternate CO source for the palladium mediated carbonylation reactions under mild condition.[18] Initial search for an

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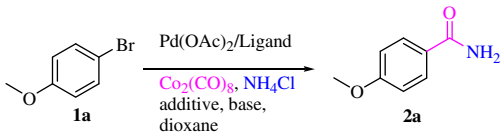
Table 1
Reaction optimisation of aminocarbonylation[a]



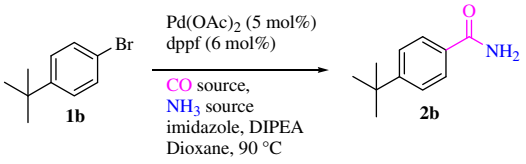
Entry	NH_4Cl (equiv)	Base (2 equiv)	Ligand (6 mol %)	Additive[b] (2 equiv)	Temp (°C)	Time (h)	Yield[c] (%)
1	4	DMAP	Xantphos	—	100	8	N.R.
2	5	DMAP	Xantphos	—	140	24	N.R.
3	3	DBU	Xantphos	—	100	24	N.R.
4	3	DIPEA	Xantphos	—	100	24	N.R.
5	3	K_2CO_3	Xantphos	—	100	24	N.R.
6	3	DMAP	dppf	—	100	8	N.R.
7	3	DMAP	PPh_3	—	100	8	N.R.
8	3	DMAP	BINAP	—	100	8	N.R.
9	3	DMAP	Xantphos	Imidazole	100	8	72
10	3	DMAP	Xantphos	Imidazole	100	5	79
11	3	DIPEA	dppf	Imidazole	90	3	84
12	2	DIPEA	dppf	Imidazole	90	3	90
13	2	—	dppf	Imidazole	90	3	35
14	2	DIPEA	dppf	Imidazole	90	3	90[d]
15	2	DIPEA	dppf	Imidazole	90	3	91[e]
16	2	DIPEA	dppf	Imidazole	90	3	94[f]
17	2	DIPEA	dppf	Imidazole	90	3	87[g]

N.R.-Desired product not obtained.
[a] All the reactions were performed with 1 mmol of **1a**.
[b] 2 equiv of additives were used.
[c] All the yields reported are isolated by column chromatography.
[d] 0.75 equiv of imidazole was used.
[e] 0.50 equiv of imidazole was used.
[f] 0.25 equiv of imidazole was used.
[g] 0.1 equiv of imidazole was used.

alternate source of gaseous NH_3 led us to report that solid ammonium chloride can successfully be used as solid in situ ammonia source for the synthesis of primary amides. NH_4Cl is much cheaper and more suitable than other ammonia sources reported for the synthesis of primary amides. Herein, we report a simple protocol for the synthesis of primary amides based on palladium-catalysed aminocarbonylation of aromatic halides (Br/I) using commercially inexpensive, stable and solid non-gaseous precursors for both ammonia and CO, that is, ammonium chloride (NH_4Cl) and cobalt carbonyl [$Co_2(CO)_8$], respectively, thus making this approach simple, comparatively safe and inexpensive.

In order to attain the optimal reaction conditions, 4-bromoanisole (**1a**) was aminocarbonylated using NH_4Cl (4 equiv) in the presence of $Pd(OAc)_2$, Xantphos, DMAP and $Co_2(CO)_8$ in dioxane following on our early Letter.[18b] However, the expected 4-methoxybenzamide (**2a**) was not observed (Table 1, entry 1). Increasing the reaction temperature to 140 °C and reaction time to 24 h (Table 1, entry 2) did not produce the desired result.

Table 2
Experiment on other solid sources of CO and NH_3[a]



Entry	Carbonyl source	Ammonia source[b]	Temp (°C)	Time (h)	Yield[c] (%)
1	$Co_2(CO)_8$	NH_4Cl	90	3	82
2	$Co_2(CO)_8$	$NH_4CO_2NH_2$	90	3	48
3	$Co_2(CO)_8$	HCO_2NH_4	90	3	Traces
4	$Co_2(CO)_8$	NH_2CONH_2	90	3	20
5	$Co_2(CO)_8$	NH_4HCO_3	90	8	Traces
6	$Co_2(CO)_8$	$NH_2OH{\cdot}HCl$	90	8	Traces
7	$Mo(CO)_6$	NH_4Cl	90	8	39
8	$Cr(CO)_6$	NH_4Cl	90	8	Traces
9	$W(CO)_6$	NH_4Cl	90	8	Traces

[a] All the reactions were executed with 1 mmol of **1b**.
[b] 2 equiv of ammonia source was used.
[c] All the yields reported are isolated by column chromatography.

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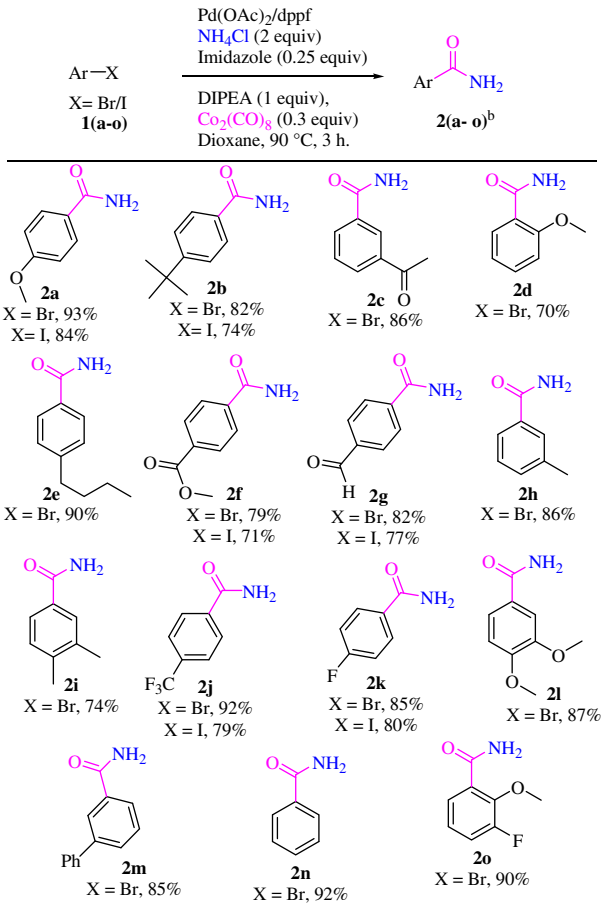
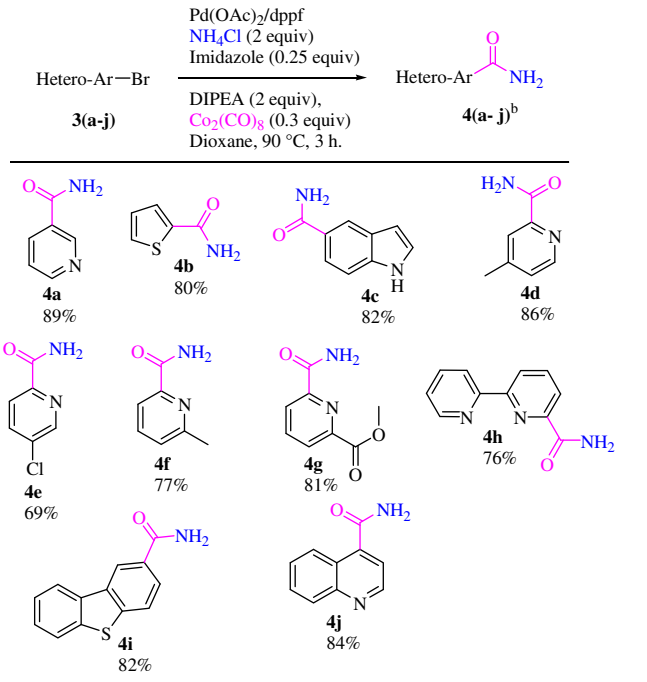
Table 3
Aminocarbonylation of aryl halides (Br/I)[a]



[b] All the yields reported are isolated by column chromatography.
[a] All the reactions were executed with 1 mmol of corresponding aryl halides **1**(**a**–**o**).

Table 4
Aminocarbonylation of hetero arylbromides[a]



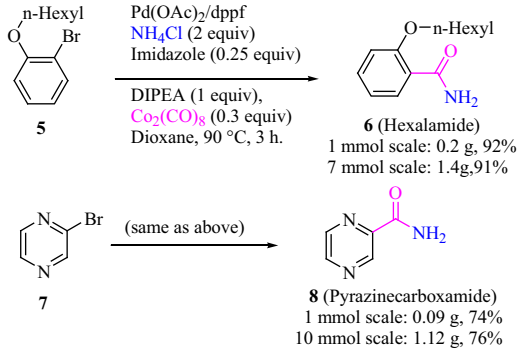
[b] All the yields reported are isolated by column chromatography.
[a] All the reactions were executed with 1 mmol of corresponding aryl halides **3**(**a**–**j**).

Screening a range of bases (Table 1, entries 3–5) and solvents such as toluene, DMF, THF and DMSO failed to produce the desired product (results are not shown). The examination of other different mono and bidentate ligands such as dppf, PPh_3, BINAP were also hopeless (Table 1, entries 6–8). During the above experiments, the observation of the de-brominated (4-methoxybenzene) and ketone bis(4-methoxyphenyl)methanone product masses in GCMS analysis indicated that the oxidative addition of the aryl halide to the palladium centre and the carbonyl insertion steps occur. But, subsequent nucleophilic addition of ammonia does not take place. This may be due to the poor nucleophilicity of ammonia making it less reactive with the active acyl-palladium centre. In general, the palladium catalysed carbonylation reaction of the less reactive nucleophiles can be improved by adding additives.[19,18c] So, we investigated the effect of additives on the reaction mixture, which initially react with the acyl palladium center and form the active acyl intermediate. To our delight, the addition of imidazole straightaway yielded 72% of amide **2a** (Table 1, entry 9). After fine tuning in the reaction parameters, it was evident that the best results for the formation of **2a** was obtained in the presence of $Pd(OAc)_2$, dppf as a ligand, 2 equiv of NH_4Cl, imidazole, DIPEA and nearly stoichiometric amount (0.3 equiv) of $Co_2(CO)_8$ in dioxane at 90 °C for 3 h (Table 1, entry 12). Next, we examined the sensitivity of the base in the reaction and found that the isolated yield of amide **2a** drastically reduced to 35% when the reaction was performed without the addition of DIPEA (Table 1, entry 13). So, we concluded that the additional base (DIPEA) in the reaction is essential to get the desired product in high yields.

Based on the above results, and using the best reaction conditions (Table 1, entry 12), the required amount of catalyst and additives was studied. After several reaction conditions with decreasing amounts of imidazole, amide **2a** was isolated in 94% yield with complete conversion of aryl halide **1a** (Table 1, entry 16) when imidazole was used in a catalytic amount (0.25 equiv).

To test the effectiveness of the optimised carbon monoxide and ammonia sources used in this carbonylation reaction, a range of other solid sources of ammonia and carbon monoxide releasing reagents were investigated using our optimised reaction conditions. The obtained results are shown in Table 2. We have chosen 1-bromo-4-tertbutylbenzene (**1b**) as model substrate and isolated the desired primary amide **2b** in 82% yield (Table 2, entry 1) under stabilized reaction conditions. Then, a number of other ammonia releasing ammonium salts (ammonium carbamate, ammonium formamide, urea, ammonium acetate and hydroxylamine hydrochloride) were screened (Table 2, entries 2–6) in place of ammonium chloride. However, the results showed that ammonium chloride (Table 2, entry 1) was superior. Similarly when CO releasing other known metal carbonyls [$Mo(CO)_6$, $Cr(CO)_6$ and $W(CO)_6$] used in carbonylation reactions were screened (Table 2, entries 7–9), the results were apparent that dicobalt octacarbonyl is much better than others.

Having established conditions for the synthesis of primary amide from the corresponding aryl bromide, we investigated the substrate scope with various aryl halides (Br/I). As shown in Table 3, the method well tolerated various electronic and steric substituent patterns of aryl bromides and aryl iodides, all ensuing good to excellent isolated yields of the primary amides. However,



Scheme 1. The synthesis of biologically active Exalamide and Pyrazinecarboxamide.

in the case of aryl iodides the isolated yields were slightly lower than the corresponding aryl bromides (**2a**, **2b**, **2f**, **2g**, **2j**, **2k**) used. Various other carbonyl functional groups such as ketone (**2c**), esters (**2f**) and aldehyde (**2g**) are compatible for this reaction condition.

The successful results obtained for the formation of aryl primary amides presented above encouraged us to explore the aminocarbonylation of various hetero aryl halides. A selection of heterocyclic aryl bromides were explored under the optimised conditions and the results are shown in Table 4. It is to be noted that 3-bromopyridine (**3a**) and 2-bromothiophene (**3b**) produced the corresponding amides in excellent yields (89% and 80%, respectively). More interestingly, a direct aminocarbonylation of the unprotected 5-bromoindole (**3c**) yielded the corresponding amide (**4c**) in 82% yield. Similarly, other interesting heterocyclic amides (**4d**–**4j**) are isolated from corresponding hetero aryl bromides in good yields with complete conversion.

To further exemplify the potential of this protocol, two biologically important pharmaceutical targets, Exalamide[20] (2-Hexyloxybenzamide, **6**) (antifungal agent) and Pyrazinecarboxamide[21] (2-Pyrazinamide, **8**) (antitubercular agent) were synthesised from commercially available 1-bromo-2-hexyloxybenzene and 2-bromopyrazine in isolated yields of 92% and 74%, respectively (Scheme 1). The reaction was also successfully repeated in gram scale without affecting the isolated yields. In conclusion, the palladium catalysed aminocarbonylation of aryl and hetero aryl halides with ammonium chloride provides a rapid route to the synthesis of primary amides. We have successfully used solid $Co_2(CO)_8$ and NH_4Cl as convenient sources of CO and NH_3 to the synthesis of primary amides in excellent isolated yields.[22] The method works well for both aryl and hetero aryl halides. The new protocol also allows the efficient synthesis of biologically active Exalamide and Pyrazinecarboxamide even at 10 mmol scale reaction in good yields which further exemplifies the importance of this method. Since non-gaseous NH_3 and CO sources are used (NH_4Cl and $Co_2(CO)_8$, respectively), this method is well suited for both laboratory scale and library synthesis of aromatic primary amides.[23]

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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.2015.06.054.

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22. *General procedure for the synthesis of primary amides:* To a stirred solution of aryl halide (Br/I) (1 mmol) in dry dioxane in a 25 mL sealed tube, was added $Pd(OAc)_2$ (5 mol %), dppf (6 mol %), DIPEA (2 mmol), imidazole (0.25 mmol), ammonium chloride (2 mmol) and then $Co_2(CO)_8$ (0.3 mmol). The seal tube was closed immediately and stirred at 90 °C for 3 h. After the reaction time the reaction mixture was cooled to room temperature. The reaction mixture was filtered through celite pad and washed with dioxane, the filtrate was concentrated under reduced pressure and the residue obtained was purified by column chromatography.
23. *Note:* Carbon monoxide gas is highly toxic and should be handled by trained professionals in well ventilated fume hood with appropriate ventilation. In all the reactions, $Co_2(CO)_8$ was handled carefully in Fume hoods and by using appropriate personal protective clothing and equipment.