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$Co_2(CO)_8$ as a convenient in situ CO source for the direct synthesis of benzamides from aryl halides (Br/I) via aminocarbonylation

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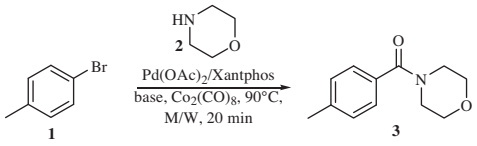
ABSTRACT

A fast, mild, and functional group tolerant method for the direct synthesis of benzamides from aryl halides (Br, I) via aminocarbonylation, using solid $Co_2(CO)_8$ as a convenient CO source, has been demonstrated. The developed method is applicable to a wide variety of 1° and cyclic and acyclic 2° amines. Nitro substituted (*o*, *m* and *p*) aryl halides have easily been converted to the corresponding benzamides, without the reduction of the nitro group, in high yields using this in situ carbonylation methodology under microwave irradiation.

The aromatic carbonyl derivatives namely esters and amides are important building blocks in the synthesis of valuable organic compounds including pharmaceuticals and agrochemicals.[1] In carbonyl derivatives, the benzamide derivatives possess important biological activities. Several methods have been published for the synthesis of benzamides.[2] Also, a variety of carbonyl derivatives have been synthesized by atom economy and functional group tolerant methods using easily available starting materials based on the palladium catalyzed carbonylation developed by Heck[3] in 1970s through the three-component coupling reaction using $CO_{(g)}$, aryl halides and a nucleophile (O^-, N^-, C^-). Such carbonylation methods, using CO gas, is based on the excellent ability of CO to act as pi-acid ligand toward transition metals.[4] However, CO is a highly toxic and flammable gas. Also, these reactions require special pressure reaction setups, and these methods are inconvenient in laboratory (small scale) and library (analogous) syntheses. To overcome this inconvenience to some extent, in 2002 Mats and coworkers have developed an in situ carbonylation method using non-gaseous CO precursors (transition metal carbonyls) employing a fast and furious microwave instrument. Subsequently, many reports have been published based on this methodology.[5] Although, they are able to overcome the inconvenience to some extent, using this methodology, higher temperatures (>120 °C) and/or higher equivalence of CO source are required to get good yields. Recently, a new ex situ method of generation of CO from $Mo(CO)_6$ using a bridged two-vial system has

Table 1
Condition optimization of aminocarbonylation



1 3

Entry	Carbonyl source	Base	Solvent[a]	Temp (°C)	Time (min)	Yield[b] (%)
1	$Co_2(CO)_8$[c]	DMAP	Toluene	90	30	81
2	$Co_2(CO)_8$[c]	DMAP	DMSO	90	30	70
3	$Co_2(CO)_8$[c]	DMAP	DMF	90	30	77
4	$Co_2(CO)_8$[c]	DMAP	DME	90	30	69
5	$Co_2(CO)_8$[c]	DMAP	THF	90	30	64
6	$Co_2(CO)_8$[c]	DMAP	Dioxane	90	30	91
7	$Co_2(CO)_8$[c]	DMAP	Dioxane	90	20	92
8	$Co_2(CO)_8$[c]	DMAP	Dioxane	90	15	88
9	$Mo(CO)_6$[d]	DMAP	Dioxane	90	30	72
10	$Cr(CO)_6$[d]	DMAP	Dioxane	90	30	35
11	$W(CO)_6$[d]	DMAP	Dioxane	90	30	30
12	$Co_2(CO)_8$[e]	DMAP	Dioxane	90	30	69

All the reactions were executed with 0.5 mmol of 4-bromotoluene, 5 mol % of $Pd(OAc)_2$, 5 mol % of ligand (4,5-bis(diphenylphosphanyl)-9,9-dimethylxanthene), 1 mmol of morpholine and 0.25 mmol of $Co_2(CO)_8$ at microwave irradiation.

[a] All the solvents were freshly distilled and used.
[b] Yield of the isolated product by column chromatography.
[c] 0.25 equiv of $Co_2(CO)_8$ were used.
[d] 0.5 equiv of metal carbonyls (Mo, Cr, W) were used.
[e] The reaction was performed with oil bath heating at 90 °C for 1 h.

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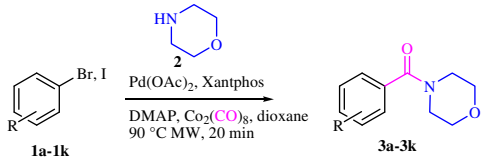
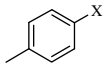
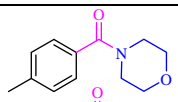
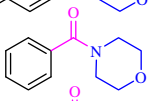
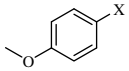
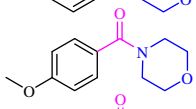
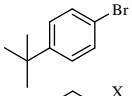
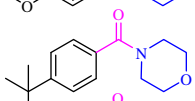
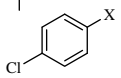
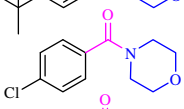
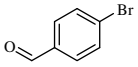
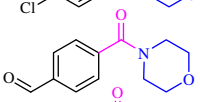
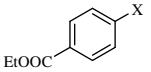
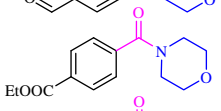
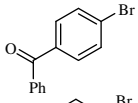
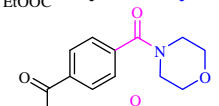
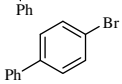
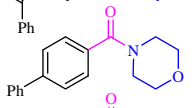
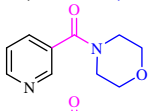
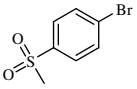
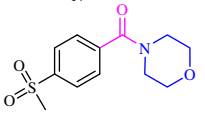
Table 2
Synthesis of morpholine amides of aryl halides



Entry	Arylhalide (1a-k)	$Co_2(CO)_8$ (eqv.)	Product (3a-k)	Yields (%)[a]
1		0.25		X=Br, 91 X=I, 88
2		0.25		X=Br, 89 X=I, 93
3		0.25		X=Br, 95 X=I, 83
4		0.30		82
5		0.25		X=Br, 92 X=I, 84
6		0.25		93
7		0.25		X=Br, 90 X=I, 86
8		0.30		82
9		0.25		X=Br, 87 X=I, 91
10		0.30		75
11		0.30		80

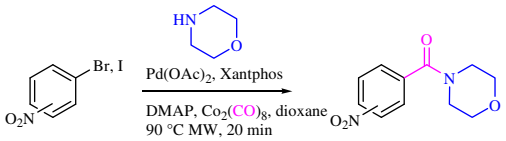
[a] Yield of isolated product.

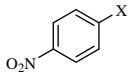
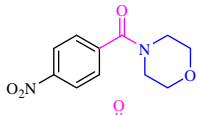
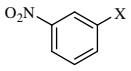
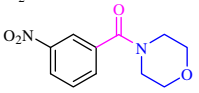
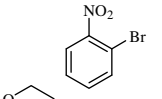
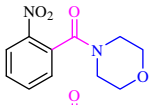
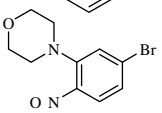
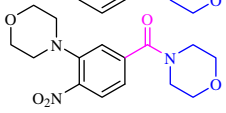
been reported for the carbonylation of nitro substituted aryl halides.[6] The major advantage of this method (i.e., carbonylation of nitro substituted aryl halides without affecting the nitro group) is based on the fact that the reduction of nitro group to aniline by $Mo(CO)_6$ is known in the literature.[7] Recently, we have described the synthesis of esters directly from aryl halides by using $Co_2(CO)_8$ as a simple and successful in situ CO source.[8] In continuation of this work, herein we report a simple and convenient protocol for the synthesis of benzamides in excellent yields through aminocarbonylation of different aryl halides including nitro substituted ones at low temperatures and at lower equivalents of CO source.

As part of our on-going work on carbonylation reactions using $Co_2(CO)_8$ as CO source, in this Letter we report a convenient method of amino carbonylation of aryl halides. With an aim to optimize the reaction conditions, 4-bromotoluene and morpholine were chosen as model substrates using microwave irradiation. As in the previous case, $Pd(OAc)_2$/xantphos in the presence of DMAP base was found to be the effective catalytic system in the present reaction also. The effect of various reaction conditions such as solvent, transition metal carbonyl, reaction time and equivalence of metal carbonyl on the isolated yield of the product is shown in Table 1.

The results given in Table 1 indicate that, among the various solvents investigated, 1,4-dioxane (Entry 4) was found to be the best solvent. Further, based on the reaction time variation studies (Entries 6–8), 20 min was fixed as the optimum time as the reaction gets completed within this period with excellent yields (Entry 7). With these stabilized reaction conditions (Entry 7), we have carried out the CO source variation study (Entries 9–11). The results showed that molybdenum hexacarbonyl (Entry 9) gave good yields (72%) and the rest of the metal carbonyls

Table 3
Aminocarbonylation of nitro substituted aryl halides



Entry	Arylhalides (**1l-o**)	$Co_2(CO)_8$ (eqv.)	Product (**3l-o**)	Yields (%)[a]
1		0 25		X=Br, 8 X=I, 90
2		0 25		X=Br, 81 X=I, 87
3		0.30		76
4		0 25		71

All the reactions were executed with 0.5 mmol of aryl halide, 1 mmol of morpholine, 5 mol % of $Pd(OAc)_2$, 5 mol % of xantphos (4,5-bis(diphenylphosphanyl)-9,9-dimethylxanthene) at microwave irradiation at 90 °C for 20 min.
[a] Yield of isolated product.

result poor yields (<35%). Thus, $Co_2(CO)_8$ was found to be the relatively best in situ CO source for the aminocarbonylation of aryl halides at lower temperatures in microwave irradiation. The reaction was also carried out with the traditional heating method (oil bath heating) at 90 °C (Entry 12) and the isolated yield is slightly lower than the microwave heating condition. In general, 0.25 equiv of $Co_2(CO)_8$ was used in the reaction. However, 0.3 equiv of it was also employed, as and when required, for completion of the reaction. With the defined protocol (Entry 7) in hand, the substrate scope with a wide variety of aryl halides (I, Br) was explored. As can be seen from Table 2, good to excellent yields of the morpholine amides were obtained from aryl halides possessing variety of substituents with the substituents remain unaffected. The hetero arylhalide (Entry 10) also gave good yields of the corresponding amide.

More importantly, in the case of nitro substituted aryl halides (Table 3), the carbonylation occurred successfully in good yields without reducing the nitro group to amine. This is because, as mentioned earlier, $Mo(CO)_6$ has been reported as a reagent in the reduction of nitro group to amine.[7] Also, it is known that the S–O bond in sulfones can be reductively cleaved by $Mo(CO)_6$.[9] In the present study, sulfone substituted aryl halide (Table 2, Entry 11) has also been converted to corresponding amide without affecting the sulfone moiety. Hence, using the present protocol, the nitro and sulfone substituted aryl halides can easily be aminocarbonylated to the corresponding benzamides.

In addition to the synthesis of morpholine amides discussed above, the proposed protocol was found to work extremely well to produce other amides by using a variety of amine nucleophiles (1° and 2° Cyclic/acyclic amines). The yields thus obtained are shown in Table 4. The results indicated that the yields of the corresponding amides were found to be good to excellent with these chosen nucleophiles. In the case of 4-methoxy benzamide (**4a**) (Entry 1), among the three different amine sources used, 0.5 M ammonia in dioxane gave excellent yields.

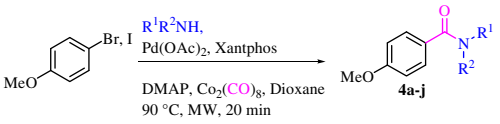
The pressure of the reaction container at varying initial concentrations of the aryl halides (1, 2.5, and 5 mmol) and $Co_2(CO)_8$ (in 1:0.25 equiv ratio) in 30 ml MW vial was monitored. The observed pressure values are given in Figure 1. When the reaction was performed with 1 mmol of aryl halide, no pressure was observed. In the case of 2.5 mmol of aryl halide, the pressure was increased up to 1.5 bar and found to decrease slowly (~1 bar) during the course of the reaction (Fig. 1, P1). Whereas in the case of 5 mmol of aryl halide, the pressure increased up to 2.5 bar and then gets decreased slowly to ~1.5 bar (Fig. 1, P2). As there is not much increase in pressure observed during the course of the reaction, it is safe to carry out the reaction in MW under the proposed conditions.

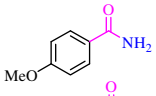
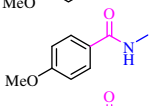
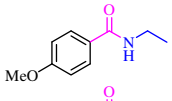
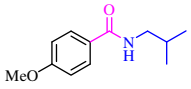
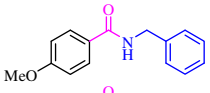
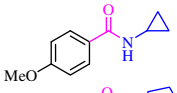
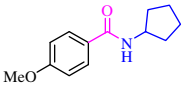
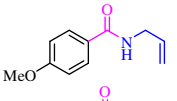
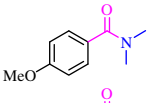
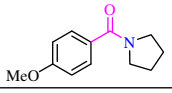
To conclude, we have demonstrated a simple and convenient one pot method of making benzamides directly from aryl halides using $Co_2(CO)_8$ as an in situ carbonyl source at low temperatures. This protocol is mainly useful in laboratory scale reactions and Library synthesis (automated platform) in medicinal chemistry field. One of the significances of the proposed protocol is that nitro substituted aryl halides can also be converted into corresponding benzamides without affecting the nitro group.

Supplementary data

Supplementary data (The experimental section and ^1H & ^{13}C NMR spectra of the compounds are provided) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.062.

Table 4
Synthesis of amides by using different amines



Entry	R^1R^2NH[a]	$Co_2(CO)_8$ (eqv.)	Product (4a-j)	Yield (%)[b]
1	NH_3	0.25		62[c]/70[d]/86[e]
2	$-NH_2$	0.25		90
3	NH_2	0.25		94
4	NH_2	0.25		79
5	NH_2	0.25		92
6	NH_2	0.25		81
7	NH_2	0.30		70
8	NH_2	0.25		82
9	H N	0.30		90
10	HN	0.25		91

All the reactions were executed with 1 mmol of aryl halide, 5 mol % of $Pd(OAc)_2$, 5 mol % of xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) and 0.25 mmol of Co_2CO_8 at microwave irradiation at 90 °C for 20 min.
[a] 2 equiv of amines was used.
[b] Yield of isolated products.
[c] Isolated yield when ammonia hydroxide solution (~25% in water) used as amine source.
[d] Isolated yield when ammonia solution (2.0 M in ethanol) used as amine source.
[e] Isolated yield when ammonia solution (0.5 M in dioxane) used as amine source.

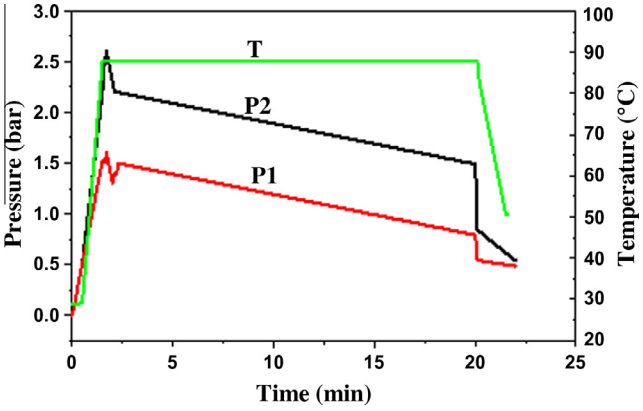


Figure 1. Temperature and pressure profiles for the microwave heated synthesis of **3b** from **1b** (Table 2, Entry 2).

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