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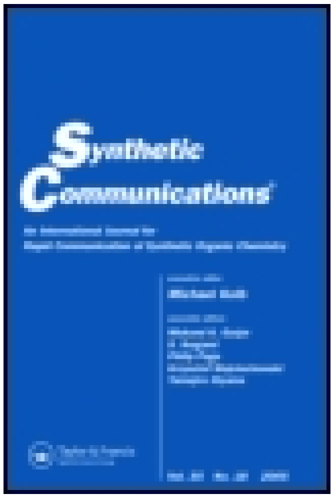

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One-Pot Direct Synthesis of Weinreb Amides from Aryl and Hetero Aryl Halides Using $Co_2(CO)_8$ as an Effective CO Source Under Conventional Thermal Heating

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One-Pot Direct Synthesis of Weinreb Amides from Aryl and Hetero Aryl Halides Using $Co_2(CO)_8$ as an Effective CO Source Under Conventional Thermal Heating

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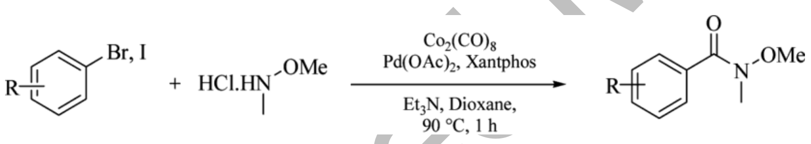
Abstract

A successful protocol for the synthesis of Weinreb amides directly from aryl halides via aminocarbonylation with *N*,*O*-dimethyl hydroxylamine using $Co_2(CO)_8$ as an *in situ* CO source has been demonstrated. The effect of various reaction parameters such as temperature, base and CO source has also been investigated and optimized.



KEYWORDS: aryl halides; Palladium acetate; $Co_2(CO)_8$; carbonylation; Weinreb amides;

INTRODUCTION

Weinreb amides are one of the key intermediates in organic chemistry for the simple reason that they can be further converted to variety of acyl derivatives by using organometallic reagents.[1] Ever since its inventive report by Nahm and Weinreb in 1981,[2] continuing efforts have been made for their preparation by using variety of starting materials.[1,3] Mostly, these methods involve traditional acid amine coupling reactions using expensive acid derivatives and coupling reagents.[1,4] Murakami et al. has developed a strategy for the synthesis of vinyl and aryl Weinreb amides using a Stille-type cross-coupling of *N*-methoxy-*N*-methylcarbamoyl chloride with vinyl or aryl stannanes.[5] Aminocarbonylation methods using carbon monoxide gas have also been reported in literature. Buchwald et al. have reported a general palladium catalysed process for the conversion of aryl bromides to corresponding Weinreb amides using *N*,*O*-dimethyl hydroxylamine at 1 atm CO_g.[6] The direct synthesis of Weinreb amides from lactam-, lactone-, and thiolactone derived triflates via aminocarbonylation has also been reported.[7] Although the methodology is useful on an industrial scale, the toxicity and flammability of carbon monoxide make it inconvenient to use in a laboratory scale synthesis. Hence, the search for alternative CO source is still on. The use of solid metal carbonyls in these reactions is reported to be a friendly method which the synthetic chemists can operate with ease.[8] In 2011, Mats Larhed and his co-workers reported a synthesis of Weinreb amides from aryl halides using metal carbonyls such as $Mo(CO)_6$ and $W(CO)_6$ under MW irradiation.[9] Though this is a useful and CO_g free method of making Weinreb amides, the formation (1% to 83%) of undesired *N*-methylamide **4a** is considerable and also with $W(CO)_6$ only the aryl bromides are converted to Weinreb amides but not the aryl iodides. The proposed reaction conditions also require excess equivalents of metal carbonyls at high temperature.

The main objective of this paper therefore is to develop a suitable method of making Weinreb amides from aryl halides under mild reaction conditions and also with the formation of lesser or no undesired product. Recently, we have demonstrated that

$Co_2(CO)_8$ can be used as an effective in situ CO source in carbonylation reactions.[10] Hence, we began our study using $Co_2(CO)_8$ as the CO source in the synthesis of Weinreb amides from variety of aryl halides (Br/I) and *N*-*O*-dimethoxyhydroxylamine hydrochloride under thermal conditions.

RESULT AND DISCUSSION

The various effects on the reaction investigated to optimize the reaction conditions are collected in Table 1. The aminocarbonylation protocol for the synthesis of *N*-Methoxy-3,*N*-dimethyl-benzamide via microwave irradiation (Table 1, Entry 1) is similar to the one we have stabilised earlier for such reactions.[10] The result indicated that the desired product is formed in good yield (74%), along with 16% of demethoxylated by-product (3,*N*-dimethyl-benzamide). Even though the isolated yield is good, further attempts were made to increase the yield of the product and to reduce the formation of the by-product.

The by-product can be formed by the cleavage of *N*-*O* bond either in **2** or **3a** by the base or high temperature of the reaction.[11] Hence, the reaction temperature was reduced to 70 °C (Table 1, Entry 2) and it was found that the by-product formation is still there. The same reaction was also carried out under traditional thermal heating at 90°C for 1 h (Entry 3). To our delight, the reaction worked well with an excellent isolated yield of **3a** (82%) along with **4a** (10%). Further reduction in temperature gave reduced yield of the product with the formation of the by-product. Therefore, the effect of different bases on the reaction was studied (Entries 3-9). The results showed that with strong bases like KHMDS, DABCO and DBU, the isolated yield of the by-product **4a** is more. Also, with the use of n-Bu_3N, though the amount of the by-product was less, the yield of the desired **3** product is relatively low. Hence, from the results, it is evident that Et_3N is comparatively a better choice for the reaction as the yield of the desired product is relatively high. The base variation studies suggested that the formation of the undesired *N*-methyl amide can occur via base initiated cleavage of *N-O* bond either in **2** or **3a**. When the isolated desired product **3a** was subjected to react under identical reaction conditions with either DMAP or Et_3N, there was no by-product (**4a)** formation. Hence, it is concluded that the formation of the by-product may occur through the reduction of Weinreb amine **2** to methylamine which undergoes aminocarbonylation. This is further substantiated by the results of the studies with varying amounts of **2** (Entries 9-14).

It is evident from the results depicted in Table 1 that use of Et_3N base with 1.5 equivalents of **2** at 90 ^oC thermal heating is the optimum condition for the synthesis of Weinreb amide **3a** in excellent yield with very less amount of the by-product (Entry 14). The same reaction was also carried out using $Mo(CO)_6$ (Entry 15) and $W(CO)_6$ (Entry 16) as the CO source under the optimized conditions. The formation of excess by-product **4a** (*N*-benzamide) was observed in both the case. This may be due to the $Mo(CO)_6$ promoted cleavage of *N-O* bond which is known in literature.[12] The result showed that $Co_2(CO)_8$ is relatively a better in situ CO source in the above reaction. To further demonstrate this observation, the reactions were performed with different aryl halides using cobalt and molybdenum metal carbonyls and the results are shown in Table 2.

The results clearly indicated that the use cobalt carbonyl as CO source produced excellent yields of the desired products with no/very less amounts of the undesired by-product. In the case of nitro substituted aryl halide (Entry 6) with molybdenum carbonyl, the yield of **3f** is very low (7%). This is due to the fact that the nitro group is non-tolerant in the presence of $Mo(CO)_6$.[12]

Encouraged by the above results, variety of aryl/hetero aryl halides (Br/I) possessing different functional groups were subjected to aminocarbonylation under similar reaction conditions to yield corresponding Weinreb amides. The results are collected in Table 3. As seen from the results shown in Table 3, both bromo- and iodo-arylhalides delivered the corresponding Weinreb amides in good to excellent yields with by-product in the range of 0-8% only. The bromo derivatives gave relatively higher yields than the iodo compounds. More importantly, the nitro substituted aryl halides produced the corresponding Weinreb amides in good yields. With an aim to check the practical utility of the Weinreb amides prepared, compound **3a** (1 mmol) was successfully taken to next step (as a representative case) to synthesis 3-methylbenzaldehyde by reacting with DIBAL-H at -78 °C for 1 h, and isolated was found to be good (102 mg, 84.5%).

CONCLUSION

In conclusion, we have developed a simple, suitable and effective one-pot Pd-catalysed synthesis of Weinreb amides by amino carbonylation of aryl and heteroaryl halides by using $Co_2(CO)_8$ as an effective *in situ* CO source. Using this proposed synthetic protocol, variety of aryl halides and hetero aryl halides containing different functional groups can be converted into their corresponding Weinreb amides in good to excellent yields. The success of this method of synthesis of valuable intermediate (Weinreb amides) is no doubt, very useful in academic and medicinal chemistry fields as it involves no CO gas. The proposed protocol can be used in small scale synthesis in laboratories as it involves no CO cylinder and the reaction is very easy to perform. Also, the method is very useful in parallel synthesis reactions.

EXPERIMENTAL

Commercially available reagents were used as received in this work. The solvents were freshly distilled and used. Purification of products was performed by silica gel column chromatography. ^{1}H NMR spectra were obtained using a 300 MHz or 400 MHz spectrometer. ^{13}C NMR spectra were obtained from a 75 MHz or 100 MHz spectrometer. All ^{1}H and ^{13}C NMR experiments are reported in parts per million (ppm) downfield from tetramethylsilane and were measured relative to the signals for residual chloroform in the deuterated solvents. The mass spectra were recorded on Liquid Chromatography-Mass Spectrometry (LCMS). All the spectral data matched well with the literature descriptions.

GENERAL PROCEDURE

Commercially available reagents were used as received in this work. The solvents were freshly distilled and used. Purification of products was performed by silica gel column chromatography. ^{1}H NMR spectra were obtained using a 300 MHz or 400 MHz spectrometer. ^{13}C NMR spectra were obtained from a 75 MHz or 100 MHz spectrometer. All ^{1}H and ^{13}C NMR experiments are reported in parts per million (ppm) downfield from

tetramethylsilane and were measured relative to the signals for residual chloroform in the deuterated solvents. The mass spectra were recorded on Liquid Chromatography-Mass Spectrometry (LCMS). All the spectral data matched well with the literature descriptions.

A mixture of aryl halide (I, Br) (1 mmol), Weinreb amine hydrochloride (1.5 mmol), $Pd(OAc)_2$ (5 mol %), Xantphos (6 mol %), triethylamine (3 mmol) and cobalt carbonyl (0.3 mmol) in 1,4-dioxane was heated at 90 °C for 1 h in a septum closed sealed tube. After cooling, the reaction mixture was concentrated in vacuum and the residue was extracted with ethyl acetate and water. The ethyl acetate layer was concentrated and the residue obtained was purified by flash column chromatography to get the desired product.

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.

3a. *N*-Methoxy-4,*N*-dimethyl-benzamide. Following the general procedure, **3a** was obtained as a colourless liquid; Yield: (164 mg, 91%); ^{1}H-NMR (300 MHz, CDCl3): δ = 7.44-7.46 (m, 2H), 7.25-7.27 (m, 2H), 3.57 (s, 3H), 3.35 (s, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.2, 137.7, 134.1, 131.2, 128.6, 127.8, 124.9, 60.9, 21.26; MS ESI calcd. For $C_9H_{11}NO_2$ $[M + H]^+ = 180$.

SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

REFERENCES

1. (a) Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15. (b) Jackson, M.; Leverett, C.; Toczko, J. F.; Roberts, J. C. *J. org. Chem.* **2002**, *67*, 5032. (c) Khlestkin, D. G.; Mazhukin, D. G. *Curr. Org. Chem.* **2003**, *7*, 967. (d) Murphy, J. A.; Commeureuc, A.; Snaddon, T. N.; McGuire, T. M.; Khan, T. A.; Hisler, K.; Dewis, M. L.; Carling, R. *Org. Lett.* **2005**, *7*, 1427. (e) Hisler, K.; Tripoli, R.; Murphy, J. A. *Tetrahedron Lett*. **2006**, *47*, 6293.

2. Nahm, S.; Weinreb, S. M. *Tedrahedron Lett.* **1981**, *22*, 3815.

3. (a) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001. (b) Chin-Kang, Sha.; Shih-Jung, Huang.; Zhuang-ping, Zhan. *J. Org. Chem.* **2002**, *67*, 831.

4. (a) Braun, M.; Waldmuller, D. *Synthesis*, **1989**, 856. (b) Niu, T.; Zhang, W.; Huang, D.; Xu, C.; Wang, H.; Yulai, Hu. *Org. Lett.* **2009**, *11*, 4474. (c) Woo, J. C. S.; Fenster, E.; Dake, G. R. *J. Org. Chem.* **2004**, *69*, 8984.

5. Murakami, M.; Hoshino, Y. Ito, H.; Ito, Y. *Chem. Lett*. **1998**, 163.

6. Martinelli, J. R.; Freckmann, D. M.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 4843.

7. Deagostino, A.; Larini, P.; Occhiato, E. G.; Pizzuto, L.; Prandi, C.; Venturello, P. *J. Org. Chem*. **2008**, *73*, 1941.

8. (a) Wannberg, J.; Larhed, m. *J. Org. Chem*. **2003**, *68*, 5750. (b) Wu. X.; Larhed, M. *Org. Lett.* **2005**, *7*, 3327. (c) Wu, X.; Wannberg, J.; Larhed, M. *Tetrahedron* **2006**, *62*,

4665. (d) Wan, Y.; Alterman, M.; Larhed, M.; Hallberg, A. *J. Org. Chem*. **2002**, *67*, 6232. (e) Luke, R.; Russo, F.; Larhed, M. *Synlett*. **2012**, *23*, 685.

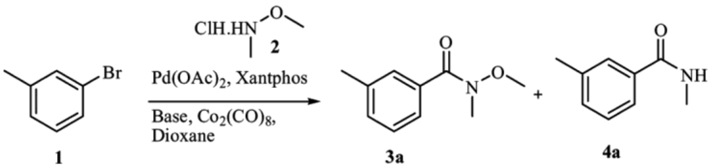
9. Anna, W.; Fransson, R.; Luke, R.; Larhed, M. *J. Org. Chem*. **2011**, *76*, 978.

10. (a) Baburajan, P.; Senthilkumaran, R.; Elango, K. P. *New J. Chem.* **2013,** *37*, 3050. (b) Baburajan, P.; Elango, K. P. *Tetrahedron Lett.* **2014**, *55*, 1006. (c) Baburajan, P.; Elango, K. P. *Tetrahedron Lett.* **2014**, *55*, 3525.

11. (a) Bickelhaupt, M. F.; Koning, L. J.; Nibberling, M. *J. Org. Chem.* **1993**, *58*, 2436. (b) Graham, S. L.; Scholz, T. H. *Tetrahedron Lett*. **1990**, *31*, 6269.

12. (a) Nielsen, S.; Smith, G.; Begtrup, M.; Kristensen, J. *Chem-Eur. J.* **2010**, *16*, 4557. (b) Spencer, J.; Rathnam, R. P.; Patel, H.; Anjum, N. *Tetrahedron* **2008**, *64*, 10195. (c) Nielsen, S. D.; Smith, G.; Begtrup, M.; Kristensen, J. L. *Eur. J. Org. Chem*. **2010**, 3704. (d) Iyer, S.; Kulkarni, G. M. *Synth. Commun*. **2004**, *34*, 721.

Table-1. Optimisation of reaction condition for the synthesis of *N*-Methoxy-3,*N*-dimethyl-benzamide.

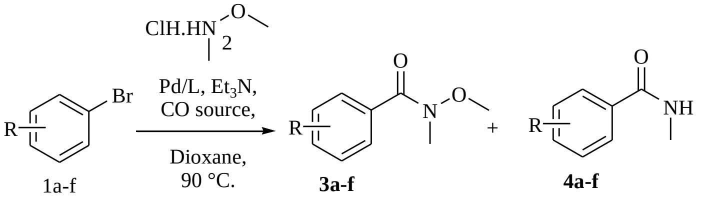


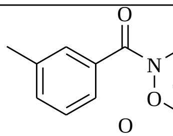
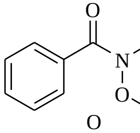
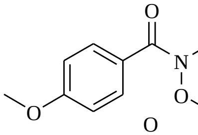
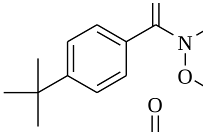
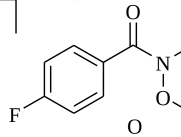
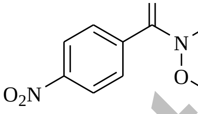
Entry	Base	Reaction condition	Weinreb amine **2** (eq)	Yield (%)[a]	
				3a	**4a**
1	DMAP	90 °C, M/W, 30 min	2	74	16
2	DMAP	70 °C, M/W, 30 min	2	69	12
3	DMAP	90 °C, thermal heating, 1 h	2	82	10
4	KHMDS	90 °C, thermal heating, 1 h	2	7	16
5	DABCO	90 °C, thermal heating, 1 h	2	40	30
6	DBU	90 °C, thermal heating, 1 h	2	51	36
7	Pyridine	90 °C, thermal heating, 1 h	2	69	18
8	*n*-Bu_3N	90 °C, thermal heating, 1 h	2	60	<1
9	Et_3N	90 °C, thermal heating, 1 h	2	87	2
10	Et_3N	90 °C, thermal heating, 1 h	4	80	10
11	DMAP	90 °C, thermal heating, 1 h	4	62	23
12	DMAP	90 °C, thermal heating, 1 h	0.5	30	11
13	Et_3N	90 °C, thermal heating, 1 h	1	75	<1
14	Et_3N	90 °C, thermal heating, 1 h	1.5	91	<1
15[b]	Et_3N	90 °C, thermal heating, 1 h	1.5	35	40

16[c]	Et_3N	90 °C, thermal heating, 1 h	1.5	63	29

All the reactions were performed with 3-bromo anisole **1** (1 mmol), $Pd(OAc)_2$ (5 mol %), Xantphos (6 mol %), Weinrebamine **2**, base, cobalt carbonyl (0.3 mmol) in 1,4-dioxane in sealed tube. [a] Yields quoted are isolated yields. [b] $Mo(CO)_6$ (0.5 eq) used as CO source. [c] $W(CO)_6$ (0.5 eq) used as CO source.

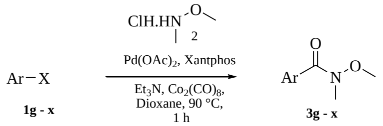
Table 2. The comparative study between $Co_2(CO)_8$ and $Mo(CO)_6$ carbonyl sources.

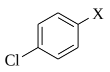
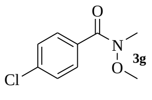
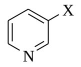
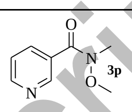
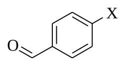
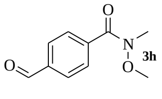
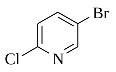
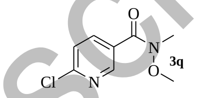
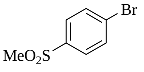
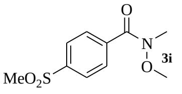
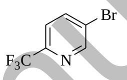
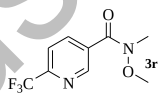
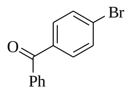
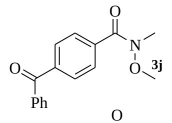
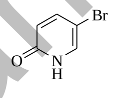
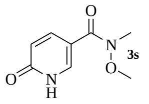
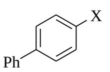
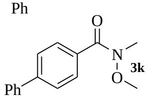
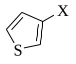
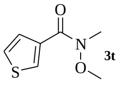
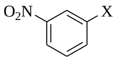
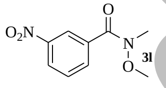
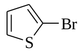
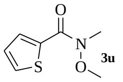
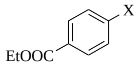
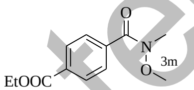
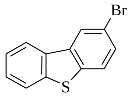
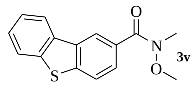
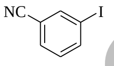
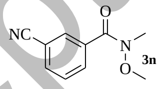
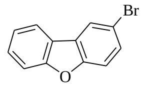
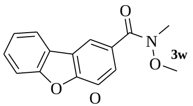
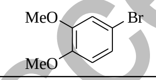
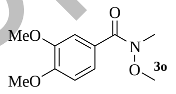
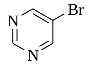
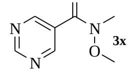


Entry	R	Product (3a-f)	CO source	Yield (%)a	
				3a-f	4a-f
1	3-Me	 3a	$Co_2(CO)_8$ $Mo(CO)_6$	91 35	<1 54
2	H	 3b	$Co_2(CO)_8$ $Mo(CO)_6$	84 51	0 40
3	4-OMe	 3c	$Co_2(CO)_8$ $Mo(CO)_6$	94 47	- 42
4	4 -tBu	 3d	$Co_2(CO)_8$ $Mo(CO)_6$	74 29	4 40
5	4-F	 3e	$Co_2(CO)_8$ $Mo(CO)_6$	80 44	<1 29
6	4-NO_2	 3f	$Co_2(CO)_8$ $Mo(CO)_6$	71 7	<1 0

Reaction Condition: Aryl halide **1a-f** (1 mmol), $Pd(OAc)_2$ (5 mol %), Xantphos (6 mol %), Weinrebamine **2** (1.5 mmol), Triethyl amine (3 mmol), cobalt carbonyl (0.3 mmol) or molebdenum carbonyl (0.5 mmol) in 1,4-dioxane, 90 °C, 1h in sealed tube. [a] Yields quoted are isolated yields.

Table 3. Synthesis of Weinreb amides from various aryl and heteroaryl halides (Br/I).



Entry	Ar−X	Product (3g-x)	Yield (%)a	Entry	Ar−Br, I	Product (3g-x)	Yield (%)a
1		 **3g**	X=Br, 82 X=I, 85	10		 **3p**	X=Br, 80 X=I, 54
2		 **3h**	X=Br, 80 X=I, 72	11		 **3q**	69
3		 **3i**	74d	12		 **3r**	79
4		 **3j**	86	13		 **3s**	74
5		 **3k**	X=Br, 80 X=I, 75	14		 **3t**	X=Br, 87 X=I, 71
6		 **3l**	X=Br, 65 X=I, 58	15		 **3u**	75
7		 3m	X=Br, 89 X=I, 80	16		 **3v**	72
8		 **3n**	69	17		 **3w**	61
9		 **3o**	90	18		 **3x**	80

Reaction Condition: Aryl halide **1g-x** (1 mmol), Pd(OAc)$_2$ (5 mol %), Xantphos (6 mol %), Weinrebamine **2** (1.5 mmol), Triethyl amine (3 mmol), cobalt carbonyl (0.3 mmol) in 1,4-dioxane, 90 °C, 1h in sealed tube. [a] Yields quoted are isolated yields.