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Rapid and Efficient Microwave-Assisted Amination of Electron-Rich Aryl Halides without a Transition-Metal Catalyst

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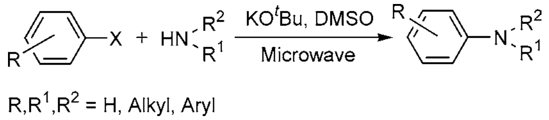
ABSTRACT



A rapid and direct amination of aryl halides has been developed in good to high yields under microwave irradiation without a transition-metal catalyst. This reaction is a particularly powerful method for the coupling of electron-rich aryl halides with various amines. In some cases, the excellent regioselectivity could be observed, which facilitated the preparation of meta-substituted anilines from ortho- or para-substituted phenylhalides. In addition, a mechanism via the interesting benzyne intermediate has been proposed.

Amination of aryl halides has been an important and frequently required reaction for the synthesis of the interesting molecules containing the *N*-aryl moiety, which have wide occurrence in many areas such as pharmaceuticals,[1a] agrochemicals,[1b] photography,[1c] xeroxography,[1d] pigments,[1e] electronic materials,[1f] and natural products.[1g] Compared with the C−N cross-coupling of electron-poor aryl halides with amines, that of aryl halides bearing electron-rich substituents is not accessed easily under mild conditions. Over the years, a number of cleverly designed and useful methods for electron-rich aryl C−N bond formation have mainly included the Ullmann reaction[2] and the Goldberg reaction[3] using Cu reagent and the Buchwald−Hartwig amination[4] utilizing palladium catalyst. However, these reported methods usually required high temperatures, long reaction times, or had a relatively narrow application scope of substrates.[2−4] In particular, the use of transition metals leads to the generation of waste and has a number of hazards associated with it.[5]

In the past few years, the utilization of microwave irradiation in chemical transformations has attracted considerable interest and is of significant importance in the search for green synthesis and sustainable chemistry.[6] More attractively, many reactions that typically required hours or days to complete full conversion with conventional heating could be realized in several minutes utilizing microwave irradiation. Microwave-mediated protocols have been widely applied to the formation of a variety of carbon−heteroatom and carbon−carbon bonds.[6] To the best of our knowledge, however, the direct metal-free amination of electron-rich aryl halides using high-speed microwave techniques has not been described. Herein we wish to report our preliminary investigation on the microwave-assisted C−N bond coupling of aryl halides with various amines.

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(1) (a) Negwer, M. *Organic-Chemical Drugs and their Synonyms* (*An International survey*), 7th ed.; Akademie Verlag GmbH: Berlin, 1994. (b) Montgomery, J. H. *Agrochemicals Desk Reference*: *Environmental Data*; Lewis Publishers: Chelsea, MI, 1993. (c) Loutfy, R. O.; Hsiao, C. K.; Kazmaier, P. M. *Photogr. Sci. Eng.* **1983**, *27*, 5. (d) Schein, L. B. *Electrophotography and Development Physics*, 2nd ed.; Springer-Verlag: Berlin, 1992. (e) *Pigment Handbook*; Lewis, P. A., Ed.; John Wiley & Sons: New York, 1988; Vol. I. (f) D'Aprano, G.; Leclerc, M., Zotti, G.; Schiavon, G. *Chem. Mater.* **1995**, *7*, 33. (g) He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1998**, *120*, 6417.

(2) Ullmann reactions, see: (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382. (b) Ma, D.-W.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc.* **1998**, *120*, 12459.

(3) Goldberg reaction, see: (a) Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691. (b) Freeman, H. S.; Butler, J. R.; Freedman, L. D. *J. Org. Chem.* **1978**, *43*, 4975.

(4) Palladium-catalyzed N-arylation of amines, see: (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (b) Wolfe, J. P.; Wagaw. S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (c) Yang, B. Y.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.

(5) Leadbeater, N. E.; Marco, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1407.

(6) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717.

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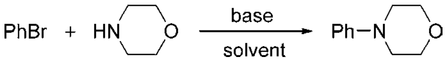
In contrast to most other C−N bond-forming protocols,[2−4] the valuable features of our reported reaction include (i) a shorter reaction time and a high yield;[7] (ii) a broader substrate scope;[7] and (iii) the eradication of the transition-metal catalyst.

As a starting point for the development of our direct amination, we initially studied the microwave-assisted coupling of PhBr with morpholine for optimizing reaction conditions, and the results are presented in Table 1. Of the bases and solvents screened, KO^{t}Bu as the base and DMSO as the solvent proved to be the most effective for this coupling. Additionally, this reaction was found to be insensitive to air and moisture; hence, there was no need for an inert atmosphere.

Table 1. Optimization Studies[a]

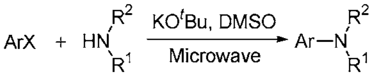


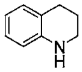
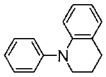
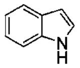
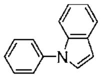
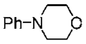
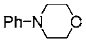
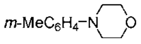
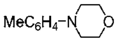
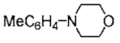
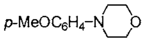
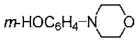
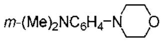
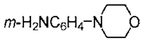
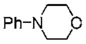
entry	base	solvent	yield (%)[b]
1	K_3PO_4	DMSO	<1
2	K_2CO_3	DMSO	<1
3	NaOH	DMSO	<1
4	NaOMe	DMSO	74
5	KO^{t}Bu	DMSO	94
6	KO^{t}Bu	benzene	<1
7	KO^{t}Bu	toluene	<1
8	KO^{t}Bu	CCl_4	<1
9	KO^{t}Bu	CH_3CN	<1
10	KO^{t}Bu	DME	<1
11	KO^{t}Bu	DMF	67

[a] All reactions were carried out within 5 min under the following conditions: PhBr, 1.0 mmol; morpholine, 1.5 mmol; base, 1.5 mmol; and solvent 5 mL. [b] Yields of isolated products.

Intrigued by the above-described results, we further investigated the coupling reaction of different aryl halides and amines. From the results shown in Table 2, it can be seen that various secondary aliphatic and aromatic amines, including bulky amines (entries 4−7), and less basic amines such as aniline (entry 1) and indole[8] (entry 9) were effective for this C−N coupling reaction (entries 2−9). The yield for employing primary amines (entry 1) is moderate and requires the use of 4-fold excess of the $PhNH_2$ in this coupling reaction, because of the formation of undesired tertiary amine ($(Ph)_3N$) as a byproduct. Additionally, both aryl chloride (e.g., entry 10) and aryl iodide (e.g., entry 11) are effective for this direct amination. Furthermore, we investigated the influence of the structure of substrates on this C−N bond coupling. Various electron-rich aryl bromides were chosen to probe whether this coupling could be easily accessed in the presence of morpholine. As expected, they still exhibited high yields and short reaction times (entries 12−19), and a wide range of functional groups were also tolerated in this reaction except for the acetyl group (entry 19). Even when there was a free OH or NH_2 group (entries 16 and 18) directly bound to the aromatic ring, which was difficult to couple under conventional conditions,[9] a considerable yield was provided in 20 min. Most notably, the steric effects and electronic effects of the substituents on aryl bromides resulted in the distinct regioselective amination[10,11] that was observed in some examples (entries 12 and 16−18).

Table 2. Direct Amination of Aryl Halides and Amines[a]



entry	ArX	amine	product	time (min)	yield (%)[b]
1	PhBr	$PhNH_2$	$(Ph)_2NH$	10	61
2	PhBr	$(CH_2)_5NH$	$(CH_2)_5NPh$	5	94
3	PhBr	$(CH_2)_4NH$	$(CH_2)_4NPh$	5	92
4	PhBr	$(C_2H_5)_2NH$	$(C_2H_5)_2NPh$	5	97
5	PhBr	$(i\text{-}Pr)_2NH$	$(i\text{-}Pr)_2NPh$	5	96
6	PhBr	$(C_6H_{11})_2NH$	$(C_6H_{11})_2NPh$	5	94
7	PhBr	$(Ph)_2NH$	$(Ph)_3N$	20	80
8	PhBr			5	90
9	PhBr			20	82
10	PhCl	morpholine		5	92
11	PhI	morpholine		5	96
12	o-MeC_6H_4Br	morpholine		5	94
13	m-MeC_6H_4Br	morpholine	 *meta*:*para* = 2:1	5	93
14	p-MeC_6H_4Br	morpholine	 *meta*:*para* = 1:1	5	94
15	p-$MeOC_6H_4Br$	morpholine		10	85[c]
16	p-HOC_6H_4Br	morpholine		20	74[d,e]
17	p-$(Me)_2NC_6H_4Br$	morpholine		10	90[d]
18	p-$H_2NC_6H_4Br$	morpholine		20	71[d,e]
19	o-AcC_6H_4Br	morpholine		10	81

[a] For a detailed experimental operation, see Supporting Information. [b] Yields of isolated products. [c] Trace meta-substituted aniline was obtained. [d] Trace para-substituted aniline was obtained. [e] Yield was based on the recovered starting material ArX.

From the results shown above (entries 12−14 and 16−18), the cine substitution[10,11] could be observed unambigu-

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(7) Some direct aminations were conducted in low yields and with a long reaction time; see: (a) Heaney, H. *Chem. Rev.* **1962**, *62*, 81. (b) Djakovitch, L.; Wagner, M.; Köhler, K. *J. Organomet. Chem.* **1999**, *592*, 225.

(8) Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684.

(9) (a) Klapars, A.; Antilla, J. C.; Huang, X.-H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (b) Klapars, A.; Huang, X.-H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

(10) Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, *49*, 273.

(11) March, J. *Advanced Organic Chemistry, Reactions, Mechanisms and Structure*, 4th ed.; John Wiley & Sons: New York, 1992; p 641.

ously. Consequently, we proposed this direct amination of aryl halides bearing electron-rich substituents most likely proceeded via a benzyne intermediate.[11] Further direct evidence for the identification of benzyne intermediate was provided by an additional experiment, where the trapping of the benzyne intermediate was successfully conducted using furan through [2 + 4] cycloaddition reaction.[12] According to the proposed benzyne intermediate, the steric or electronic effect of a substituent on aromatic ring could be interpreted. For example, the direct amination of *ortho*-methyl phenylbromide (entry 12) only gave the meta-amination product, possibly because the steric effects of the methyl group of the benzyne intermediate resulted in the less sterically hindered meta-attack of the nucleophilic amines. However, the para-substituted analogues with a strong electron-donating group such as OH, NH_2, or $N(CH_3)_2$ give, with excellent regioselectivity, the meta-amination product (entries 16−18), which is consistent with electronic effects of the electron-rich substituent.[11] In contrast, *meta*- or *para*-methyl phenylbromide (entry13 and 14), where there was no distinct steric effect or electronic effect, provided a mixture of meta- and para-amination products. Unexpectedly, *para*-methoxy phenylbromide (entry 15) gave the predominant para-amination product, for reasons that are still unclear. For the example of entry 19, formation of the same product as that in entry 5 of Table 1 could be explained via the benzyne intermediate formed through the elimination of *ortho*-acetyl group.

In summary, we have established a rapid and direct amination method without a transition-metal catalyst that could be performed in good to excellent yields under microwave irradiation. Particularly valuable features of this method included the short reaction time, high yield, and broad substrate scope, as well as convenient operation. Additionally, the reaction was developed to meet the increasing demand for environmentally benign chemical processes. Efforts to expand the scope of the method in combination with its application to the synthesis of pharmaceutical molecules are ongoing in our laboratory.

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Supporting Information Available: Experimental details and data on the C−N cross-coupling reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0353868

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[12] Chapman, O. L.; Mattes, K.; McIntosh, C. L.; Pacansky, J.; Calder, G. V.; Orr, G. *J. Am. Chem. Soc.* **1973**, *95*, 6134.