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Rapid Microwave-Assisted Copper-Catalyzed Nitration of Aromatic Halides with Nitrite Salts

Seunguk Paik* **and Myoung Geun Jung**

*Department of Chemical System Engineering, Keimyung University, Taegu 704-701, Korea. *E-mail: paiksu@kmu.ac.kr*
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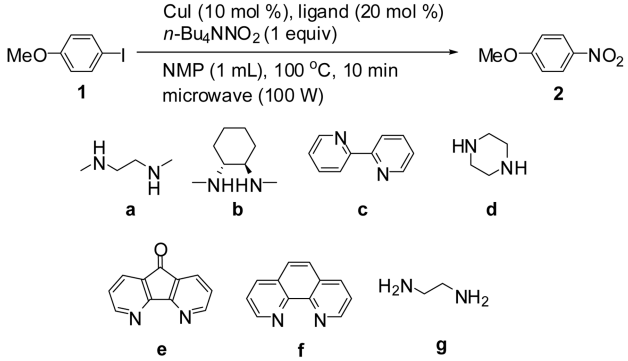
Nitration of aromatic compounds is one of the important industrial processes as underlying intermediates in the manufacture of a wide range of chemicals such as dyes, pharmaceuticals, agrochemicals and explosives.[1] General methods for the nitration of aromatic compounds utilize strongly acidic conditions employing nitric acid or a mixture of nitric and sulfuric acids, sometimes leading to problems with poor regioselectivity, overnitration, oxidized byproducts and excess acid waste in many cases of functionalized aromatic compounds.[2] Several other nitrating agents or methods avoiding harsh reaction conditions have been explored using metal nitrates,[3] nitrite salts,[4] and ionic liquid-mediated or microwave-assisted nitrations.[5] Recently, copper or palladium compounds have been successfully used as efficient catalysts for the arylation of amines with aryl halides under mild conditions.[6] In this context, Saito and Koizumi reported an efficient nitration method of aromatic halides with sodium nitrite-18-crown-6, or tetrabutylammonium nitrite (n-Bu_4NNO_2) as nitrating agents in the presence of Cu bronze catalyst.[7] More recently, the Pd-catalyzed nitration of aryl chlorides, triflates and nonaflates with sodium nitrite has been disclosed showing a broad scope and excellent functional group compatibility.[8] Although the latter two methods came up with excellent results depending on the reaction scope and materials, novel process protocols are still required in the respect of regioselectivity, economical efficiency, and green chemistry.

Microwave irradiation is a convenient process for conducting various reactions in minutes that otherwise would require hours or days under conventional heating. To our knowledge, microwave-mediated nitrations of aryl halides catalyzed by palladium or copper compounds have not been described. Herein, we report our results on the improved nitration of aryl halides with various nitrating agents in the presence of copper catalysts under microwave irradiation. We also show that reasonable yields can be achieved using potassium nitrite as a nitrating agent in DMSO as solvent.

In order to examine the effect of ligands and solvents in our initial screening experiments, a general condition of the Cu-catalyzed Ullmann-type reaction using 10 mol % of CuI, 20 mol % of ligand, and 1 equiv of nitrite salt was employed with 4-iodoanisole (**1**) as a model substrate[7] under microwave irradiation for 10 min (Table 1).[9] Of the diamine ligands examined, both *N,N′*-dimethylethylenediamine (**a**) and *trans*-*N,N′*-dimethyl-1,2-cyclohexanediamine (**b**) were the most effective to provide the desired compound **2** in 84% and 83% yields, respectively (entries 1 and 5). However, the other ligands (**c**-**g**) gave little to no desired product (entries 6-10). These results indicated that *N,N′*-dimethyl moiety was essential to the reactivity of this catalytic system. The reactions were also influenced by solvents of which NMP and DMSO were found to be equally effective leading to **2** in 84% and 82% yields, respectively (entries 1 and 2); DMF and toluene turned out to be less effective to provide the product in 77% an 51% yields, respectively.

Using the selected *N,N′*-dimethylethylenediamine as the ligand in DMSO or NMP, we also have explored a series of experiments employing several readily available copper sources and nitrating agents to find optimum conditions for

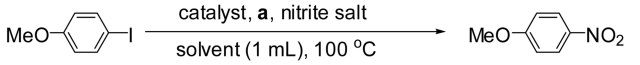
Table 1. Nitration of 4-nitroanisole with various ligands and solvents[a]



Entry	Ligand	Solvent	Yield (%)[b]
1	**a**	NMP	84
2	**a**	DMSO	82
3	**a**	DMF	77
4	**a**	Toluene	51
5	**b**	NMP	83
6	**c**	NMP	4
7	**d**	NMP	2
8	**e**	NMP	2
9	**f**	NMP	0
10	**g**	NMP	0

[a]All reactions were performed on a 1 mmol scale with microwave iradiation in a single-mode CEM Discover®. [b]Conversion yield based on the intergration of peaks at 6.69 ppm and 7.01 ppm, respectively.

Table 2. Optimization of reaction conditions for the preparation of 4-nitroanisole[a]



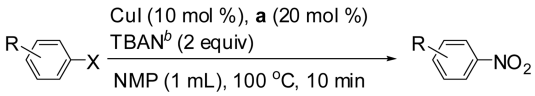
Entry	Catalyst	Solvent	Nitrite (equiv)	Yield (%)[b]
1	CuI	NMP	TBAN[c] (2)	99 (94)[d]
2	CuI	DMSO	TBAN (1.5)	90
3	CuI	DMSO	TBAN (2)	99
4	Cu powder	NMP	TBAN (1)	82
5	Cu powder	NMP	TBAN (2)	99
6	CuOAc	NMP	TBAN (1)	80
7	$Cu(NO_3)_2$	NMP	TBAN (1)	72
8	$Cu(OAc)_2$	NMP	TBAN (1)	51
9	Cu_2O	NMP	TBAN (1)	51
10	$CuCO_3$	NMP	TBAN (1)	17
11	$CuCl_2$	NMP	TBAN (1)	17
12	CuO	NMP	TBAN (1)	4
13	CuI	DMSO (2 mL)	KNO_2 (2)	79
14	CuI	DMSO (2 mL)	KNO_2 (2)[e]	99
15	CuI	NMP (2 mL)	KNO_2 (2)	6
16	CuI	NMP (2 mL)	KNO_2 (2)[e]	71
17	CuI	DMSO (2 mL)	$NaNO_2$ (2)	62
18	CuI	DMSO (1.5 mL)	Nitrite on polymer support (2)[f]	40

[a]All reactions were performed on a 1 mmol scale with microwave iradiation in a single-mode CEM Discover®. [b]Conversion yield based on the intergration of peaks at 6.69 ppm and 7.01 ppm, respectively. [c]TBAN: *n*-Bu_4NNO_2. [d]Isolated yield. [e]2 equiv of 18-crown-6 was added. [f]Purchased from Aldrich®.

the copper-catalyzed nitration of 4-iodoanisole (Table 2).

Among the copper sources examined, CuI, Cu powder and CuOAc with 1 equiv of tetrabutylammonium nitrite as a nitrating agent produced relatively good yields of 84, 82, and 80%, respectively (entries 4 and 6). $Cu(NO_3)_2$, $Cu(OAc)_2$, and Cu_2O resulted in moderate yields (72, 51, and 51%, respectively), while $CuCO_3$, $CuCl_2$, and CuO gave poor yields (entries 6-12). Using CuI, which provided the highest converted yield, we observed almost complete conversion with increasing the amount of tetrabutylammonium nitrite in DMSO or NMP to 2 equivalents affording **2** in 99% (entries 1 and 3); copper powder with 2 equiv of tetrabutylammonium nitrite in NMP afforded 99% yield of **1** (entry 5). On the basis of the experimental results above, CuI was chosen as the catalyst for subsequent experiments using other nitrite salts. Potassium nitrite (KNO_2) and sodium nitrite ($NaNO_2$) as a nitrating agent are cheaper and more easily available than tetrabutylammonium nitrite. Nitration of **1** with 2 equiv of KNO_2 in NMP (2 mL) produced a poor yield (6 %, entry 15); the use of 18-crown-6 (2 equiv) as an additive, however, resulted in 71% yield (entry 16) similar to those reported by Saito *et al.* Interestingly, the reaction in DMSO without the aid of 18-crown-6 produced **2** in 79% (entry 13); in the presence of 18-crown-6 (2 equiv), nearly complete conversion was observed (entry 14). $NaNO_2$ and nitrite on polymer support as nitrating sources produced moderated

Table 3. CuI-catalyzed nitration of aryl halides[a]



Entry	R	X	Yield (%)[c]
1	4-MeO	I	99
2	4-Me	I	99
3	*m*-xylene	I	99
4	H	I	99
5	4-NH_2	I	87
6	3-MeO	I	73
7	2-MeO	I	5
8	2-NH_2	I	35
9	H	Br	44
10	*m*-xylene	Br	33
11	4-NH_2	Br	0

[a]All reactions were performed on a 1 mmol scale with microwave iradiation in a single-mode CEM Discover®. [b]TBAN: *n*-Bu_4NNO_2. [c]Conversion yield based on ^{1}H NMR of the reaction mixtures.

yields of 62% and 40% respectively (entries 17-18). Thus, DMSO turned out to be the most efficient solvent for the nitration with inorganic nitrite salts such as KNO_2.

The established catalytic system, 10 mol % of CuI, 20 mol % of *N,N'*-dimethylethylenediamine, and 2 equiv of tetrabutylammonium nitrite in NMP at 100 °C with microwave irradiation for 10 min, were applied to the nitration of various aryl halides (Table 3). 4-Iodoansole and 4-iodotoluene bearing a electron-rich substituent at the 4-position were almost completely converted to the corresponding nitrated products (entries 1 and 2).

Iodobenzene and 1-iodo-3,5-dimethybenzene were also good substrates in almost complete conversion (entries 3 and 4), while 4-iodoaniline and 3-iodoanisole with a meta substituent gave slightly decreased yields in 87% and 73%, respectively (entries 5 and 6). On the other hand, 2-iodoanisole and 2-iodoaniline bearing an ortho substituent gave poor yields (entries 7 and 8); aryl bromides such as bromobenzene were also turned out to be poor substrates (entries 9-11).

In summary, a rapid and efficient copper-catalyzed nitration of aryl halides has been established under microwave irradiation. The catalytic systems were found to be the most effective with 4-substituted aryl iodides leading to nearly complete conversions.

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9. General procedure for the nitration: A pressure-rated glass tube (10 mL) was charged with 4-iodoanisole (1 mmol), ligand (0.2 mmol), *n*-Bu_4NNO_2 (1 mmol), CuI (0.1 mmol), and solvent (1 mL), evacuated, and backfilled with nitrogen. The reaction mixture was irradiated at 100 °C for 10 min by a single-mode CEM Discover® with 100 W of the initial power. After cooling, the mixture was analyzed by NMR spectroscopy based on the intergration of peaks at 6.69 ppm and 7.01 ppm, respectively.