

구리 촉매에 의한 할로젠화 아릴과 아지도 소듐의 선택적 아지드화 및 아민화 반응

백승욱[†]

계명대학교 화학공학과
(2021년 2월 9일 접수, 2021년 3월 12일 수정, 2021년 3월 12일 채택)

Selective Copper-Catalyzed Azidation and Amination of Aryl Halides with Sodium Azide

Seunguk Paik[†]

Department of Chemical Engineering, Keimyung University, Daegu 42601, Korea
(Received February 9, 2021; Revised March 12, 2021; Accepted March 12, 2021)

Abstract

A rapid and selective copper-catalyzed amination of aryl halides with sodium azide was established by using 10 mol % of CuI, and 20 mol % of *N,N'*-dimethylethylenediamine in DMSO under microwave irradiation for 10 min. The catalytic system with 4-substituted aryl iodides was found to be the most effective leading to a nearly complete conversion.

Keywords: Azidation, Amination, Microwave irradiation, Copper catalyst, Aryl halides

Azidation of aromatic compounds is one of the useful chemical transformations leading to versatile synthetic intermediates and industrially important derivatives with nitrogen-containing functionalities [1,2]. In general, aromatic azides can be prepared by conventional methods such as displacement of the appropriate diazonium salt with azide ions, nucleophilic aromatic substitution of aryl halides, and diazotization of aryl hydrazines[3,4]. However, these methods have sometimes led to problems with functional group tolerance, poor regioselectivity, reaction scope, and yields in many cases of functionalized aromatic compounds. Among the recently improved synthetic methods of aryl azides, copper-catalyzed azidation of aryl halide with inorganic azides has been explored to be an attractive alternative under rather mild conditions[5,6].

Along with successful application of this copper-catalyzed azidation, amination of aryl halide with various nitrogen-based nucleophiles also has been achieved with much progress[7,8]. More interestingly, few studies of copper catalyzed azidation of aryl halides with sodium azide revealed that the corresponding aryl amines rather than the expected azides were produced depending on substituent pattern of aryl halides and/or reaction conditions[9-12]. Quio et al. reported a copper catalyzed direct amination of ortho-functionalized haloarenes bearing carboxyl or carbamoyl groups using sodium azide[9]. Ham and coworkers

also reported an interesting few cases of the direct amine formation from haloaryltrifluoroborates having meta-substituted trifluoromethoxy or chloro substituents employing NaN_3 in the presence of CuI and *N,N'*-dimethylethylenediamine in DMSO[10]. Recently, Helquist et al. pointed out some confused results in previous literature with respect to whether products are aryl azides or the corresponding amines on the copper-catalyzed reaction of aryl halides with metal azide, and have reported a selective amination protocol of aryl halides in the presence of 100 mol % of CuI and described that a large excess of azide ion was crucial to obtain amines in DMSO at 100 °C [11]. During the course of our research on copper catalyzed azidation of aryl halides with sodium azide, we also observed a mixture of aryl amines and azides as products in most cases.

Herein, we report our findings on a selective copper-catalyzed azidation and amination of aryl halides with sodium azide under microwave irradiation leading to rapid reactions within 10 min. We also first report that a selective amination of aryl halides with sodium azide can be achieved increasing the reaction temperature in DMSO as solvent.

In order to find an optimal reaction condition for Cu-catalyzed amination using NaN_3 and clarify a little confusing results on Cu-catalyzed azidation with NaN_3 as indicated by Helquist[11], our previously established condition for Cu-catalyzed nitration (10 mol % of CuI, 20 mol % of ligand, 20 mol % of base) was attempted using 4-iodoanisole (1) as a model substrate with NaN_3 under microwave irradiation for 10 min (Table 1)[13]. Most of the reactions ended up with a mixture of 4-azidoanisole (2) with varying amounts of 4-aminoanisole (3) relying on the reaction conditions such as catalysts, ligands, bases, solvents, temper-

[†] Corresponding Author: Keimyung University,
Department of Chemical Engineering, Daegu 42601, Korea
Tel: +82-53-580-5350 e-mail: paiksu@kmu.ac.kr

Table 1. Copper-Catalyzed Amination and Azidation of 4-Iodoanisole with NaN_3 ^a

$\text{MeO-C}_6\text{H}_4\text{-I}$ (1) $\xrightarrow[\text{solvent (1 mL), 100}^\circ\text{C, 10 min microwave (100 W)}]{\text{catalyst, 20 mol\% ligand, 20 mol\% base, 1.2 equiv NaN}_3}$ $\text{MeO-C}_6\text{H}_4\text{-N}_3$ (2) + $\text{MeO-C}_6\text{H}_4\text{-NH}_2$ (3)

Entry	Catalyst	Ligand	Base	Solvent	Yield (%) ^b 2/3
1	CuI	DMEDA		DMSO	86/14
2	CuI	DMEDA	Cs_2CO_3	DMSO	95/5
3	CuI	Proline	Cs_2CO_3	DMSO	70/0
4	CuO	Proline	Cs_2CO_3	DMSO	98 : 1
5	CuI	DMEDA	Cs_2CO_3	NMP	93/3
6	CuI	DMEDA	Cs_2CO_3	DMF	95/5
7	CuI	DMEDA	Cs_2CO_3	80% EtOH	97/2
8	Cu	DMEDA	Cs_2CO_3	DMSO	97/3
9	CuO	DMEDA	Cs_2CO_3	DMSO	98/1
10	Cu_2O	DMEDA	Cs_2CO_3	DMSO	98/1
11	CuCN	DMEDA	Cs_2CO_3	DMSO	94/3
12	CuOAc	DMEDA	Cs_2CO_3	DMSO	90/10
13	$\text{Cu}(\text{OAc})_2$	DMEDA	Cs_2CO_3	DMSO	90/10
14	$\text{Cu}(\text{NO}_3)_2$	DMEDA	Cs_2CO_3	DMSO	96/4
15	CuCO_3	DMEDA	Cs_2CO_3	DMSO	92/8

^a All reactions were performed on a 1 mmol scale with microwave irradiation in a single-mode CEM Discover[®]. ^b Conversion yield based on the intergration of peaks on aromatic regions in ¹H NMR.

Table 2. Optimization of Selective Copper-Catalyzed Amination of 4-Iodoanisole^a

entry	CuI (mol %)	Solvent	Temp. (°C)	NaN_3 (equiv)	Conversion ^b (%) 2 : 3
1		DMSO	100	1.2	0
2	50	DMSO	100	1.2	38 : 53 ^c
3	100	DMSO	100	1.2	29 : 38 ^d
4	50	DMSO	150	1.2	32 : 65
5	10	DMSO	180	1.2	17 : 83
6	10	DMSO	180	1.5	10 : 90
7	10	DMSO	180	2	0 : 100

^a All reactions were performed on a 1 mmol scale of 1 with microwave irradiation in a single-mode CEM Discover[®]. ^b Conversion yield based on the analysis of ¹H-NMR. ^c remaining 9% unidentified. ^d remaining 33% unidentified.

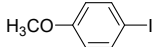
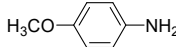
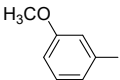
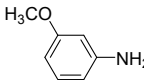
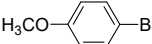
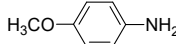
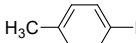
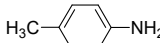
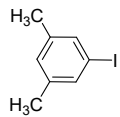
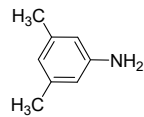

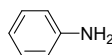
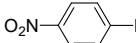
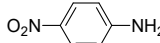
atures, etc. Above 85% yields of 2 were obtained regardless of copper sources such as CuI, CuO, CuCN, Cu_2O , Cu, CuOAc, $\text{Cu}(\text{OAc})_2$, $\text{Cu}(\text{NO}_3)_2$ and CuCO_3 , of which CuI was selected for further selective amination due to the formation of aminoanisole 3 in a considerable amount depending on reaction conditions (Table 1). Of the various diamine ligands examined, *N,N'*-dimethylethylenediamine (DMEDA) was the most effective for the transformation to the azide 2 in above 90% yields; the use of proline as a ligand afforded 2 in 70% with 30% of unchanged starting material (entry 3). The reactions were also influenced by solvents, of which polar solvents such as DMSO, NMP, DMF and 80% EtOH were found to be equally effective leading to 2 in above 90% yields (entries 2 and 4–15).

With the formation of a significant amount of the amine 3 (5–14%; entries 1, 2 and 4–15) along with the corresponding azide 2 as a major product depending on the reaction conditions, the possibility of the se-

lective amination of aryl iodide with NaN_3 was further examined using CuI and DMEDA as catalyst and ligand respectively (Table 2).

In general, it has been well known that aryl azides are readily converted to the corresponding amines by a variety of reducing agents such as metal catalysts and hydride reducing agents, and more recently copper nanoparticle has also been reported to be the active reducing species for aryl azides[14]. Thus, an attempt to find an optimum condition for the selective amination of iodoanisole as a model compound with NaN_3 was first examined with a varied amount of CuI, which could be expected to function as reducing active species of aryl azide. As shown in Table 2, the reaction in the absence of CuI in DMSO at 100 °C was unchanged indicating that a copper catalyst was crucial for the azidation and amination (Table 2, entry 1). A gradual increase of the catalyst loading from 10 to 50 mol % enhanced the amination to 53% with 9% of unidentified impurities (Table 1, entry 2 and Table

Table 3. CuI-Catalyzed Amination of Aryl Halides^a

Entry	Aryl halide	Aryl amine	Yield (%) ^b
1			100
2			66
3			61
4			100
5			100
6			94
7			79

^a Reaction conditions: CuI (10 mol %), DMEDA (20 mol %), and NaN₃ (2 equiv), DMSO, 180 °C, 10 min (microwave irradiation). ^b Conversion yield based on the analysis of ¹H-NMR.

2, entry 2); the use of 100 mol % CuI, however, led to an increase of the unidentified impurities (33%) with 38% of the amination product (entry 3). These results indicated that the catalytic loading of CuI had limited effects on the selective amination of aryl iodide with NaN₃. Next, the reaction temperature was gradually increased with caution due to a potential problem for explosions of azides[15]. At 180 °C with 10 mol % CuI and 1.2 equiv NaN₃, complete conversion of the aryl iodide was observed affording 83% of the amine 3 with 17% of the azide 2 (entries 4 and 5). Finally, almost a complete amination (> 99%) was achieved by using 2 equiv of NaN₃ in the presence of 10 mol % CuI in DMSO (entries 6 and 7); no other impurities was observed. This successful selective amination protocol (10 mol % CuI, 20 mol % of DMEDA, and 2 equiv of NaN₃ in DMSO at 180 °C with microwave irradiation for 10 min) were applied to the amination of various aryl halides to study the scope of the reaction (Table 3).

4-Iodotoluene and 1-iodo-3,5-dimethyltoluene also led to the complete conversion to the corresponding amines (entries 4 and 5). The reaction of iodobenzene as a substrate afforded a mixture of the amine as the major product (94% conversion) with 6% of the corresponding azide (entry 6). However, meta-substituted 3-iodoanisole or 4-bromoanisole having a bromide substituent in place of iodide resulted in lower conversions in the same reaction condition (entries 2 and 3). A substrate containing electron-withdrawing nitro group was evaluated to be relatively good providing 79% conversion (entry 7).

In summary, a rapid and selective copper-catalyzed amination of aryl halides has been most efficiently carried out under microwave irradiation using 2 equiv of NaN₃ at 180 °C. The catalytic systems were found to be the most effective with 4-substituted aryl iodides leading to nearly complete conversions.

Acknowledgements

This research has been conducted by the Bisa Research Grant of Keimyung University.

References

1. E. V. Scriven and K. Turnbull, Azides: Their preparation and synthetic uses, *Chem. Rev.*, **88**, 297-368 (1988).
2. S. Brase, C. Gil, K. Knepper, and V. Zimmermann, Organic azides: An exploding diversity of a unique class of compounds, *Angew. Chem. Int. Ed.*, **44**, 5188-5240 (2005).
3. K. V. Kutonova, M. E. Trusova, P. S. Postnikov, V. D. Filimonov, and J. Parello, A simple and effective synthesis of aryl azide via arenediazonium tosylates, *Synthesis*, **45**, 2706-2710 (2013).
4. J. F. Bunnett, and R. E. Zahler, Aromatic nucleophilic substitution reactions, *Chem. Rev.*, **49**, 273-412 (1951).
5. J. Andersen, U. Madsen, F. Björklund, and X. Liang, Rapid synthesis of aryl azides from aryl halides under mild conditions, *Synlett*, **14**, 2209-2213 (2005).
6. D. Ma and Q. Cai, Copper/amino acids catalyzed cross-couplings of aryl and vinyl halides with nucleophiles, *Acc. Chem. Res.*, **41**, 1450-1460 (2008).
7. F. Y. Kwong and S. L. Buchwald, Mild and efficient copper-catalyzed amination of aryl bromides with primary alkyl amines, *Org. Lett.*, **5**, 793-796 (2003).
8. P. Ji, J. H. Atherton, and M. I. Page, Copper-catalyzed amination of aryl halides in liquid ammonia, *J. Org. Chem.*, **77**, 7471-7478 (2012).
9. H. Zhao, H. Fu, and R. Qiao, Copper-catalyzed direct amination of ortho-functionalized haloarenes with sodium azide, *J. Org. Chem.*, **75**, 3311-3316 (2010).

10. Y. A. Cho, D. S. Kim, H. R. Ahn, B. Canturk, G. A. Molander, and J. Ham, Preparation of potassium azidoaryltrifluoroborates and their cross-coupling with aryl halides, *Org. Lett.*, **11**, 4330-4333 (2009).
11. J. T. Markiewicz, O. Wiest, and P. Helquist, Synthesis of primary amines through a copper-assisted aromatic substitution reaction with sodium azide, *J. Org. Chem.*, **75**, 4887-4890 (2010).
12. A. Monguchi, T. Maejima, S. Mori, T. Maegawa, and H. Sajika, Copper-mediated reductive amination of aryl halides with trimethylsilyl azide, *Chem. Eur. J.*, **16**, 7372-7375 (2010).
13. S. Paik, M. G. Jung, Rapid microwave-assisted copper-catalyzed nitration of aromatic halides with nitrite salts, *Bull. Korean Chem. Soc.*, **33**, 689-691 (2012).
14. S. Ahammed, A. Saha, and B. C. Ranu, Hydrogenation of azides over copper nanoparticle surface using ammonium formate in water, *J. Org. Chem.*, **76**, 7235-7239 (2011).
15. Great caution should be taken during experiments in a microwave since sodium azide has been reported to be decomposed upon heating to above 275 °C.

Authors

Seunguk Paik; Professor, Department of Chemical Engineering, Keimyung University, Daegu 42601, Korea; paiksu@kmu.ac.kr