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An expeditious and environmentally benign preparation of aryl halides from aryl amines by solvent-free grinding

Mi Eun Moon[a], Younghwa Choi[a], Young Min Lee[a], Vaishali Vajpayee[a], Marina Trusova[b], Victor D. Filimonov[b,*], Ki-Whan Chi[a,*]

[a] Department of Chemistry, University of Ulsan, Ulsan 680-749, Republic of Korea
[b] Department of Organic Chemistry, Tomsk Polytechnic University, Tomsk 634050, Russia

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ABSTRACT

An efficient solvent-free methodology for conversion of various aryl amines into bromides and chlorides via arenediazonium tosylate salts under grinding conditions is disclosed. This new methodology not only avoids the use of strong acids and expensive reagents for diazotization-halogenation reactions, but also decreases the amount of organic waste from the reaction process.

The versatile applicability of diazonium salts for Matsuda–Heck coupling, Sandmeyer and other cross-coupling reactions has been well-established.[1,2] Taking into account the numerous applications of arenediazonium salts, we recently reported a facile synthesis and isolation of pure and unusually stable arenediazonium tosylate salts in excellent yields.[3] The exceptional stability of these salts can be rationalized on the basis of close and multiple contacts between the nitrogen atom of the diazonium cation and the oxygen atoms of the tosylate moiety. Most other diazonium salts have drawbacks, such as difficulty in isolation, air and thermal sensitivity, tedious preparation, or further work-up of precursors.[4] The easy synthesis of pure and thermally stable arenediazonium tosylate salts is advantageous for their use in various reactions. Furthermore, we have been interested in exploring the application of these tosylate salts in organic synthesis, and in this context we have published a couple of reports on efficient and economical diazotization-iodination reaction which could be accomplished with or without solvent.[5–7] In addition, these tosylate salts were efficiently employed in bromination and chlorination reactions under solvent conditions.[8] There is copious literature demonstrating the importance of aryl halides for various organic transformations, including substitution reactions[9] that produce compounds containing new carbon–carbon[10] or carbon–heteroatom[11] bonds in high yields.

A number of methods have been reported for the synthesis of aryl halides, either by the Sandmeyer reaction involving the use of an equimolar amount of Cu salt or by the direct halogenation;[12] however, all of the procedures reported to date have potentially serious environmental concerns as they involve directly or indirectly toxic reagents, use expensive catalysts, or require tedious purification processes. Considering the wide range of aryl halide applications, it is worthwhile to develop a practical, cost-effective, simple, fast, and environmentally benign protocol for the synthesis of aryl bromides and chlorides. It is known that, the high redox potentials of chloride and bromide anions make chlorination and bromination reactions more challenging and demanding than iodination reactions. In this context, the reaction conditions for the effective bromination and chlorination of aryl amines make this report noteworthy.

Herein, we wish to report for the first time, a solvent-free grinding process for the fast and efficient conversion of aryl amines into aryl bromides and chlorides via arenediazonium tosylate salts. The one-pot sequential diazotization-halogenation reaction for the synthesis of aryl bromides and chlorides involves a solvent-free reaction of various anilines with halogenating reagent, *tert*-butyl nitrite, *p*-TsOH, and a catalytic amount of a copper(II) salt (Scheme 1) and avoids the isolation of intermediate diazonium tosylate salts. Unlike the corresponding solution reactions, this solid-phase synthesis is not only clean and fast, but also avoids the formation of organic wastes.

The main features of this protocol include an easy solvent-free process and use of only a catalytic amount of Cu(II) halides for the conversion under grinding conditions, thus offering an

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* Corresponding authors. Tel.: +82 52 259 2344; fax: +82 52 259 2348 (K.-W.C.).
E-mail addresses: filimonov@tpu.ru (V.D. Filimonov), kwchi@ulsan.ac.kr (K.-W. Chi).

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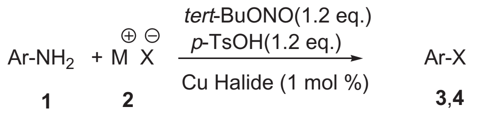

1,**3**,**4**: a, Ar =2-NO_2-C_6H_4 ; b,Ar = 3-$NO_2C_6H_4$; c,Ar =4-$NO_2C_6H_4$; d,Ar = 2-CNC_6H_4;e,Ar= 4-CNC6H4;
f,Ar = 4-IC_6H_4; g,Ar = 4-BrC_6H_4;h,Ar = 4-ClC_6H_4; i,Ar = 2-$OCH_3C_6H_4$; j, Ar = 4-$OCH_3C_6H_4$;
k, Ar = 4-NO_2-2-$OCH_3C_6H_3$; l,Ar = 2-NO_2-4-$OCH_3C_6H_3$
2: benzyltriethylammonium chloride(BTAC),sodium bromide, tertabutylammonium bromide(TBAB)
3: X = Br, **4**: X = Cl

Scheme 1. Synthesis of aryl bromides and chlorides by diazotization–halogenation of aryl amines.

environmentally and economically favourable alternative over other reported protocols that employ organic solvents, a desirable goal for current green synthetic chemistry methodologies.

The reaction of various anilines with sodium bromide in the presence of a catalytic amount of Cu(II) bromide, *tert*-butyl nitrite, *p*-TsOH and a few drops of water produced aryl bromides in moderate yields (Table 1) after 15–20 min of grinding. A limitation of the aniline substrate, that it requires a strong electron-withdrawing group, was observed. To overcome this drawback, we used tetrabutylammonium bromide (TBAB) as the bromide source in the absence of water; the desired products were obtained in less than 20 min in higher yields (Table 1) after grinding in a quartz mortar.[13] This variation works well with electron-donating as well as electron-withdrawing substituents. The *p*-TsOH also plays significant role in facilitating the reaction since no conversion was observed in the absence of *p*-TsOH.

Similarly, aryl chlorides (Table 2) were synthesized in good yields by treatment of anilines with benzyltriethylammonium chloride (BTAC) in the presence of $CuCl_2$ as a catalyst via diazonium tosylate salts.[14] The comparatively lower yield of aryl chlorides to aryl bromides can be explained in terms of the lower nucleophilicity or the difficult electron transfer of chloride anions, as compared to bromide anions as a result of their higher redox potential.

In summary, we have presented a simple, environmentally benign, cost-effective, and practical method for the synthesis of aryl bromides and chlorides from aryl amines via arenediazonium tosylate salts by a simple solvent-free process. This methodology provides an efficient alternative to existing methods for the synthesis of aryl bromides and chlorides.

Table 1
Solvent-free bromination of various aryl amines

Entry	Substrate	Yield (%) of **3** by method 1	Yield (%) of **3** by method 2	Mp (°C)
1	2-$NO_2C_6H_4$(**1a**)	55	71	38–39.5 (40[a])
2	3-$NO_2C_6H_4$(**1b**)	58	77	51–52 (52[a])
3	4-$NO_2C_6H_4$(**1c**)	65	87	123–124 (124[a])
4	2-CNC_6H_4(**1d**)	42	68	52–54 (53–57[a])
5	4-CNC_6H_4(**1e**)	54	82	109–111 (110[a])
6	4-IC_6H_4(**1f**)	30	64	87–89 (89[a])
7	4-BrC_6H_4(**1g**)	16	60	82–84 (83[a])
8	4-ClC_6H_4(**1h**)	10	46	64–66 (64–67[a])
9	2-$MeOC_6H_4$(**1i**)	0	44	Oil (2[a])
10	4-$MeOC_6H_4$(**1j**)	0	45	Oil (9[a])
11	4-NO_2-2-$MeOC_6H_3$ (**1k**)	24	80	101–102
12	2-NO_2-4-$MeOC_6H_3$(**1l**)	25	78	31–33 (32–33[a])

Method 1: *tert*-BuONO, *p*-TsOH, Cu(II) bromide, NaBr, a few drops of water.
Method 2: *tert*-BuONO, *p*-TsOH, Cu(II) bromide, TBAB.
[a] Reference mp (Aldrich Handbook of Fine Chemicals).

Table 2
Solvent-free chlorination of various aryl amines

Entry	Substrate	Yield (%) of **4** by method 3	Mp (°C)
1	2-$NO_2C_6H_4$(**1a**)	53	Oil (33[a])
2	3-$NO_2C_6H_4$(**1b**)	65	46–47 (47[a])
3	4-$NO_2C_6H_4$(**1c**)	70	80–81 (81[a])
4	2-CNC_6H_4(**1d**)	33	41–43 (43[a])
5	4-CNC_6H_4(**1e**)	54	90–92 (91[a])
6	4-$MeOC_6H_4$(**1j**)	54	87–89 (89[a])
7	4-NO_2-2-$MeOC_6H_3$(**1k**)	65	76–80
8	2-NO_2-4-$MeOC_6H_3$(**1l**)	69	38–41 (41[a])

Method 3: *tert*-BuONO, *p*-TsOH, Cu(II) chloride, BTAC.
[a] Reference mp (Aldrich Handbook of Fine Chemicals).

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References and notes

1. (a) Zollinger, H. In *The Chemistry of Amino, Nitroso, Nitro and Related Groups*; Patai, S., Ed.; Wiley & Sons: New York, 1996; pp 636–637; (b) Moro, A. V.; Cardoso, F. S. P.; Correia, C. R. D. *Tetrahedron Lett.* **2008**, *49*, 5668; (c) Roglans, A.; Pla-Quintana, A.; Moreno-Manas, M. *Chem. Rev.* **2006**, *106*, 4622; (d) Heinrich, M. R.; Blank, O.; Ullrich, D.; Kirschstein, M. *J. Org. Chem.* **2007**, *72*, 9609; (e) Kikukawa, K.; Kono, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* **1983**, *48*, 1333; (f) Kikukawa, K.; Kono, K.; Wada, F.; Matsuda, T. *Chem. Lett.* **1982**, 35; (g) Garcia, A. L. L.; Carpes, M. J. S.; Montes de Oca, A. C. B.; dos Santos, M. A. G.; Santana, C. C.; Correia, C. R. D. *J. Org. Chem.* **2005**, *70*, 1050.
2. (a) Jiang, H.; Zhu, S. *J. Fluorine Chem.* **2008**, *129*, 40; (b) Sabino, A. A.; Machado, A. H. L.; Correia, C. R. D.; Eberlin, M. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 4389; (c) Masllorens, J.; Bouquillon, S.; Roglans, A.; Hénin, F.; Muzart, J. *J. Organomet. Chem.* **2005**, *690*, 3822; (d) Artuso, E.; Barbero, M.; Degani, I.; Dughera, S.; Fochi, R. *Tetrahedron* **2006**, *62*, 3146; (e) Kaupp, G.; Herrmann, A.; Schmeyers, J. *Chem. Eur. J.* **2002**, *8*, 1395; (f) Sengupta, S.; Bhattacharyya, S. *Tetrahedron Lett.* **1995**, *36*, 4475.
3. Filimonov, V. D.; Trusova, M.; Postnikov, P.; Krasnokutskaya, E. A.; Lee, Y. M.; Hwang, H. Y.; Kim, H.; Chi, K. W. *Org. Lett.* **2008**, *10*, 3961.
4. (a) Cygler, M.; Przybylska, M.; Elofson, R. M. *Can. J. Chem.* **1982**, *60*, 2852; (b) Galli, C. *Chem. Rev.* **1988**, *88*, 765; (c) Barbero, M.; Crisma, M.; Degani, I.; Fochi, R.; Perracino, P. *Synthesis* **1998**, 1171.
5. Gorlushko, D. A.; Filimonov, V. D.; Krasnokutskaya, E. A.; Semenishcheva, N. I.; Go, B. S.; Hwang, H. Y.; Cha, E. H.; Chi, K. W. *Tetrahedron Lett.* **2008**, *49*, 1080.
6. Filimonov, V. D.; Semenischeva, N. I.; Krasnokutskaya, E. A.; Tretyakov, A. N.; Hwang, H. Y.; Chi, K. W. *Synthesis* **2008**, *2*, 185.
7. Gorlushko, D. A.; Filimonov, V. D.; Semenishcheva, N. I.; Krasnokutskaya, E. A.; Tret'yakov, A. N.; Go, B. S.; Hwang, H. Y.; Cha, E. H.; Chi, K. W. *Russ. J. Org. Chem.* **2008**, *44*, 1243.
8. Lee, Y. M.; Moon, M. E.; Vajpayee, V.; Filimonov, V. D.; Chi, K. W. *Tetrahedron* **2010**, *66*, 7418.
9. (a) Han, X.; Weng, Z.; Andy Hor, T. S. *J. Organomet. Chem.* **2007**, *692*, 5690; (b) Manolikakes, G.; Hernandez, C. M.; Schade, M. A.; Metzger, A.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 8422; (c) Ye, Z.-W.; Yi, W.-B. *J. Fluorine Chem.* **2008**, *129*, 1124; (d) Farina, V. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: Oxford, 1995; Vol. 12, pp 161–240; (e) Soderbegr, B. C. G. *Coord. Chem. Rev.* **2004**, *248*, 1085.
10. (a) Phan, N. T. S.; Styring, P. *Green Chem.* **2008**, *10*, 1055; (b) Lehmann, U.; Awasthi, S.; Minehan, T. *Org. Lett.* **2003**, *5*, 2405; (c) Milton, E. J.; Clarke, M. L.

Green Chem. **2010**, *12*, 381; (d) Thorwirth, R.; Stolle, A.; Ondruschka, B. *Green Chem.* **2010**, *12*, 985.

11. (a) Li, X.; Yang, D.; Jiang, Y.; Fu, H. *Green Chem.* **2010**, *12*, 1097; (b) Patil, N. M.; Gupte, S. P.; Chaudhari, R. V. *Appl. Catal. A: General* **2010**, *372*, 73; (c) Benyahya, S.; Monnier, F.; Man, M. W. C.; Bied, C.; Ouazzani, F.; Taillefer, M. *Green Chem.* **2009**, *11*, 1121.
12. (a) Sandmeyer, T. *Chem. Ber.* **1884**, *17*, 1633; (b) Hodgson, H. H. *Chem. Rev.* **1947**, *40*, 251; (c) Zollinger, H. *Azo and Diazo Chemistry*; Interscience: NY, 1961; (d) Doyle, M. P.; Siegfried, B., Jr.; Dellaria, J. F. *J. Org. Chem.* **1977**, *42*, 2426; (e) Doyle, M. P.; Van Lente, M. A.; Mowat, R.; Fobare, W. F. *J. Org. Chem.* **1980**, *45*, 2570; (f) Barbero, M.; Degani, I.; Dughero, S.; Fochi, R. *J. Org. Chem.* **1999**, *64*, 3448.
13. Grinding method for diazotization–halogenation of aryl bromides: into an agate mortar, aniline (1.0 equiv), *p*-TsOH (1.2 equiv), *tert*-butyl nitrite (1.2 equiv), TBAB (1.2 equiv), and a catalytic amount of copper(II) bromide (1 mol %) were added, and the mixture was ground vigorously. An immediate evolution of N_2 was observed. After completion of the reaction (confirmed by TLC), the solid was washed with water and extracted with CH_2Cl_2.The resulting solution was dried with anhydrous $MgSO_4$, and the solvent was removed in a rotary evaporator under reduced pressure. Further purification of the product was performed by column chromatography using hexane: dichloromethane as eluting solvents. All physical and ^1H NMR data of the products were identical to those from commercially available samples of analytical purity.
14. Grinding method for diazotization–halogenation of aryl chlorides: *p*-TsOH (1.2 equiv), *tert*-butyl nitrite (1.2 equiv), benzyltriethylammonium chloride (1.2 equiv) and a catalytic amount of copper salt (1 mol %) were combined in an agate mortar-containing aniline (1.0 equiv) and the mixture was vigorously ground for 15–20 min, until the evolution of N_2 completely stopped. After completion of the reaction (confirmed by TLC), the crude residue was worked up, as described for the aryl bromide reaction, and was purified by column chromatography using hexane: dichloromethane as eluting solvents. All physical and ^1H NMR data of the products were identical to those from commercially available samples of analytical purity.