



Electrophilic aryl-halogenation using N-halosuccinimides under ball-milling



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ABSTRACT

We report here a methodology of chemo- and regio-selective aryl bromination and iodination using respective N-halosuccinimides at room temperature in the absence of any solvents, catalyst/additives under ball-milling condition. However, for chlorination ceric ammonium nitrate was used as additive. The coupled product succinimide, produced from the reactions, was recycled via regeneration of NBS. This methodology works with the electron-donor substituted or unsubstituted arenes.

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It is essential to minimize the usage of chemicals, solvents and catalysts in routine organic synthesis to do chemical reactions in greener way.^{1,2} Aryl halides are well known synthetic intermediates towards the synthesis of natural or pharmaceutical products.³ The aryl halogenation methodologies are well known over a century but still need modifications because of high demand for better methodologies. For example, bromination reactions using elemental bromine may lead to unwanted side reactions at harsh conditions⁴ and chlorination reagents are generally non-eco-friendly. We did focus on a few literature known halogenation procedures relevant to our studies (a) brominations using NBS⁵ (N-bromosuccinimide): NBS–acetonitrile,⁶ NBS–H₂SO₄–TFA,⁷ NBS–BF₃–H₂O,⁸ NBS–Al₂O₃ (solvent free condition⁹ and Vilsmeier–Haack bromination¹⁰ (b) for chlorinations: NCS (N-chlorosuccinimide)–acetonitrile,¹¹ NCS–CuCl¹² and NCS–BF₃–H₂O⁸ (c) iodinations: NIS (N-iodosuccinimide)–TFA,¹³ NIS–In(OTf)₃¹⁴ NIS–BF₃–H₂O⁸ and NO₂–I₂¹⁵ etc.

We report a synthetic methodology for electrophilic aryl halogenations under ball-milling^{16–18} conditions and solvent-free conditions at room temperature. To the best of our knowledge, only one example of aryl-bromination under ball-milling condition using oxone–NaBr is known in literature.^{19,20}

Herein, we have demonstrated the bromination and iodination reactions using NBS and NIS, respectively. This methodology works

in the absence of any catalyst or additives. However, chlorination was done using NCS–CAN (ceric ammonium nitrate) combination. Interestingly, the coupled product succinimide, obtained from the reaction, was reprocessed for preparation of NBS. It has been found that this newly generated NBS works efficiently without losing its activity. This is an unprecedented example in the literature where NBS and NIS work efficiently in the absence of any additive/catalyst.

The results of aryl brominations are presented in Figure 1. Brominated products were obtained in very good to excellent yield for the derivatives of anilines, anisoles, benzaldehydes, nitrobenzene, alkyl benzenes etc. Taking a few examples into consideration, we are now examining the efficiency of our methodology. As shown in Figure 1, **2h** was prepared in **2h** using only NBS under ball-milling condition compared to a literature reported procedure in which the bromination was done for 18 h using NBS–TFA–H₂SO₄.²¹ We have successfully done the bromination of alkyl benzenes (**2c–2f**, Fig. 1) in the absence of hazardous molecular bromine.⁴ The ring brominations of anisole derivatives are generally performed in toxic acetonitrile solvent and NBS.⁶ However, the synthesis of **2m** was done at 45 min at ambient temperature under ball-milling rather than 24 h at reflux condition (Table 1).⁶ In a similar manner we have made a few comparisons with literature reported data and our method (ball milling). These data are shown in Table 1.

The reactions were done under ball-milling condition (frequency 21 Hz), in solid state and at room temperature. The progress of the reactions was monitored by either TLC (thin layer

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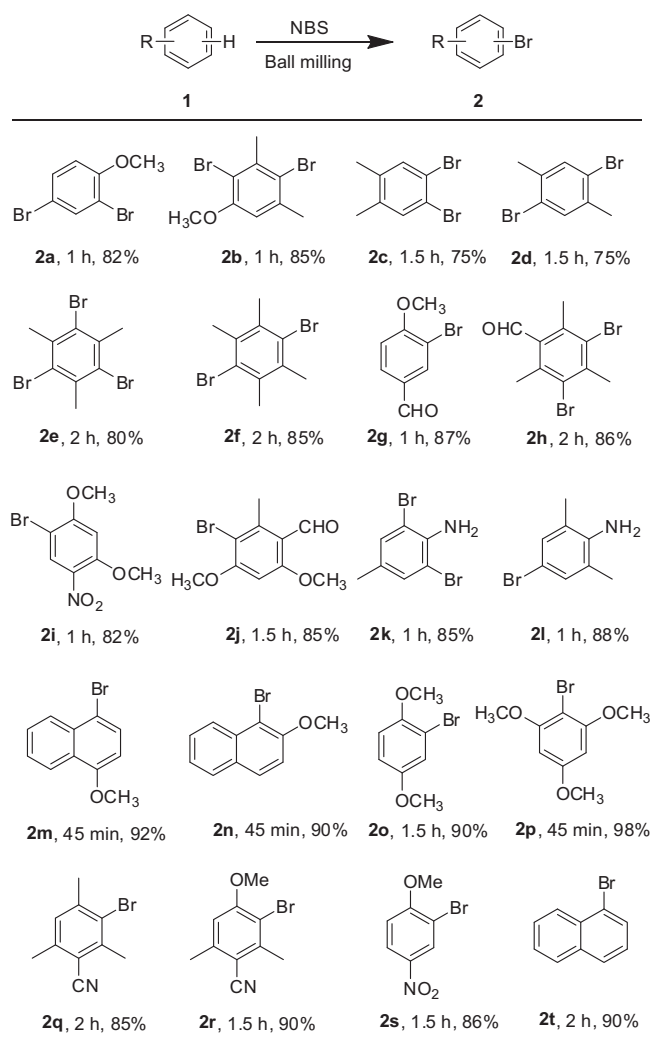


Figure 1. Catalyst and solvent-free bromination using N-bromosuccinimide (NBS). Compound's identification numbers, reaction times and isolated yields are also shown.

chromatography) or ^1H NMR.²² Thus the reaction time and yields were optimized. A significant loss of the materials was observed if the reactions were continued over prolonged period of time. After the reaction, the products were isolated by dissolving the reaction mixture in ethyl acetate and subsequent paper filtration. The brominated products were obtained after evaporation of the solvent and purified by either chromatographically or recrystallization methods. As a precipitate the coupled product succinimide

was isolated and recycled after regeneration of NBS using standard procedure.

Remarkably, this methodology is found to be chemoselective²³ and no benzylic bromination was observed for the alkyl benzenes.²⁴ We have also observed the *para*-selectivity (with one equivalent of NBS) for electron rich aromatics for example, anisoles, anilines (**2i**) and *meta*-selectivity for benzaldehyde (**2g** and **2j**), nitrobenzenes (**2i**, Fig. 1) etc. This regioselectivity clearly establishes that the reactions proceed via aromatic electrophilic substitution.⁸

Using NBS-ball milling methods, we have successfully brominated the benzaldehyde derivatives and no over-oxidation to benzoic acids was found.³⁰ Compounds **2h**, **2j** were isolated in very good yields (Fig. 1).

The bromination methodology is found to be efficient and convenient. This fact encouraged us to further explore the chlorination and iodination of aromatic compounds using NXS (X = Cl, I), respectively. The direct iodination of aromatic compounds via electrophilic aromatic halogenation is cumbersome due to the low electrophilicity of molecular iodine.¹⁵ Therefore, aromatic iodination requires either Lewis acid activator or oxidative and/or acidic reaction conditions.^{31,32} Again, use of such reaction condition may cause serious problem during the synthesis of the compounds having labile functionalities.

The results of aryl iodination with NIS under ball-milling are shown in Figure 2. We have successfully done the iodination of electron rich compounds. Like NBS-milling method, iodination reactions were done in the absence of additive/catalyst and the reactions were also found to be chemo- and regioselective. The regioselectivity for the synthesis of **4b**, **4c** and **4e** is observed due to steric (like methyl vs methoxy group in **4b**) and electronic (e.g., +R effect of OMe and -R effect of -CHO etc.) effect. Mono-iodination of 3,5-dimethyl anisole led to the formation of a single regio isomer that is, *p*-iodo derivative (yield >99%). No benzylic iodinations were detected because the reaction proceeded via aromatic electrophilic substitution.

The direct uncatalysed aromatic chlorinations are not known in the literature due to in situ generation of unreactive chlorine (Cl_2).³³ As expected, we were unsuccessful to do chlorination with NCS alone under ball-milling condition. However, chlorination of activated (electron rich) aromatic compounds was done in the presence of CAN (ceric ammonium nitrate) and NCS under ball milling. It is anticipated that CAN may get involved in the oxidative electron transfer process³⁴ to generate chloronium cation because Ce^{IV} is a stronger oxidizing agent ($E^\circ \sim 1.61$ V vs NHE) than Cl_2 ($E^\circ \sim 1.36$ V). The results of chlorinations are depicted in Figure 3. The yields are found to be very good to excellent. In literature CAN- Br_2 -silica gel combination was used for the bromination of certain aromatic aldehydes.³⁵

Table 1
Comparison data of literature report (traditional) and our method (ball milling)

Entry	Compd	Traditional			Ball-Mill	
		Reagent ^a	Condition	Yield (%)	Time (h)	Yield (%)
1	2h	NBS-TFA ²¹	18 h, rt	88	2	86
2	2m	NBS- CCl_4 ⁶	24 h, reflux	94	0.75	92
3	2t	KBr- HNO_3 ²⁵	3 h, rt	52	2	90
4	8b	BuLi, Br_2 ²⁶	24 h, -78 °C	76	2	75
5	8c	NBS- CCl_4 , $h\nu$ ²⁷	0.5 h, reflux	75	1.5	95 ^b
6	2c	NaBrO_3 - CH_3CN ²⁸	4 h, rt	51	1.5	75 ^b
7	2p	NBS- CCl_4 ⁶	4 h, rt	92	0.75	98
8	2r	NBS- CH_3CN ²⁹	48 h, rt	91	1.5	90

^a References are shown as superscript.

^b Exclusive ring bromination was observed as a proof for high chemoselectivity in contrast to the literature report; compd = compound; rt = room temperature.

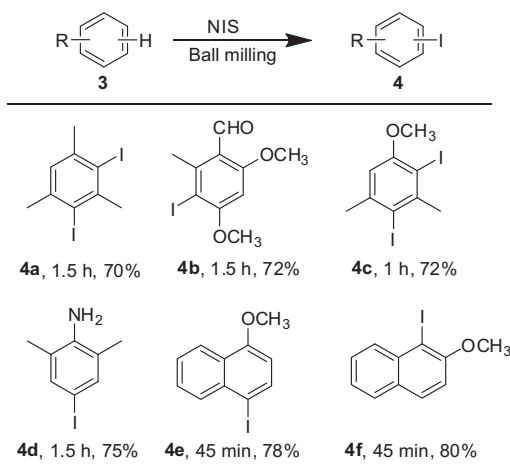


Figure 2. Iodination of electron rich aromatics using N-iodosuccinimide (NIS) alone.

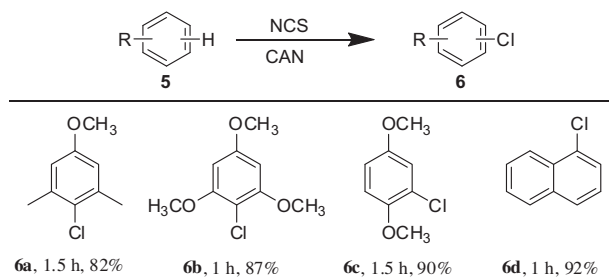


Figure 3. Chlorination with CAN–NCS combinations.

Herein, we have demonstrated an efficient methodology of aryl halogenations, but this method has certain limitations. These are: (a) while working with volatile compounds like xylenes and mesitylene the mass balance could not be accounted (b) aniline derivatives led to a significant amount of unidentified products and poor yields were observed (c) all the halogenation methods were unsuccessful for nitrobenzenes, benzaldehydes and benzonitriles.

We have also done bromination of aniline and anisoles with 1.0 equiv of NBS to establish the regio-selectivity on bromination.^{36,37} 4-Bromo anisole and 4-bromo aniline were isolated in good to excellent yield (Fig. 4) and no other isomers were detected.

In conclusion, we have demonstrated that a wide range of substrates were compatible with N-halosuccinimides for chemo- and regio-selective electrophilic aryl halogenation under solvent-free and ball-milling conditions at room temperature. The reactions were found to be environment friendly, did not require aqueous

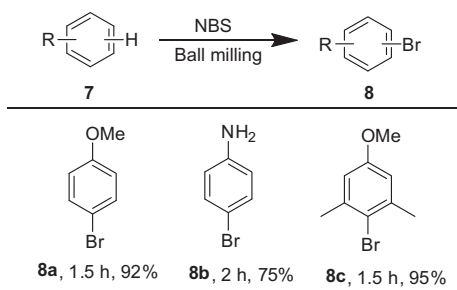


Figure 4. Regio-selectivity on brominations.

work-up, adopted milder reaction condition and are economical. Succinimide which is the coupled product produced from the bromination reaction was also recyclable.

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Supplementary data

Supplementary data (NMR spectra and data for all the compounds) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2014.02.064>.

References and notes

- Nonappa; Ahonen, K.; Lahtinen, M.; Kolehmainen, E. *Green Chem.* **2011**, *13*, 1203–1209.
- Baig, R. B. N.; Varma, R. S. *Chem. Soc. Rev.* **2012**, *41*, 1559–1584.
- Gribble, G. W. *Chem. Soc. Rev.* **1999**, *28*, 335–346.
- Varma, P. S.; Subrahmanian, T. S. *J. Indian Chem. Soc.* **1936**, *13*, 192–193.
- Djerassi, C. *Chem. Rev.* **1948**, *43*, 271–317.
- Carreno, M. C.; Garcia Ruano, J. L.; Sanz, G.; Toledo, M. A.; Urbano, A. *J. Org. Chem.* **1995**, *60*, 5328–5331.
- Duan, J.; Zhang, L. H.; Dolbier, W. R., Jr. *Synlett* **1999**, 1245–1246.
- Prakash, G. K. S.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A. *J. Am. Chem. Soc.* **2004**, *126*, 15770–15776.
- Imanzadeh, G. K.; Zamanloo, M. R.; Eskandari, H.; Shayesteh, K. *J. Chem. Res.* **2006**, 151–153.
- Chakradhar, A.; Roopa, R.; Rajanna, K. C.; Saiprakash, P. K. *Synth. Commun.* **2009**, *39*, 1817–1824.
- Carreño, M. C.; Garcia Ruano, J.; Sanz, G.; Toledo, M. A.; Urbano, A. *Tetrahedron Lett.* **1996**, *37*, 4081–4084.
- Wu, H.; Hynes, J. *Org. Lett.* **2010**, *12*, 1192–1195.
- Olah, G. A.; Wang, Q.; Sandford, G.; Prakash, G. K. S. *J. Org. Chem.* **1993**, *58*, 3194–3195.
- Zhou, C.-Y.; Li, J.; Peddibhotla, S.; Romo, D. *Org. Lett.* **2010**, *12*, 2104–2107.
- Ren, Y.-L.; Shang, H.; Wang, J.; Tian, X.; Zhao, S.; Wang, Q.; Li, F. *Adv. Synth. Catal.* **2013**, *355*, 3437–3442.
- Stolle, A.; Szuppa, T.; Leonhardt, S. E. S.; Ondruschka, B. *Chem. Soc. Rev.* **2011**, *40*, 2317–2329.
- Wang, G.-W. *Chem. Soc. Rev.* **2013**, *42*, 7668–7700.
- James, S. L.; Adams, C. J.; Bolm, C.; Braga, D.; Collier, P.; Friscic, T.; Grepioni, F.; Harris, K. D. M.; Hyett, G.; Jones, W.; Krebs, A.; Mack, J.; Maini, L.; Orpen, A. G.; Parkin, I. P.; Shearouse, W. C.; Steed, J. W.; Waddell, D. C. *Chem. Soc. Rev.* **2012**, *41*, 413–447.
- Wang, G.-W.; Gao, J. *Green Chem.* **2012**, *14*, 1125–1131.
- Schmidt, R.; Stolle, A.; Ondruschka, B. *Green Chem.* **2012**, *14*, 1673–1679.
- Moorthy, J. N.; Mal, P.; Natarajan, R.; Venugopalan, P. *J. Org. Chem.* **2001**, *66*, 7013–7019.
- The milling apparatus was stopped and small portion of the sample was collected from the reaction jar to study either TLC/ proton NMR. After this action, the reaction was started again and this operation time was excluded for reporting the reaction timing.
- Duan, S.; Turk, J.; Speigle, J.; Corbin, J.; Masnovi, J.; Baker, R. J. *J. Org. Chem.* **2000**, *65*, 3005–3009.
- Pearson, R. E.; Martin, J. C. *J. Am. Chem. Soc.* **1963**, *85*, 354–355.
- Joshi, A. V.; Baidossi, M.; Mukhopadhyay, S.; Sasson, Y. *Org. Process Res. Dev.* **2004**, *8*, 568–570.
- Smith, M. B.; Guo, L.; Okeyo, S.; Stenzel, J.; Yanella, J.; LaChapelle, E. *Org. Lett.* **2002**, *4*, 2321–2323.
- Gruter, G.-J. M.; Akkerman, O. S.; Bickelhaupt, F. J. *J. Org. Chem.* **1994**, *59*, 4473–4481.
- Kikuchi, D.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1998**, *63*, 6023–6026.
- Moorthy, J. N.; Mal, P.; Singhal, N.; Venkatakrisnan, P.; Malik, R.; Venugopalan, P. *J. Org. Chem.* **2004**, *69*, 8459–8466.
- Barker, I. R. L.; Dahm, R. H. *J. Chem. Soc. B* **1970**, 650.
- Kamei, T.; Shibaguchi, H.; Sako, M.; Toribatake, K.; Shimada, T. *Tetrahedron Lett.* **2012**, *53*, 3894–3896.
- Bovonsombat, P.; Leykajarakul, J.; Khan, C.; Pla-on, K.; Krause, M. M.; Khantapura, P.; Ali, R.; Doowa, N. *Tetrahedron Lett.* **2009**, *50*, 2664–2667.
- Neale, R. S.; Schepers, R. G.; Walsh, M. R. *J. Org. Chem.* **1964**, *29*, 3390–3393.
- Nair, V.; Balagopal, L.; Rajan, R.; Mathew, J. *Acc. Chem. Res.* **2003**, *37*, 21–30.
- Wang, L.; Jing, H.; Bu, X.; Chang, T.; Jin, L.; Liang, Y. *Catal. Commun.* **2007**, *8*, 80–82.
- Kim, B. R.; Kim, E. J.; Sung, G. H.; Kim, J.-J.; Shin, D.-S.; Lee, S.-G.; Yoon, Y.-J. *Eur. J. Org. Chem.* **2013**, *2013*, 2788–2791.
- Pla, D.; Albericio, F.; Álvarez, M. *Eur. J. Org. Chem.* **2007**, 1921–1924.