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Efficient and Practical Oxidative Bromination and Iodination of Arenes and Heteroarenes with DMSO and Hydrogen Halide: A Mild Protocol for Late-Stage Functionalization

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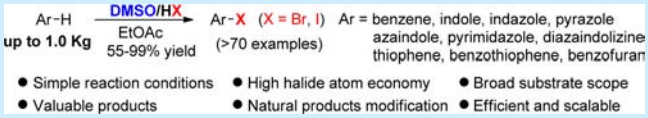
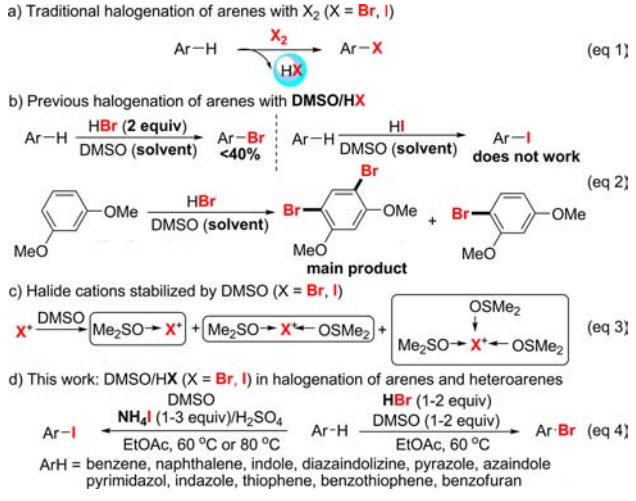
Supporting Information

ABSTRACT: An efficient and practical system for inexpensive bromination and iodination of arenes as well as heteroarenes by using readily available dimethyl sulfoxide (DMSO) and HX (X = Br, I) reagents is reported. This mild oxidative system demonstrates a versatile protocol for the synthesis of aryl halides. HX (X = Br, I) are employed as halogenating reagents when combined with DMSO which participates in the present chemistry as a mild and inexpensive oxidant. This oxidative system is amenable to late-stage bromination of natural products. The kilogram-scale experiment (>95% yield) shows great potential for industrial application.



Aryl halides are among the most common and important chemicals[1] and are present in many natural products.[2] The current dominant industrial approach to aryl bromides and iodides is the halogenation of arenes with X_2 (X = Br, I) which suffers from obvious limitations (Scheme 1a): (1) X_2 are hazardous, toxic, and corrosive reagents; (2) Halide-atom economy is below 50% with HX as the byproduct; (3) Sometimes, the undesirable byproducts are uncontrollable. To avoid the use of X_2, some modified reagents such as *N*-halosuccinimides (NBS or NIS) and their analogues which are operationally safe in comparison with that of X_2 and do not produce HX, have been developed.[3,4] However, these reagents are not good choices for large scale halogenations because of the expensive price and the generation of organic wastes.

Scheme 1. Bromination and Iodination of Arenes



Hydrogen halides (HX), the byproduct of X_2-based halogenations, are readily available, inexpensive, and easy to store and transport. Inspired by the enzyme-catalyzed oxidative halogenation in nature,[5] various oxidative halogenations consisting of generating the halogenating reagent *in situ* from halide are reported in the literature,[6] where residual HX is oxidized by the oxidants such as selectfluor, persulfates, hypervalent iodine, molecular oxygen, hydrogen peroxide, etc. However, limited substrate scope, low atom economy, poor regioselectivity, or the potential explosivity of oxidants substantially restricts the utility of these oxidative halogenations. Importantly, the reported oxidative systems show limitations in halogenation of heteroarenes.[6]

Dimethyl sulfoxide (DMSO), which is industrially produced by oxidation of dimethyl sulfide with nitrogen dioxide or oxygen,[7] is utilized as the oxygen,[8] carbon,[9] or sulfur[10] source in many reactions. The combination of DMSO and HBr has been used in the bromination of arenes (Scheme 1b, eq 2).[11] However, the reported reactions suffered from several drawbacks (Scheme 1b): (1) The bromination of heteroarenes with DMSO/HBr has not been reported except for pyrrole derivatives; (2) the iodination of arenes cannot be achieved by their strategies; (3) the dibromination was uncontrollable due to the use of >9 equiv of HBr (thus, the bromination of electron-rich arenes such as *m*-dimethoxybenzene mainly afforded the dibrominated product); (4) a less than 40% yield was obtained when 2 equiv of HBr were employed. The

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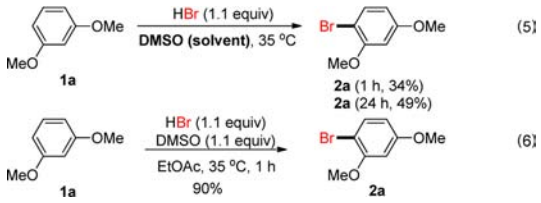
above-mentioned limitations are why this reaction rarely has been used in organic synthesis.

According to Yoshida's report, the halide cation would form $X^+(DMSO)_n$ in the presence of DMSO (Scheme 1c, eq 3).[12] We hypothesized that the excess DMSO strongly reduced the reactivity of X^+ generated from DMSO/HX in Majetich's report.[11a] Therefore, we speculated that the efficient halogenation of arenes with stoichiometric HX would be possible if stoichiometric DMSO was used as the oxidant instead of as the solvent. Herein, we describe the simple and practical bromination and iodination of arenes as well as various heteroarenes with stoichiometric aqueous HX (X = Br, I) and DMSO performed in EtOAc (Scheme 1d, eq 4). The high halide-atom economy, broad substrate scope, easy accessibility, and low cost of aqueous HX and DMSO make this strategy extremely attractive in the development of efficient approaches to aryl bromides and iodides. The mild and simple conditions are amenable to late-stage functionalization of natural products.

Initially, we chose *m*-dimethoxybenzene **1a** as the substrate, from which the bromination afforded mono- and dibrominated products in Majetich's report (Scheme 1b, eq 2).[11a] The bromination of **1a** with 1.1 equiv of HBr in DMSO as solvent at 35 °C afforded **2a** in only 34% (for 1 h) and 49% yield (for 24 h), respectively (Scheme 2, eq 5), which were in accordance

Scheme 2. Bromination of *m*-Dimethoxybenzene

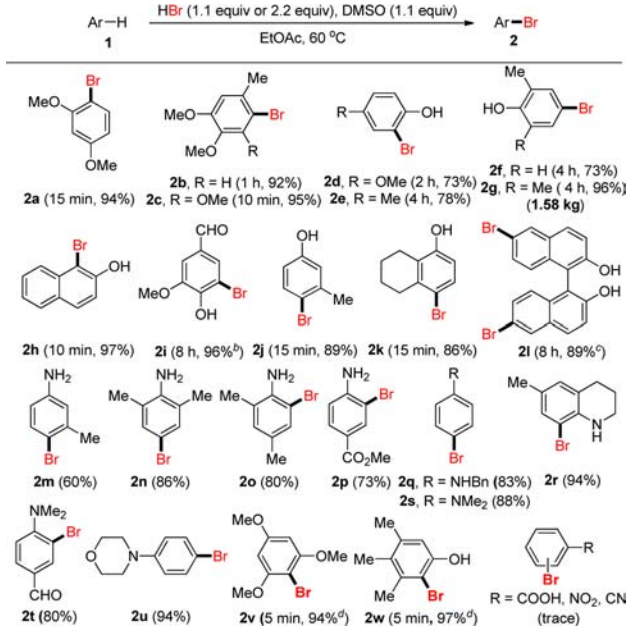


with Majetich's report[11a] (Scheme 1b) and proved that the reactivity of Br^+ in DMSO was very low. To our delight, with 1.1 equiv of DMSO and aqueous HBr (48%) in EtOAc at 35 °C for 1 h, **2a** was obtained as the sole product in 90% yield (Scheme 2, eq 6).

The bromination of **1a** proceeded rapidly (15 min) to afford **2a** in 94% yield at 60 °C (Scheme 3). Under these conditions, arenes **1b**–**k** bearing methoxy or hydroxy substituents were monobrominated in high to excellent yields with selectivity that at first approximation parallels Friedel–Crafts reactivity (Scheme 3). The bromination of some electron-rich substrates **1c**, **1h**, **1j**, and **1k** performed very rapidly (10–15 min) in high yields. Vanilli **1i** was brominated in 96% yield and the aldehyde group, which is easily oxidized under oxidative conditions, was retained.[13] Notably, 2,2′-Binol **1l** was dibrominated smoothly in 89% yield.

This efficient system could cover the aniline derivatives (**1m**–**u**, Scheme 3). A series of primary **1m**–**p**, secondary **1q**–**r**, and tertiary amines **1s**–**u** were monobrominated in high yields with 1.1 equiv of DMSO and 2.2 equiv of HBr. Notably, the bromination of substrates **1q**, **1s**, and **1u** with unsubstituted *ortho* and *para* positions gave *para*-brominated products. Furthermore, the bromination at the benzyl position, which usually happened in other oxidative processes,[14] was not detected in the present system. The electron-poor arenes such as benzoic acid, nitrobenzene, or benzonitrile did not work in the present DMSO/HBr system.

Scheme 3. DMSO/HBr for Bromination of Arenes[a]



[a]The solution of **1** (0.5 mmol), DMSO (0.55 mmol), and HBr (48%) in EtOAc (2 mL) was stirred under air at 60 °C. For **1a**–**k**, 1.1 equiv of HBr was used. For **1m**–**u**, 2.2 equiv of HBr were used. Isolated yields. [b]With 4 equiv of DMSO and HBr. [c]With 8 equiv of DMSO and HBr in AcOH (2 mL). [d]With 1.05 equiv of DMSO and HBr.

Furthermore, the 1.0 kg scale bromination of **1g** with a 96% yield shows great potential for industrial applications of this low-cost protocol (Scheme 3).

Heteroaromatic halogenations are very important because they are ubiquitous in modern medicinal chemistry.[15] Therefore, the development of new approaches to heteroaromatic halides has always drawn chemists' attention.[16] Very recently, Glorius and co-workers reported the Rh-catalyzed regioselective halogenation of heterocycles.[16a] The chlorination of heteroarenes was realized by using Palau'chlor developed by Baran.[16b] We then investigated the heteroaromatic brominations with the present DMSO/HBr system (Scheme 4). Indole compounds **3a**–**k** were brominated in excellent yields within an hour. It is noteworthy that the oxidative bromination of indole compounds without the protecting group on the nitrogen atom could not be achieved using other oxidants such as O_2[6c] or selectfluor.[6i] Other heteroarenes including 7-azaindole **3l**, indazole **3m**, pyrazoles **3n**–**o**, pyrimidazole **3p**, 1,7-diazaindolizine **3q**, thiophene **3r**, benzothiophene **3s**, and benzofuran **3t** could all be regioselectively brominated in good yields.

The bromide substituent can greatly change the drugs' or natural products' properties.[17] We tried to expand our simple and mild method to the direct bromination of natural or bioactive compounds (Scheme 5). The selective bromination of *δ*-tocopherol **5a** with Br_2 was a challenge and showed poor regioselectivity even at very low temperature.[18] Gratifyingly, the bromination of **5a** with the DMSO/HBr system afforded monobrominated product **6a** as the sole product in 94% yield. Xanthotoxin **5b** was brominated in high yield without affecting the furan or lactone group. The bromination of two alkaloid natural products[19] esermethole **5c** and desoxyeseroline **5d** proceeded smoothly to afford monobrominated alkaloids **6c**–**d** in high yields. Sinomenine **5e** was brominated in 75% yield tolerating ketone, amino, and alkene groups. Furthermore,

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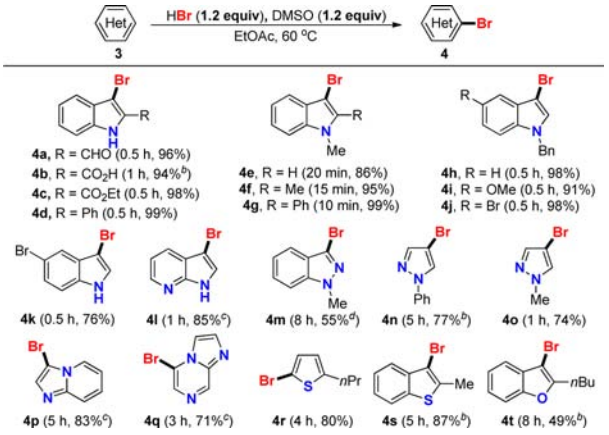
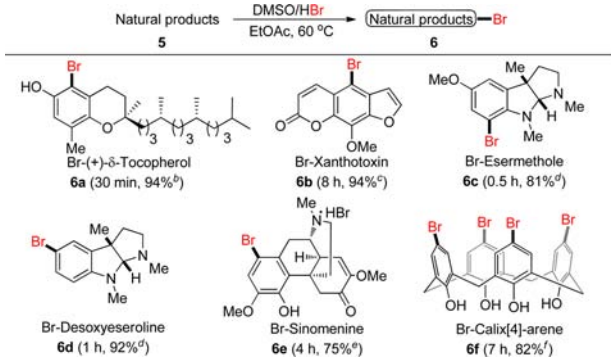
Scheme 4. DMSO/HBr for Bromination of Heteroarenes[a]



[a]The solution of **3** (0.5 mmol), DMSO (0.6 mmol), and HBr (48%, 0.6 mmol) in EtOAc (2 mL) was stirred under air at 60 °C. Isolated yield. [b]With 1.5 equiv of DMSO and HBr. [c]With 1.5 equiv of DMSO and 2.5 equiv of HBr. [d]With 4 equiv of DMSO and HBr.

Scheme 5. DMSO/HBr for Bromination of Natural Products[a]



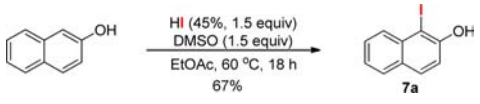
[a]The solution of **5**, DMSO (1.1 equiv), and aquesous HBr in EtOAc was stirred under air at 60 °C. [b]With 1.1 equiv of HBr. [c]With 3 equiv of DMSO and HBr. [d]With 3 equiv of HBr. [e]With 2.2 equiv of HBr in $CHCl_3$/EtOAc (1:3). [f]With 8 equiv of DMSO and HBr.

exposure of calix[4]arene **5f** to 8 equiv of DMSO and HBr in EtOAc afforded the desired tetrabrominated product **6f** in 82% yield. These brominations indicate that the DMSO/HBr system is amenable to late-stage functionalization of natural products and show high potential applications in biological evaluation.

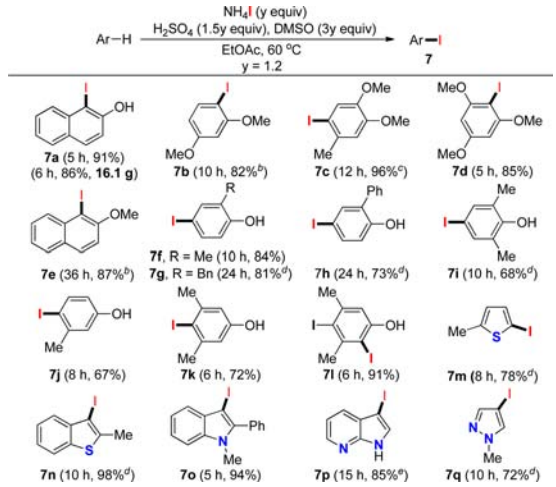
Majetich and co-workers investigated the iodination of arenes with HI in DMSO; however, no aryl iodides were obtained.[11a] Inspired by the above bromination reaction, we expected that if stoichiometric DMSO was used as the oxidant, the iodination of arenes would be possible. As expected, with 1.5 equiv of HI and DMSO in EtOAc at 60 °C, the iodination of 2-naphthol afforded **7a** in 67% yield (Scheme 6).

After extensively screening parameters of the reaction conditions, we were delighted to find that the best yield was obtained with 1.2 equiv of NH_4I, 1.8 equiv of H_2SO_4, and 3.6 equiv of DMSO in EtOAc at 60 °C (see Supporting Information). Under the optimized conditions, a series of arenes were iodinated successfully (Scheme 7). The iodination

Scheme 6. Iodination of 2-Naphthol



Scheme 7. DMSO/NH_4I for Iodination of Arenes[a]

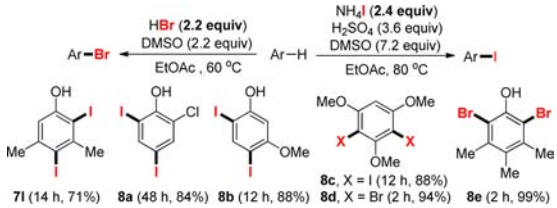


[a]The solution of arene, DMSO, NH_4I (y equiv), and H_2SO_4 in EtOAc was stirred under air at 60 °C. [b]80 °C. [c]y = 3, 80 °C. [d]y = 2, 80 °C. [e]y = 2, 80 °C, 3.5 equiv of H_2SO_4.

of anisole derivatives performed well to afford **7b**–**e** in high yields. Phenol derivatives bearing methyl **7f**, **7i**–**l**, benzyl **7g**, phenyl **7h**, or iodo **7l** substituents were iodinated in good to high yields. Heteroaromatic iodides including thiophene **7m**, benzothiophene **7n**, indole **7o**, 7-azaindole **7p**, and pyrazole **7q** were also synthesized by the present DMSO/HI system. The gram-scale synthesis of 1-iodo-2-naphthol **7a** (16.1 g) was also achieved in 86% yield.

Notably, the mono- and dihalogenation could be efficiently controlled by only adjusting the dosage of HX (X = Br, I) and DMSO (Scheme 8). For example, diiodinated or dibrominated

Scheme 8. DMSO/HX for Dihalogenation of Arenes



arenes **8** were obtained in high yields with 2 equiv of HX. Compared to the previous reports on the adjustment of mono- and dihalogenation by the reaction time or reaction temperature,[6c,11] the present strategy shows higher selectivity.

According to previous research,[20] $[Br^+DMS]Br^-$ would be generated *in situ* from DMSO and HBr.[21] Based on previous reports and our experimental results, we proposed the mechanism of halogenations with DMSO/HX (Scheme 9). We thought that the HX was oxidized by DMSO to X_2 or DMS·X_2. The reaction of X_2 or DMS·X_2 with arene afforded the aryl halides with the formation of HX which was oxidized by DMSO for the next oxidative cycle. Thus, stoichiometric DMSO and HX is sufficient for full conversion of the arenes. The slow generation of X_2 *in situ* is crucial for highly regioselective halogenation of arenes in our strategy.

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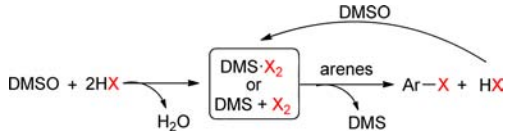
Scheme 9. Proposal Mechanism



In conclusion, we have demonstrated an efficient and practical oxidative DMSO/HX system for the halogenation of arenes and heteroarenes. This mild oxidative system is effective as a versatile protocol for the synthesis of aryl halides and a mild method for late-stage modification of natural products. Efforts to expand this DMSO/HX system to other reactions are continuing.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full characterization of products, and copies of NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00932.

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Notes

The authors declare no competing financial interest.

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