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Bromination of phenyl ether and other aromatics with bromoisobutyrate and dimethyl sulfoxide

Jia-Qin Li [a], Xiao-Hui Chen [a,b], Xian-Xun Wang [b], Hai-Lei Cui [a,*]

[a] Laboratory of Asymmetric Synthesis, Chongqing University of Arts and Sciences, Yongchuan, Chongqing 402160, PR China
[b] Tonichem Pharmaceutical Technology Co., Ltd, Huizhou 516008, PR China

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ABSTRACT

Bromoisobutyrate has been used for the first time as a general brominating source for the direct bromination of a diverse of simple phenyl ethers. Aromatic ethers bearing various substituents could be compatible in this reaction system delivering brominated arenes in moderate to good yields. The reaction system can also be expanded to bromination of phenols and unactivated arene. This process can be regarded as an alternative for the well-established bromination systems for bromoarene synthesis.

Bromoarenes are common units appearing in a large number of natural products, pharmaceuticals and agrochemicals of great interest as core structures [1]. Brominated aromatics are also important synthetically useful building blocks and starting materials in the construction of structurally complex molecules and pharmaceutically important compounds [2]. Therefore, a great number of brominating reagents and reaction systems have been developed efficiently in this regard [3].

From the view of green and sustainable chemistry, the development of safe, environmentally friendly methodologies for bromination is an urgent task. To avoid the use of hazard, toxic and harmful reagent such as Br_2, a series of efficient brominating reagents and convenient reaction systems have been established. Bromoamide derivatives such as NBS are widely used brominating reagents for the synthesis of aromatic bromides [4]. Besides, NBS can also be utilized together with a series of activators such as Lewis acids, Bronsted acids, Lewis bases and oxidants to realize bromination of different arenes [5]. Other Br-containing chemicals such as HBr [6], CBr_4 [7] and bromine salts [8] etc [9] have also been employed frequently as brominating reagents accompanying with activators, or under special reaction conditions.

The combination of bromide and dimethyl sulfoxide as formylating reagents and brominating reagents has attracted increasing attention owing to its efficiency, safety, less pollution and easy operation [10]. DMSO can be used not only as activator of bromine source, but also as solvent, oxidant and carbon source for a diverse of reaction systems [11].

For example, as a pioneering work in this research field, Fletcher and Pan have realized a *N*-monoalkylation and aryl bromination of aromatic amines using the combination of ethyl bromide and DMSO in 1956 [11a]; Megyeri et al have achieved the C-5 bromination of indole alkaloids utilizing HBr/DMSO as brominating reagent [11b]; Majetich and co-workers have developed an electrophilic aromatic bromination with the in situ generated bromodimethylsulfonium bromide from HBr and DMSO [11c]; The Dai group have brominated aromatic amines and pyrroles with HBr/DMSO [11d]; Jiao et al have reached the bromination of a series of important arenes and heteroarenes such as phenols, phenyl ethers, indoles, pyrazoles etc. using only 1.1 or 2.2 equivalents of HBr/DMSO in EtOAc [11e]. These reaction systems can be regarded as attractive alternatives for the well-developed brominating systems.

Very recently, we have developed an efficient formylation and bromination of pyrroloisoquinolines utilizing ethyl bromoisobutyrate and dimethyl sulfoxide as formylating reagent as well as brominating reagent (Eq. (6), Scheme 1). During the study, it was found that when pyrroloisoquinolines without methoxy groups were treated under the reaction system, bromination occurred instead of formylation at C-2 position of the pyrrole ring [12a]. What's more, a formylation/aromatization/bromination cascade product was obtained unexpectedly in the case of a substrate bearing dimethoxyphenyl group. Bromination occurred at the

* Corresponding author.
E-mail address: cuihailei616@163.com (H.-L. Cui).

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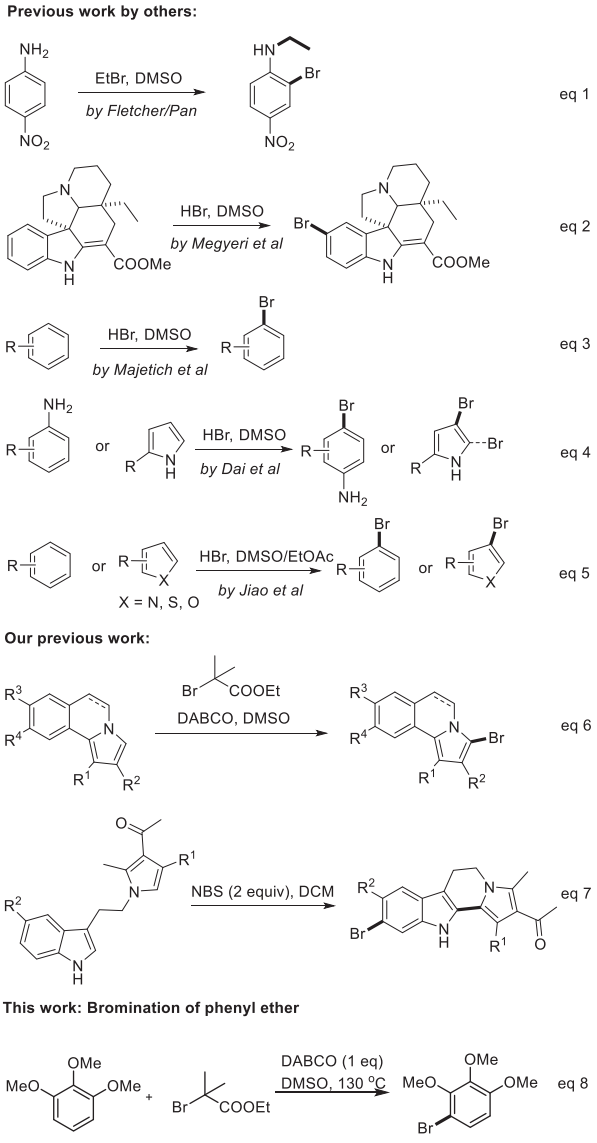
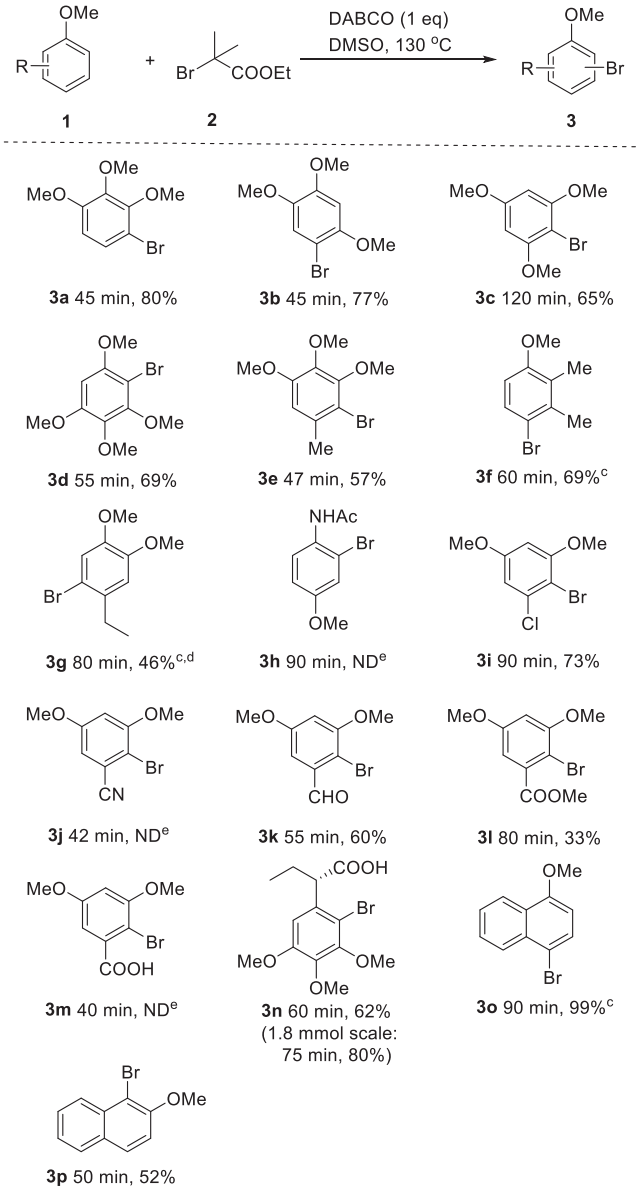


Scheme 1. Bromination of aromatics based on transformation of DMSO and bromide and our previous work.

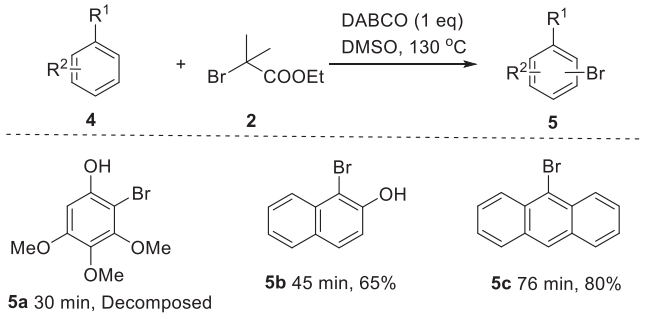


Scheme 2. Bromination of phenyl ethers. a Reaction conditions: 1 (0.4 mmol), 2 (5 equiv), and DABCO (1 equiv) in DMSO (2.0) mL at 130 oC. b Isolated yields. c The yields were determined by 1H NMR using CH2Br2 as internal standard. d Based on the recovery of starting material. e Not detected.

electron-rich dimethoxyphenyl ring. A reasonable explanation for this phenomenon is that the dimethoxy groups act as activating group for electrophilic bromination. At the same time, we have reached a mild NBS-mediated construction of 9-bromo-6,11-dihydro-5*H*-indolizino[8,7–b]indole derivatives through a cyclization/bromination cascade (Eq. (7)) [12b]. Encouraged by these results, we envisioned that electron-rich phenyl ethers can be brominated by the treatment of bromoisobutyrate and dimethyl sulfoxide affording synthetically useful aromatic bromide [13]. Herein, we report our development of a convenient bromination of phenyl ethers and other aromatics using bromoisobutyrate and dimethyl sulfoxide as brominating reagents.

As shown in Scheme 2, trimethoxybenzenes can be easily brominated giving compounds **3a**-**3d** (65%–80% yields) [14]. Good yields were observed in these cases. Alkyl groups such as methyl and ethyl groups could be introduced into methoxyarenes successfully yielding compounds **3e-3g** (46%–69% yields). Unfortunately, the presence of amide at the phenyl ring resulted in the decomposition of starting material (**3h**). Incorporation of Cl under the current system was achieved leading to the formation of compound **3i** in 73% yield. Cyano group has a negative effect for this reaction as no product can be obtained in this case (**3j**). Compounds **3k** and **3l** possessing carbonyl group can be produced readily under the reaction system in 60% and 33% yield respectively. Disappointingly, 3,5-dimethoxybenzoic acid was not suitable substrate for this reaction (**3m**). Pleasingly, a chiral acid can be brominated successfully leading to the formation of compound **3n.** A scaled-up reaction (1.8 mmol) was also successful giving chiral acid **3n** in 80% yield. The use of 1-methoxynaphthalene and 2-methoxynaphthalene resulted in production of corresponding bromoarenes **3o** and **3p** in 99% and 52% yield respectively. Dibrominated products can be detected by HRMS in some cases with relatively lower monobromination yields such as **3c** and **3e**, but no pure products could be isolated.

We wondered whether this brominating system can be used for the bromination of other aromatics such as phenol and unactivated arene. As shown in Scheme 3, attempts of other aromatics have

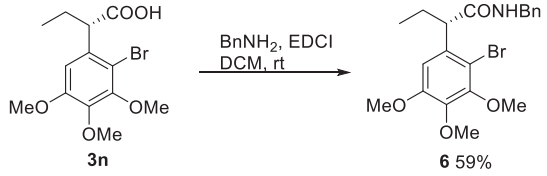


Scheme 3. Expansion of the substrate scope to other aromatics.

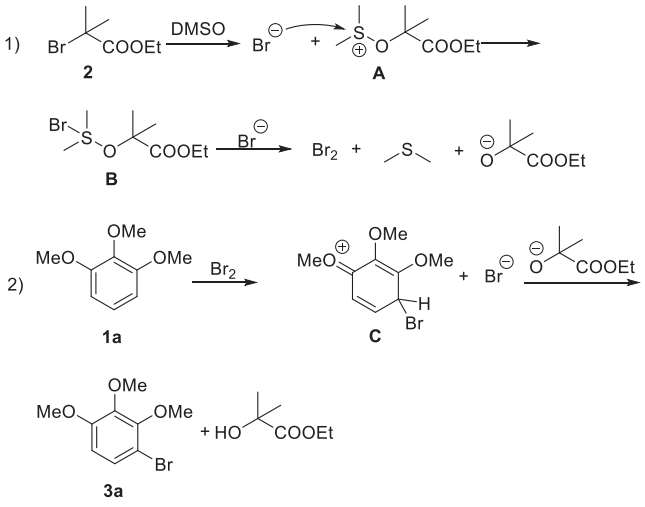
been conducted. No product **5a** was detected in the case using trimethoxyphenol due to decomposition. Bromination of 2-naphthol can be achieved giving compound **5b** in 65% yield. 9-bromoanthracene **5c** can be obtained under the current reaction system in 80% yield.

Brominated arenes are useful synthetic intermediates for complex molecules construction and starting material for organometallic reagent synthesis. To show the potent application of the obtained bromides, transformation of **3n** has been carried out (Scheme 4). Treatment of compound **3n** with $BnNH_2$ and EDCI gave chiral amide **6** in 59% yield.

On the basis of our results and previous studies [11,12], a plausible mechanism has been proposed as shown in Scheme 5. Nucleophilic attack of DMSO to ethyl bromoisobutyrate **2** would lead to the formation of intermediate A, which would then react with bromine ion to give intermediate B. Molecular bromine can be generated by attack of bromine ion to intermediate B. Bromination of **1a** can be finally realized by electrophilic addition of molecular bromine with trimethoxybenzene **3a** and rearomatization. Ethyl 2-hydroxy-2-methylpropanoate can be observed by crude ^{1}H NMR, providing evidence for our proposal on reaction mechanism. The role of DABCO might be to facilitate the proton transfer in this process and to neutralize the reaction system preventing further side reactions of product **3** [15].



Scheme 4. Synthesis of compound 6.



Scheme 5. Proposed mechanism.

In conclusion, we have developed an efficient bromination of phenyl ethers with bromoisobutyrate and dimethyl sulfoxide as brominating reagent. To the best of our knowledge, it is the first time that bromoisobutyrate has been used as a general brominating source for the bromination of a diverse of simple electron-rich aromatic ethers. The current reaction system could also be expanded to bromination of other aromatics such as phenol and unactivated arene. In this process, DMSO acts as the solvent as well as activator of bromoisobutyrate and an oxidant. This process can be regarded as an alternative way for the well-developed bromination systems of arenes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153375.

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[14] The use of less amount of ethyl bromoisobutyrate 2 (2.5 equiv) gave descreased yield (45%, 2 h).
[15] Dramatically decreased yield (31%, 35 min) was obtained in the absence of DABCO. While the use of DIPEA (1 equiv, 45 min) instead of DABCO afforded 54% yield.