Green Chemistry

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c5gc00528k

Received 9th March 2015,
Accepted 14th April 2015

DOI: 10.1039/c5gc00528k

www.rsc.org/greenchem

Efficient bromination of olefins, alkynes, and ketones with dimethyl sulfoxide and hydrobromic acid†

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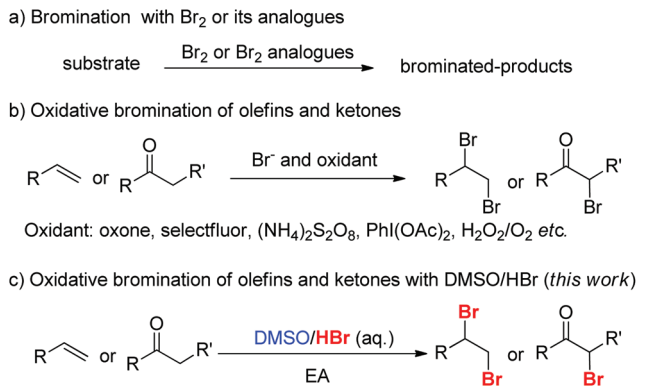
The oxidative bromination of olefins, alkynes, and ketones has been developed with HBr as the brominating reagent and DMSO as the mild oxidant. The simple conditions, high bromide-atom-economy, as well as easy accessibility and low cost of DMSO and HBr make the present strategy prospective for the synthesis of dibrominated alkanes, dibrominated alkenes and α-bromoketones.

It is difficult to imagine synthesis without organobromides,[1] which are conventionally prepared by bromination protocols using hazardous, toxic, and corrosive molecular bromine (Scheme 1a). In order to avoid the use of bromine, some modified brominating reagents (for example, NBS and ammonium tribromides) have been developed.[2] However, these reagents produce large quantities of organic wastes and employ bromine for their preparations. Interestingly, the enzyme-catalyzed oxidative halogenations are special and efficient processes in nature.[3] Inspired by these transformations in nature, a sophisticated approach, which consists of generating the brominating reagent *in situ* from a bromide salt, was adopted for the preparation of organobromides. So far, many oxidants such as oxone, $NaIO_4$, Selectfluor, and $PhI(OAc)_2$, O_2, H_2O_2, *etc*. have been developed for the oxidative bromination.[4,5]

Olefins and ketones are useful precursors for investigating the nature of active halogenating agents and have been used frequently in oxidative brominations. Importantly, dibrominated alkanes[1] and α-bromoketones[6] are privileged motifs in organic synthesis. In 2008, Eissen and Lenoir[7] concluded 24 brominations of olefins, and pointed out that most of these reactions suffer from low atom economy, higher waste production or higher cost compared to the bromination with Br_2 (Schemes 1a and b).[5] Therefore, the development of new efficient approaches for bromination of olefins as well as other substrates was highly desirable.

Recently, some new strategies for oxidative bromination have been developed.[8] For example, Iskra and coworkers reported an efficient and green oxidative bromination of ketones[8a] and olefins[8b] using O_2 and H_2O_2 as the green oxidants. Gao and coworkers realized the bromination of olefins with oxone promoted by mechanical milling.[8c] Mizuno realized the vanadium-catalyzed bromination of unsaturated compounds.[8d]

Dimethyl sulfoxide (DMSO), one of the most used aprotic polar solvents, is primarily utilized as an efficient reagent for the oxidation of alcohols,[9] and is widely used as an oxygen,[10] carbon,[11] or sulfur source[12] in organic synthesis. Moreover, DMSO also participates in the oxidative brominations as the mild oxidant when combined with HBr.[13] The groups of Majetich[13a] and Dai[13b] reported the bromination of arenes using the DMSO/HBr system. We realized the efficient and practical hydroxybromination of olefins with HBr in DMSO recently in which DMSO showed its versatile role as a solvent, an essential oxidant, and also an oxygen source.[14] However, to the best of our knowledge, the efficient oxidative brominations of olefins, alkynes, and ketones with the DMSO/HBr system have not been reported yet.



Scheme 1 The development of DMSO-based oxidative brominations.

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†Electronic supplementary information (ESI) available. See DOI: 10.1039/c5gc00528k

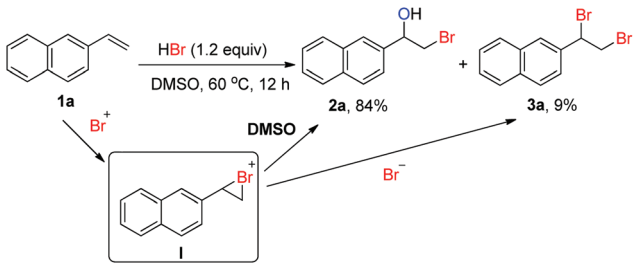
Herein, as our continuous efforts in developing DMSO-based reactions, we report the oxidative bromination of olefins, alkynes, and ketones using DMSO/HBr for the first time (Scheme 1c). The mild conditions, low cost of DMSO and HBr, broad substrate scope make the present strategy extremely attractive and prospective for the efficient and low-cost synthesis of dibrominated alkanes and α-bromoketones.

Our initial study began with the hydroxybromination of 2-vinylnaphthalene **1a**. It was very interesting to find that when the reaction was carried out in the presence of 1.2 equiv. of aqueous HBr in DMSO at 60 °C for 12 h, 9% yield of the dibrominated byproduct **3a** was obtained along with the bromohydrin product **2a**.[14] As intermediate **I** was generated from **1a** and Br^+, we speculated that the dibrominated alkane **3a** could be produced when **I** undergoes nucleophilic attack by Br^-. This preliminary discovery revealed the possibility of dibromination of olefins with simple and readily available DMSO and HBr (Scheme 2).

In order to selectively control the generation of dibromination product **3a**, the DMSO/HBr system was investigated in different solvents instead of using DMSO as the solvent under an air atmosphere at 60 °C (entries 1–6, Table 1). To our delight, the yield of **3a** increased to 75% when **1a** was stirred in EA in the presence of 2.4 equiv. of HBr and 2.6 equiv. of DMSO (entry 2). Only traces of **3a** were obtained in acetone or water as the solvent (entries 5 and 6). The amount of DMSO influenced the yield of **3a** strongly (entries 7–10). The reaction occurred very quickly (0.5 h) in the presence of 1.2 equiv. of DMSO as the oxidant and afforded the highest yield (80%) in this case (entry 9). On increasing the amount of DMSO to 4 equiv. the yield decreased to 61% (entry 10). The reaction of **1a** at 40 °C also worked well leading to **3a** in 68% yield. However, a longer reaction time was required (2 h, entry 11, Table 1).

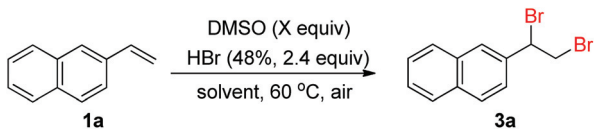
Under the optimum conditions (entry 9, Table 1), a series of styrenes bearing various groups (R = Me, NO_2, Cl, Br, Ph) furnished the dibromination transformation producing the desired dibromoalkanes **3a–i** in good yields (Table 2). The bromination of *o*-, *m*-, *p*-substituted styrenes in which the substituent group showed different steric hindrance afforded the products in similar yields. α-Methyl styrene **1j** was dibrominated smoothly to give **3j** bearing tertiary bromide in 73% yield. The dibromination of (*E*)-β-methyl styrene **1k** produced *anti*-**3k** in 78% yield. For cyclic alkenes, the *trans*-brominated products **3l–n** were highly selectively obtained in 73–85% yields.

It is noteworthy that the dibromination of aliphatic olefins also worked well (**3o–v**, Table 2). The mono- (**1o–q**), di- (**1r–u**), and even tri-substituted (**1v**) olefins furnished the corresponding products **3o–v** in high yields (81–94%, Table 2). On exposure of the aliphatic cyclic olefins to the optimum con-



Scheme 2 The observation of oxidative dibromination of olefins.

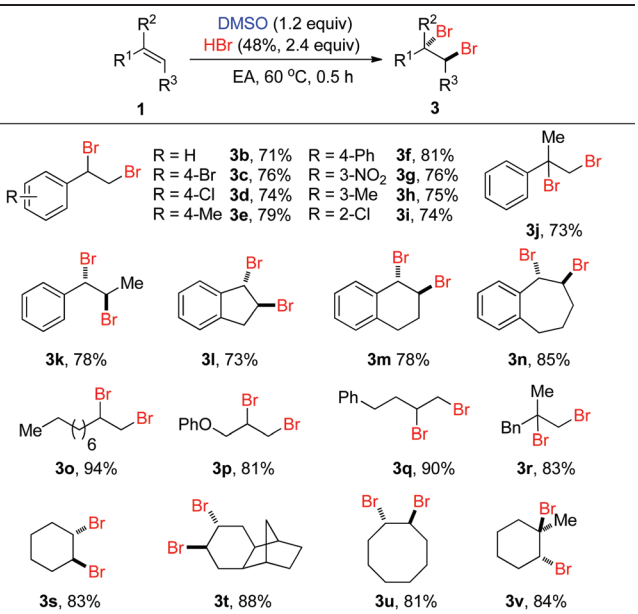
Table 1 Optimization of the reaction conditions[a]



Entry	Solvent	*X*	Time	Yield[b] of **3a** (%)
1	$CHCl_3$	2.6	1 h	62
2	EA	2.6	1 h	75
3	Toluene	2.6	1 h	65
4	MeCN	2.6	1 h	44
5	Acetone	2.6	10 h	Trace
6	H_2O	2.6	10 h	Trace
7	EA	0	10 h	27
8	EA	0.5	10 h	48
9	**EA**	**1.2**	**0.5 h**	**80**
10	EA	4	1 h	61
11[c]	EA	1.2	2 h	78

[a] Reaction conditions: a solution of **1a** (0.5 mmol), HBr (1.2 mmol), and DMSO in a solvent (2 mL) was stirred at 60 °C under an air atmosphere. [b] Isolated yields. [c] The reaction was carried out at 40 °C.

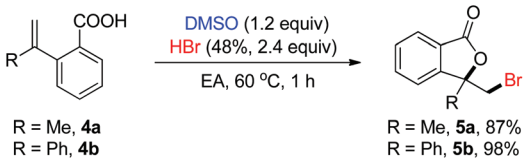
Table 2 Substrate scope of olefins[a]



[a] Reaction conditions: HBr (48%, 1.2 mmol) was added to a solution of olefin **1** (0.5 mmol) and DMSO (0.6 mmol) in EA (2 mL) at 60 °C. The solution was stirred at 60 °C for 0.5 h under an air atmosphere. Isolated yields.

ditions, *trans*-bromoalkanes (**3s–v**) were highly selectively produced.

Remarkably, the reactions of alkenes **4a–b** bearing the *ortho*-carboxy group gave the bromolactonization products **5** in high yields in this efficient DMSO/HBr system at 60 °C (eqn (1)). Compared to the previous reports on bromolactonization using NBS or its analogues,[15] our DMSO/HBr system features low cost and high atom economy.

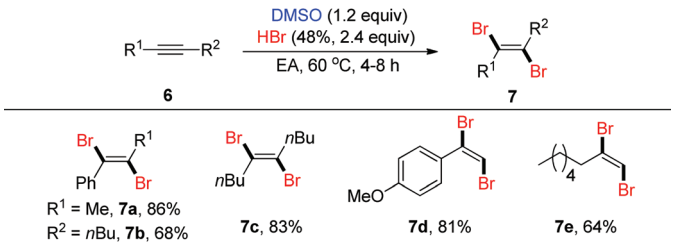


(1)

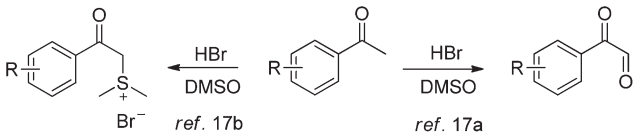
Inspired by these results, the bromination of alkynes was also investigated by employing this efficient DMSO/HBr system to try the efficient synthesis of dibromoolefin. It is very interesting that when alkyne **6a** was exposed to HBr and DMSO in EA at 60 °C, (*E*)-dibromoolefin **7a** was obtained as the only product in 86% yield (Table 3), which demonstrated that the present DMSO/HBr system could be successfully employed in the dibromination of alkynes. Dibutyl substituted acetylene **6c** was dibrominated in 83% yield. Besides internal alkynes, the bromination of terminal alkynes such as phenylacetylene (**6d**) and octyne (**6e**) afforded *trans*-brominated olefins in good yields.

Encouraged by the successful application of the DMSO/HBr system in bromination of olefins and alkynes, we further expanded the present system in oxidative bromination of ketones. Up to now, various oxidative systems[16] including HBr/H_2O_2,[8a] NaBr/$NaBrO_3$,[16b] $CuBr_2$,[16c] TMSBr/KNO_3,[16d] NH_4Br/oxone,[16e] and HBr/TBHP[16f] have been used in oxidative bromination of ketones. Although the reactions between ketone and DMSO/HBr have been reported,[17] unfortunately phenylglyoxals[17a] and dimethyl aryl acylsulfonium bromides[17b] instead of α-bromoketones were obtained (Scheme 3). The mechanism showed that α-bromoketone, which was generated from ketones and DMSO/HBr, was converted to other products because of the excess amount of DMSO or aqueous HBr.

Table 3 Substrate scope of alkynes[a]

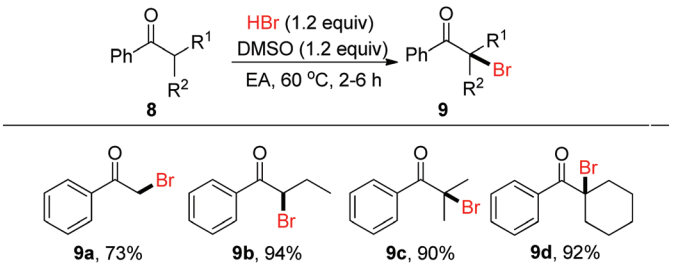


[a] Reaction conditions: HBr (48%, 1.2 mmol) was added to a solution of alkyne **6** (0.5 mmol) and DMSO (0.6 mmol) in EA (2 mL) at 60 °C. The solution was stirred at 60 °C under an air atmosphere. Isolated yields.



Scheme 3 Previously reported reactions of ketones with the DMSO/HBr system.

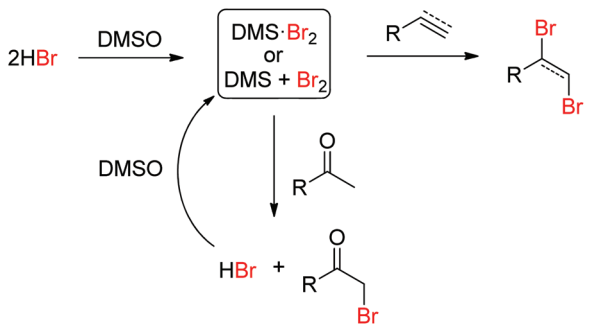
Table 4 Substrate scope of ketones[a]



[a] Reaction conditions: a solution of **8** (0.5 mmol) and aqueous hydrobromic acid (48%, 0.6 mmol) in EA (2 mL) was stirred under air at 60 °C for 2–6 hours. Isolated yields.

We hypothesized that the α-bromoketone might be obtained if the present DMSO/HBr system (in which DMSO was used in a stoichiometric amount) was employed instead of using DMSO as the solvent in the reported literature[17] (Scheme 3). To our delight, when acetophenone **8a** reacted with 1.2 equiv. of HBr and DMSO in EA at 60 °C, α-bromoacetophenone **9a** was obtained in 73% yield (Table 4). Besides methyl ketones, propyl, isopropyl, and cyclohexyl substituted ketones were smoothly monobrominated to bromoketones in high yields (90–94%, Table 4) in the presence of 1.2 equiv. of DMSO and HBr. The present approach provides efficient and simple access to α-bromoketones.

On the basis of the previous reports,[14,17,18] we proposed the mechanism of DMSO-based oxidative brominations (Scheme 4). Initially, HBr was oxidized with stoichiometric DMSO to Br_2 or DMS·Br_2 in EA. The Br_2 or DMS·Br_2 enabled



Scheme 4 Proposed mechanism.

the dibromination of alkenes smoothly to produce dibrominated alkanes. The reaction of Br_2 or DMS·Br_2 with a ketone afforded the bromoketone with the formation of HBr which was oxidized by DMSO for the next oxidative cycle.

Conclusions

In conclusion, we have developed a novel and efficient approach for the dibromination of olefins, dibromination of alkynes and bromination of ketones by using the simple DMSO/HBr system. This chemistry is appreciable due to the safety, the simplicity, the availability, and the cheapness of the DMSO and HBr reagents, and it also provides an alternative approach to the dibrominated alkanes, dibrominated alkenes, bromolactones and α-bromoketones, which are very important reagents and have been widely used in organic synthesis. The simple conditions made the present protocol very attractive and prospective. Studies on further applications of this protocol and the use of DMSO as an oxidant are ongoing in our laboratory.

Acknowledgements

Financial support from the National Basic Research Program of China (973 Program) (grant No. 2015CB856600), the National Natural Science Foundation of China (no. 21325206, 21172006) and the National Young Top-notch Talent Support Program is greatly appreciated. We thank Xiang Sun in this group for reproducing the results of **4e** and **5e**.

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