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DMSO-triggered complete oxygen transfer leading to accelerated aqueous hydrolysis of organohalides under mild conditions

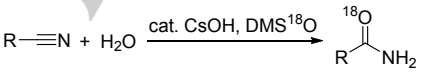
Haicheng Liu,[a] Jianping Liu,*[a] Xiaokai Cheng,[a] Xiaojuan Jia,[a] Lei Yu[b] and Qing Xu*[a,b]

Abstract: Addition of DMSO is capable of accelerating the aqueous hydrolysis of organohalides to alcohols greatly, providing a neutral, more efficient, milder and more economic new process. Mechanistic studies using ^{18}O-DMSO and ^{18}O-H_2O showed that, contrary to the opinion that DMSO works as a dipolar solvent to enhance water's nucleophilicity, DMSO's accelerating effect comes from a complete oxygen transfer from DMSO to organohalides through generation of $ROS^+Me_2{\cdot}X^-$ salts via C-O bonding, followed by O-S bond disassociated hydrolysis of $ROS^+Me_2{\cdot}X^-$ with water. This method is applicable to a wide range of organohalides and thus may be of potential practical industrial applications due to easy recovery of DMSO from H_2O/DMSO mixture by usual vacuum rectification.

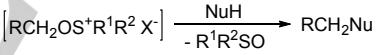
Alcohols are a class of cheaper, less toxic, less odor, and more stable chemical easier to store and treat than many other compounds.[1] Hence they are not only useful chemicals abundantly used in various fields, they are also a class of greener compounds intensively used in synthesis.[1] Among the methods for alcohol preparation, hydrolysis or hydroxylation of organohalides, the redox neutral substitution of a halogen by a hydroxyl derived either from water or other O-nucleophiles, is one of the major ways since many organohalides are industrially manufactured through Friedal-Crafts chloromethylation of aromatic compounds.[2] Also known as the hydrolytic dehalogenation reaction, hydrolysis of organohalides is also a significant biological process in the nature due to the occurrence of numerous naturally-halogenated compounds.[3] Therefore, organohalide hydrolysis to alcohols is always a significant functional group transformation in synthetic and biological chemistry.[2-12] However, due to the weak nucleophilicity of water, hydrolysis of organohalides was conventionally accomplished with the more nucleophilic hydroxy anion generated under basic conditions employing alkali or alkali-earth bases.[2] Limitations of the method are thus obvious. Firstly, it is unsuitable for base-sensitive functional groups. Secondly, generation of alkene byproducts with secondary and tertiary halides due to competing elimination side reactions and generation of ether byproducts by coupling side reactions are also inevitable. Therefore, alternative reagents or modified conditions were attempted to overcome these disadvantages. Two step methods via the formation of formate or acetate esters,[4] transition metal-catalyzed or -assisted methods,[5] phase transfer-catalyzed methods,[6] direct oxidation of organohalides by peracids[7] or oxidation of organometal intermediates[8] were later developed. Moreover, microwave irraddiation-,[9] ionic liquid-[10] or dipolar aprotic solvents[11]-facilitated methods, and even the currently-popular photocatalytic methods[12] have also been developed more lately.

In a previous study, we found dimethylsulfinyl anion generated from DMSO and CsOH could add to nitriles to furnish a CsOH/DMSO-catalyzed mild, efficient, and controllable nitrile hydration reaction involving a DMSO-participated oxygen transfer mechanism (Scheme 1A).[13a] Since, as documented in the literature, DMSO is also a good O-nucleophile[13] and alkoxysulfonium salts $ROS^+R^1R^2{\cdot}X^-$ generated in different ways could react with some nucleophlies to afford substitution products (Scheme 1B),[14] we hypothesize that DMSO may also react with the electrophilic organohalides to give $ROS^+Me_2{\cdot}X^-$ intermediates and further react with H_2O or OH^-, consequently facilitating the hydrolysis reaction (Scheme 1C). However, to our knowledge, similar reactions of organohalides and DMSO known in the literature is only the Kornblum oxidation, in which Me_2S is eliminated from $ROS^+Me_2{\cdot}X^-$ in the presence of a base to afford oxidized carbonyl products (Scheme 1D).[15] To our surprise, a redox neutral substitution of water and $ROS^+Me_2{\cdot}X^-$ generated from RX and DMSO (Scheme 1C) was not known yet.[16]

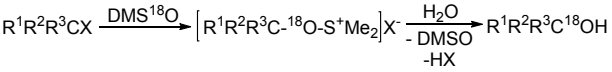
A) Previous work: CsOH/DMSO-catalyzed nitrile hydration with O-transfer[13a]



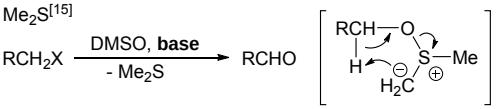
B) Substitution reactions of alkoxysulfonium salts with nucleophiles[14]



C) This work: DMSO-accelerated neutral hydrolysis with complete O-transfer from DMSO to organohalides



D) Kornblum oxidation of organohalides by DMSO by basic elimination of Me_2S[15]



Scheme 1. Reactions based on DMSO or alkoxysulfonium salts.

With the curiosity whether DMSO can facilitate the organohalide hydrolysis reaction and an intention to develop a more sustainable method, we initiated the study by investigating the reaction of benzyl bromide (**1a**) under neutral condition (Table 1). As shown in entry 1, in a blank reaction at a mild temperature of 50 °C without DMSO and base, hydrolysis of **1a** in pure water proceeded sluggishly. Only a low conversion of **1a** and a low yield of the target benzyl alcohol (**2a**) was observed in 24 h. The reaction generated small amounts of byproducts benzaldehyde (**3a**) and dibenzyl ether (**4a**) as well.[17] Under similar conditions, when mixed H_2O/DMSO solvent with DMSO ratio gradually increased were used (entries 2-6),[18] both conversions of **1a** and yields of **2a** were enhanced greatly, clearly demonstrating the accelerating effect of DMSO on the reaction. H_2O/DMSO mixture with a ratio 1/2 was found the best (entry 6), with which the reaction was almost complete to give **2a**

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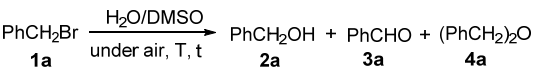
in the highest selectivity (94%) and yield (93% GC yield and 83% isolated yield). However, with even higher ratios of DMSO (entry 7), the yield of **2a** began to drop. Similar to the reaction in pure water (entry 1), the one in pure DMSO was also ineffective (entry 8), which may be explained by slow hydrolysis of the $PhCH_2OS^+Me_2 \cdot Br^-$ intermediate due to lack of water in dry DMSO (*vide infra*). However, this result (entry 8) suggests that organohalides can directly react with DMSO through an interesting mechanism (*vide infra*).

Table 1. Condition screening for DMSO-facilitated hydrolysis of $PhCH_2Br$.[a]

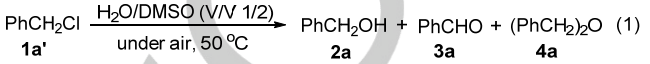


entry	V_{H2O} / V_{DMSO}	*T, t*	**1a%** (**2a**/**3a**/**4a**)[b]	**2a**%[c]
1	100/0	50 °C, 24 h	42 (93/2/5)	39
2	7/1	50 °C, 24 h	66 (82/2/16)	54
3	4/1	50 °C, 24 h	87 (91/1/8)	79
4	2/1	50 °C, 24 h	98 (85/1/14)	83
5	1/1	50 °C, 24 h	98 (85/1/14)	83
6	***1/2***	***50 °C, 24 h***	***99 (94/1/5)***	***93 (83)***
7	1/4	50 °C, 24 h	97 (88/4/8)	85
8	0/100	50 °C, 24 h	47 (68/13/19)	32
9	1/2	30 °C, 24 h	62 (98/1/1)	61
10	1/2	80 °C, 24 h	98 (51/21/28)	50
11[d]	1/2	50 °C, 24 h	100 (37/1/62)	37
12[e]	1/2	50 °C, 24 h	96 (88/2/10)	84

[a] Unless otherwise noted, the solution of **1a** (1.0 mmol) in mixed H_2O/DMSO solvent (0.5 mL, commercial extra dry DMSO) was sealed under air in a 10 mL Schlenk tube and then heated and monitored by TLC/GC-MS. [b] Conversion of **1a** and ratios of **2a**/**3a**/**4a** were determined by GC-MS analysis. [c] GC yields (isolated yields in parenthesis) based on **1a**. [d] 1.0 equiv. of NaOH added. [e] Under N_2.

The reaction was then investigated at higher or lower temperatures (entries 9-10). At 30 °C, although the selectivity for **2a** was still high, the reaction was even more sluggish, giving a lower yield of **2a** (entry 9). At higher temperatures such as 80 °C (entry 10), the yield of **2a** was also lower most likely due to the easier generation of byproducts at high temperatures as indicated by the ratios of **3a** and **4a**. A control reaction with addition of 1 equiv. of base revealed that base is not beneficial for the reaction, leading only to a higher yield of ether byproduct (entry 11). Another control reaction under N_2 also showed that inert atmosphere protection is unnecessary (entry 12). Therefore, the reaction was best carried out in neutral H_2O/DMSO (V/V 1/2) at 50 °C for 24 h. *It should also be noted that DMSO can be easily recovered pure from the H_2O/DMSO mixture by usual vacuum rectification, suggesting that this method may have potential practical applications in industrial scale preparations.*

This method was then tested with the more economic organochlorides. Although hydrolysis of benzyl chloride (**1a'**) was found slower than that of bromide (**1a**) due to its less reactive nature, **2a** could still be produced in a high selectivity of 96% (eq. 1, entry 1). Further condition screening to optimize the reaction by modifying the H_2O/DMSO ratio, reaction temperature, and other parameters showed that prolonged reaction time is more preferable (entry 2),[19] giving **2a** in a high selectivity and a moderate yield.



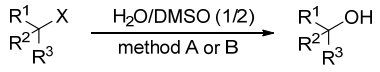
entry	t	**1a'**% (**2a**/**3a**/**4a**)	**2a**%
1)	24 h	57 (96/2/2)	55
2)	48 h	78 (94/3/3)	73 (65)

The above optimized conditions were then applied to various organohalides (X = Br, Cl, I) to extend the scope of the method (method A). Like **1a**, other substituted benzylic bromides, including electron-rich and -deficient ones and the sterically more bulky *ortho*-substituted ones (entries 7 and 10), all gave good to high yields of the target benzylic alcohols (entries 3-13). This method could also be applied to secondary benzylic bromides, affording the corresponding secondary benzylic alcohols **2m** and **2n** in moderate to good yields (entries 14-15). For cinnamyl bromide, the yield of cinnamyl alcohol **2o** was low under the same conditions (entry 16). Further modification of the conditions to improve the yield of **2o** was not successful, which is most likely due to the reactive nature of **1o** since considerable amounts of byproducts were always observed in the reactions.

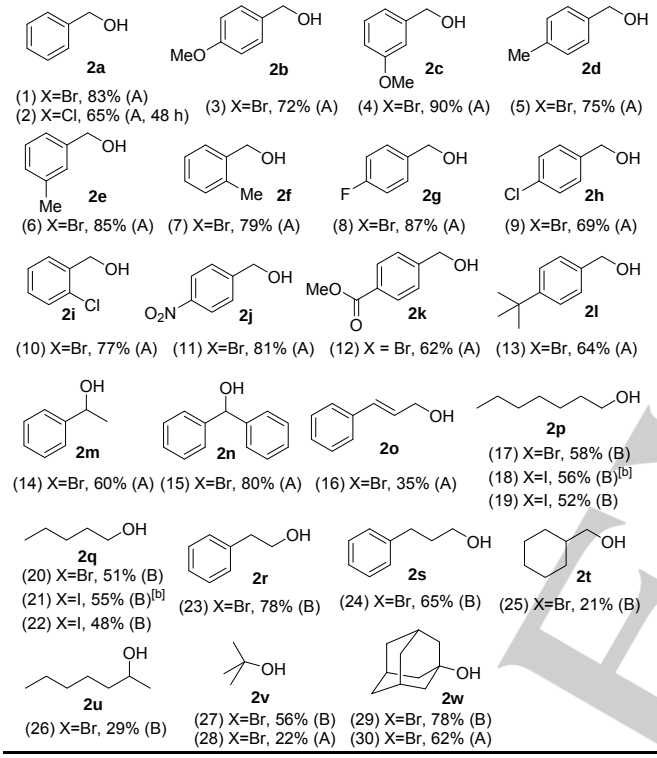
Aliphatic halides were then investigated to further extend the scope of the method. However, only a very low yield of *n*-heptanol was observed in the reaction of *n*-heptyl bromide,[19] which is most likely due to the much lower reactivity of the aliphatic halides than benzylic ones. The conditions were then modified.[19] After a carful evaluation of the reaction conditions, it was found addition of catalytic amounts of Cs_2CO_3 and tetrabutylammoniun iodide (TBAI) can greatly enhance the reaction efficiency (method B) to give a moderate yield of *n*-heptanol (entry 17). Herein Cs_2CO_3 may work as a weak base to enhance the nucleophilicity of O nucleophiles and TBAI as the phase transfer catalyst or halide exchange catalyst for activation of the alkyl bromide. *n*-Heptyl iodide was also investigated, giving a close result (entry 18) with that of the bromide (entry 17). TBAI seemed to be not effective to improve the product yield in the reaction of iodide (entry 19). Similarly, the reactions of *n*-pentyl bromide and iodide gave moderate yields of *n*-pentanol with or without TBAI (entries 20-22). 2-Phenylethyl and 3-phenylpropyl bromides were found more reactive and gave higher yields of the corresponding 2-phenylethanol and 3-phenylpropanol under the same conditions (entries 23-24). In contrast, cyclohexylmethyl bromide and a secondary halide, 2-heptyl bromide, were found less reactive, giving much lower yields of the products (entries 25-26). In contrast to secondary aliphatic halides, the reactions of tertiary halides such as *t*-butyl and adamantyl bromides were more effective and gave higher yields of the corresponding *t*-butyl alcohol and adamantanol

(entries 27 and 29). More surprisingly, these tertiary halides could even be treated under condition A without the use of Cs_2CO_3 and TBAI (entries 28 and 30). In particularly, the reaction of adamantyl bromide under condition A gave a moderate yield of the product (entry 30).

Table 2. Substrate Extension for DMSO-facilitated hydrolysis of organohalides.[a]



1 **2**

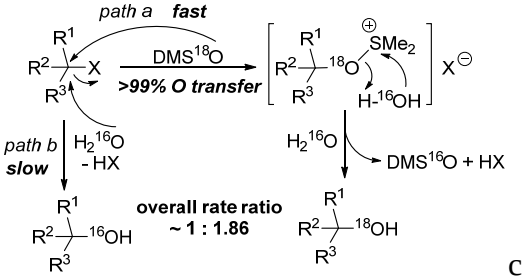


[a] For method A, see entry 6 of Table 1 for detail. Method B:[19] the solution of 1.0 mmol organohalide (**1**) in H_2O/DMSO (0.5 mL, V/V 1/2) was sealed in a 10 mL Schlenk tube under air and then heated at 100 °C for 24 h in the presence of Cs_2CO_3 (20 mol%) and TBAI (20 mol%). All yields are isolated yields based on **1**. [b] Without addition of TBAI.

Although DMSO had been used as a dipolar aprotic solvent to promote organohalide hydrolysis reaction in metal-mediated, photo-catalyzed, and metal-free reactions,[5c,11c,12c] how DMSO facilitated the reactions was limited to the understanding as a dipolar solvent to enhance water's nucleophilicity. Based on our previous findings in nitrile hydration reaction[13a] and those in the condition screening (Table 1, entry 8), we reckon an interesting mechanism may present in the reaction (Scheme 1C).

To probe the reaction mechanism, ^{18}O-labled DMSO was prepared according to the literature procedure[13a,20] and used to react with **1a**. As shown in eq. 2, when **1a** was heated with ^{18}O-DMSO (94% ^{18}O) at 50 °C, 93% ^{18}O-enriched $PhCH_2OH$ (**2a**) could be obtained as determined by HRMS analysis.[19] This result, 99% selectivity for ^{18}O transfer in the reaction,[21] suggests that a complete reaction of DMSO as an O nucleophile and organohalide as an electrophile must have occurred with C-^{18}O bonding and generation of an alkoxysulfonium intermediate $PhCH_2{}^{18}OS^+Me_2{\cdot}Br^-$, followed by >99% ^{18}O-transferred hydrolysis of $PhCH_2{}^{18}OS^+Me_2{\cdot}Br^-$ with normal ^{16}O-H_2O to produce ^{18}O-**2a** and ^{16}O-DMSO. Moreover, 65% ^{16}O-**2a** and 35% ^{18}O-**2a** could be obtained from the reaction of **1a** in mixed ^{16}O-DMSO/^{18}O-H_2O solvent with the same concentration of ^{16}O-DMSO and ^{18}O-H_2O (eq. 3).[19] This suggests a ca. 1.86/1 ratio between the reaction rates of ^{16}O-DMSO with **1a** and ^{18}O-H_2O with **1a**, further implying that DMSO reacts more effectively than H_2O with **1a**. This result also supports the observed complete reaction of $PhCH_2Br$ (**1a**) with ^{18}O-DMSO (eq. 2) as well as the complete O transfer from DMSO to the organohalides.

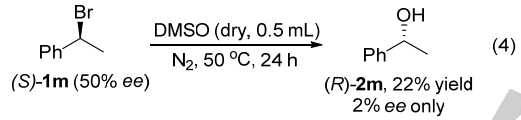
A plausible mechanism was then proposed for the DMSO-accelerated organohalide hydrolysis reaction (Scheme 2). Thus, DMSO may firstly work as an O-nucleophile to attack the organohalide to give an alkoxysulfonium intermediate $R^1R^2R^3C$-$OS^+Me_2{\cdot}X^-$ (path a), which then hydrolyzes with water to produce the target alcohol, regenerate DMSO and release byproduct HX. Differently, in Kornblum oxidation reaction under basic conditions, deprotonation of the Me in $R^1R^2R^3C$-$OS^+Me_2{\cdot}X^-$ by a strong base is the dominant reaction, which finally led to oxidized aldehyde products via an intramolecular cyclic transition state (Scheme 1D). On the other hand, since organohalide could also smoothly undergo a DMSO-free hydrolysis reaction with water (entry 1 of Table 1 and eq. 3), anther path (path b) of direct organohalide hydrolysis with water also exists in the reaction.



Scheme 2. Plausible mechanism for DMSO-facilitated organohalide hydrolysis reaction.

To explore whether this method can be employed to prepare optically active alcohols from the corresponding optically active alkyl halides, stereochemistry of the reaction was considered. According to the mechanisms of nucleophilic substitution reactions well-documented in the text books, with the sterically least hindered primary halides, DMSO may attack the halides from backside *via* a S_N2 mechanism with inversion of configuration at the carbon. Even though, since benzylic cations

are relatively stable compared with usual primary aliphatic cations, the S_N1 mechanism through formation of benzylic cations can still not be excluded completely for the primary benzylic halides. With the sterically most bulky tertiary halides, S_N2 mechanism should be impossible, especially in the case of adamantyl bromide (Table 2, entries 29-30) that cannot allow backside attack of DMSO. Instead, S_N1 mechanism should occur with formation of the stable tertiary carbon cations. Except the adamantyl bromide to which DMSO can only attack from outside and give configuration-reserved intermediates and products, usual tertiary halides should afford racemized intermediates and products via attack of DMSO from both side of the tertiary cations. Although both S_N1 and S_N2 mechanisms may work with secondary halides according to the text book knowledge, it is still unknown which one would dominate the reaction. Therefore, an optically-enriched (*S*)-1-phenylethyl bromide (**1m**)[19,22] was employed to react with DMSO. As shown in eq. 4, when (*S*)-**1m** of 50% *ee* was treated with DMSO under the standard conditions, only a very low *ee* (2%) of the target (*R*)-**2m** was obtained. This result suggests that, on one hand, S_N1 mechanism is the dominant process in the reaction of secondary halides with DMSO that leads to almost complete racemization of the product alcohols; on the other hand, this method is unfortunately not suitable for preparation of optically active alcohols from the corresponding optically active alkyl halides.



(*S*)-**1m** (50% *ee*) (*R*)-**2m**, 22% yield 2% *ee* only (4)

In conclusion, we developed a DMSO-accelerated aqueous hydrolysis of organohalides by adding DMSO as a co-solvent, providing a neutral, more efficient, milder and more economic new process for preparation of alcohols from organohalides. Mechanistic studies using ^{18}O-DMSO and ^{18}O-H_2O revealed that the accelerating effect of DMSO comes from a DMSO-triggered complete oxygen transfer process through O-attack of DMSO at the electrophilic RX and generation of alkoxysulfonium salts $ROS^+Me_2{\cdot}X^-$ with C-O bonding, followed by O-S bond disassociated hydrolysis of $ROS^+Me_2{\cdot}X^-$ with water. This new finding is different to the commonly-held view that DMSO works merely as a dipolar solvent to enhance the nucleophilicity of water in the hydrolysis reaction.[5c,11,12c] This work may thus be a good advance in the field by clarifying the true role of DMSO in the reaction mechanism. Since a wide range of organohalides can be used as the substrate and due to the easy recovery of DMSO from H_2O/DMSO mixture by usual vacuum rectification, this method may be of potential practical applications in industrial synthesis. Further applications of the DMSO-triggered oxygen transfer reaction in other types of organic reactions are underway in this group.

Experimental Section

Typical procedure for DMSO-facilitated neutral hydrolysis of organohalides (method A): The mixture of benzyl bromide (0.12 mL, 1 mmol), extra dry DMSO (0.33 mL), and H_2O (0.17 mL), sealed directly in a 10 mL Schlenk tube under air, was stirred at 50 °C for 24 h, monitored by TLC and/or GC-MS, and purified by thin layer chromatography on silica gel using ethyl acetate and petroleum ether (0~1/10) as the eluent. **2a** was obtained in 83% isolated yield.

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Keywords: alcohols • dimethyl sulfoxide • hydrolysis • organohalides • oxygen transfer

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[16] Different to dehalogenation reactions of organohalides (the Kornblum oxidation[15] and our present work), Jiao and co-workers recently reported an alternative bromine-repositioned reaction of organobromides and DMSO to afford bromohydrins. See ref. 13d.

[17] Small amounts of **3a** and **4a** were very possibly generated via the Kornblum oxidation and the reaction of **1a** with in situ produced **2a**, respectively, under the neutral conditions.

[18] Since usual DMSO may contain certain amounts of water due to its hydrophilic nature, to obtain precise and repeatable results, commercial extra dry DMSO was used.

[19] See the Supporting Information for detail.

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[22] (*S*)-**1m** was prepared according to the literature procedures: a) J. Guo, J. Chen, Z. Lu, *Chem. Commun.* **2015**, *51*, 5725-5727; b) A. López-Pérez, J. Adrio, J. C. Carretero, *Org. Lett*. **2009**, *11*, 5514-5517.

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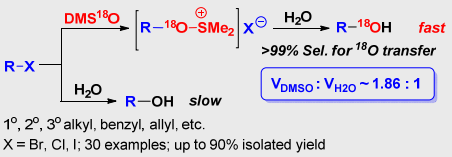

Addition of DMSO is capable of accelerating the aqueous hydrolysis of organohalides to alcohols greatly, providing a neutral, more efficient, milder and more economic new process. Mechanistic studies using ^{18}O-DMSO and ^{18}O-H_2O showed that, contrary to the opinion that DMSO works as a dipolar solvent to enhance water's nucleophilicity, DMSO's accelerating effect comes from a complete oxygen transfer from DMSO to organohalides through generation of $ROS^+Me_2{\cdot}X^-$ salts by C-O bonding, followed by O-S bond disassociated hydrolysis of $ROS^+Me_2{\cdot}X^-$ with water. This method is applicable to a wide range of organohalides and thus may be of potential practical industrial applications due to easy recovery of DMSO from H_2O/DMSO mixture by usual vacuum rectification.

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DMSO-triggered complete oxygen transfer leading to accelerated aqueous hydrolysis of organohalides under mild conditions