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Recent advances in the application of bromodimethylsulfonium bromide (BDMS) in organic synthesis

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This paper is dedicated to my mentor Professor Dr. R.R. Schmidt, Universitaet Konstanz, Germany on the occasion of his 75th birthday

Contents

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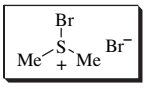
1. Introduction

The exploitation of reagents for developing new synthetic methods is an art and constitutes a challenging process in organic chemistry. Consequentially, considerable efforts have been made over the years to find newer reagents, which can minimize the drawbacks of those presently in use. The bromination of organic substrates is a hot topic in the list of useful transformations in organic synthesis. For this purpose, molecular bromine has been extensively used, although it has several limitations including its volatile, irritating and corrosive nature that make it a less than preferable reagent. Consequently, a large number of brominating reagents have been developed in recent years. Meerwein's discovery[1] of bromodimethylsulfonium bromide (BDMS) in 1965 led to the beginning of halodimethylsulfonium halide chemistry and, subsequently, Corey et al.[2] began using chlorodimethylsulfonium chloride (CDMS). In the early 1980s, Olah et al.[3] first demonstrated BDMS as a unique reagent for organic transformations, which was further explored by Chow and Bakker.[4] To the best of our knowledge, however, its catalytic activity was unexplored prior to our report[5] in 2003. Continuous efforts have been made over the past few years towards the development of new synthetic methodologies using various reagents as well as catalysts. On further study, we realized that BDMS is a potent reagent in organic synthesis. Moreover, BDMS has been explored by us and by other groups as a potentially useful reagent as well as an effective catalyst in organic synthesis. Over recent years, we have witnessed a phenomenal growth in its applications in various organic transformations. The aim of this article is to focus on the applicability of BDMS in organic synthesis, which will provide a better opportunity for the synthetic chemist to further explore its potential.

BDMS can be considered to serve as a convenient storage of molecular bromine, which exhibits both the properties of a brominating reagent as well as an effective catalyst. It acts as a source of bromonium ion by analogy either with hypobromite,[6] *N*-bromosuccinimide,[7] bromoazide[8] or with any other brominating reagents such as organic ammonium tribromides.[9] On preparation, it is easier to handle as compared to hazardous molecular bromine. In addition, BDMS exhibits efficient catalytic properties, which might be due to its ability to generate in situ dry HBr in the reaction medium, and acts as an efficient pre-catalyst for various acid-catalyzed organic transformations. Thus, BDMS plays a dual role as a unique brominating reagent as well as an effective pre-catalyst and offers considerable promise as a potent reagent in current organic chemistry.

2. Preparation of bromodimethylsulfonium bromide

BDMS is a light-orange solid, which can be easily prepared from molecular bromine and dimethyl sulfide.[3] The product obtained from the reaction of dimethyl sulfide and molecular bromine is usually reaction-condition dependent. When prepared at room temperature, it may exist as a charge-transfer form [$Me_2S \rightarrow Br_2$], as evident from a Raman spectroscopic study.[10a] On the other hand, addition of the two reagents at −30 °C provides an orange compound, which might exist in an ionic form, $Me_2S^+BrBr^-$. The structure of the reagent was studied by Vaughan et al. using powder X-ray diffraction.[10b] The ionic form is metastable with respect to the charge-transfer form. On storage for a period of 1 week at room temperature, the metastable form transforms into the charge-transfer form. Moreover, BDMS can also be generated in situ by treating dimethyl sulfoxide with aqueous HBr.[10c]



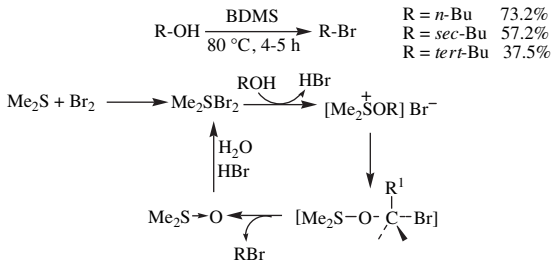
BDMS

3. Bromodimethylsulfonium bromide as a brominating reagent

3.1. Conversion of alcohols into the corresponding bromides

The conversion of alcohols into the corresponding bromides is an important transformation in organic synthesis. The usual methods such as HBr/H_2SO_4[11] or HBr in the presence of Bu_4NBr/Aliquat 336[12] give a mixture of products in the case of secondary alcohols, due to isomerization. Thus, Furukawa et al. first introduced BDMS as an effective reagent for the conversion of alcohols into bromides in high yields.[13] The reaction mainly proceeds through an inversion process, i.e., an optically active alcohol provides the corresponding bromide with inversion of configuration. During the course of the reaction, the generation of DMSO, which might be formed from the decomposition of an intermediate sulfoxonium salt was not detected. This may be due to the regeneration of BDMS from the reaction of DMSO and HBr, as shown in Scheme 1.

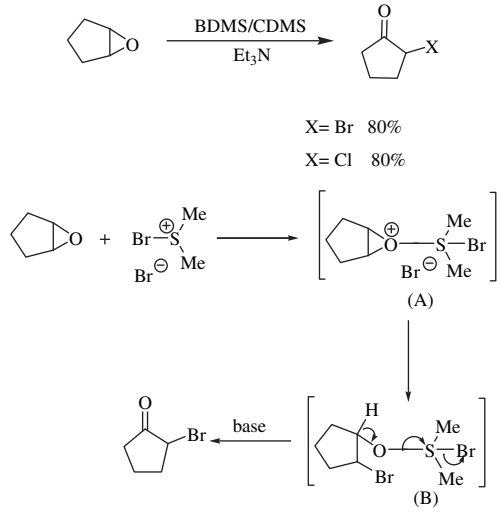
Using this reagent, a wide range of aliphatic alcohols undergo conversion into the corresponding bromides within 4–5 h in fairly good yields. Usually, primary and secondary alcohols provide better yields as compared to tertiary alcohols under these experimental conditions.



Scheme 1.

3.2. Preparation of α-halo ketones

In 1979, Olah et al. extended the scope of halodimethylsulfonium halides to the preparation of α-halo carbonyl compounds from the epoxides and enamines.[14a] These α-halo carbonyl compounds are useful synthetic intermediates for the synthesis of α-aryl ketones.[14b] It was observed that various epoxides were converted into the corresponding α-halo ketones upon treatment with halodimethylsulfonium halides (chlorides/bromides) in the presence of triethylamine (Scheme 2). The reaction proceeds well with alkene oxides and cycloalkene oxides of small ring sizes. In the case of medium- and large-ring-size epoxides, however, transannular rearrangements occurred, giving a mixture of products. The suggested mechanism involves the epoxide oxygen combining with the electrophilic sulfur of BDMS or CDMS to give an intermediate (**A**), which, on ring opening by halide ion, gives a second intermediate **B**, which, in turn, upon treatment with a base provides the corresponding α-halo ketones, as depicted in Scheme 2.



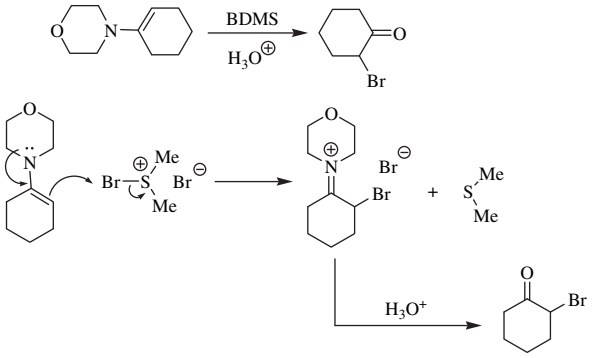
Scheme 2.

Similarly, morpholino enamines of cyclic ketones on treatment with BDMS followed by hydrolysis provide α-bromo ketones, as shown in Scheme 3. The mechanism of this transformation is also illustrated in Scheme 3.

An interesting feature of this reagent can be readily visualized from the last two schemes. In Scheme 2, BDMS is acting as a source of nucleophile (Br^-), whereas, in Scheme 3, it is providing a source of bromonium ion (Br^+). It behaves in a different way, depending upon the nature of the substrate.

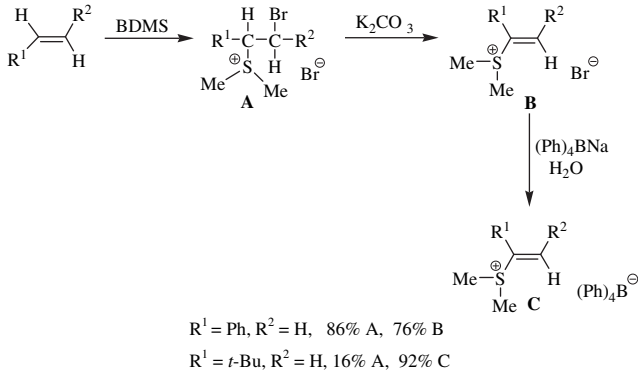
3.3. Preparation of vinylsulfonium bromides

Interestingly, in contrast to molecular bromine, the reagent BDMS provides different products on treatment with alkenes.



Scheme 3.

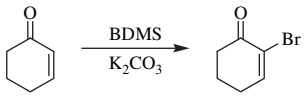
Chow et al. demonstrated that BDMS reacts with various alkenes to provide the corresponding sulfonium bromide addition product **A** instead of the expected dibromide in good yields.[4] The resultant sulfonium bromide on treatment with aqueous potassium carbonate affords dehydrobrominated product **B**, which, on treatment with sodium tetraphenylborate in water, give **C**, as shown in Scheme 4. In an attempt to obtain the sulfonium salt of type **A**, the reaction of 1,2-dibromophenylethane with dimethyl sulfide failed to provide any sulfonium salt. In this reaction, the stereochemical course of the addition gives a trans configuration. Mechanistically, it is proposed that the reaction proceeds via a bromonium ion-initiated electrophilic addition to the olefin followed by a nucleophilic attack of Me_2S. A radical mechanism is rather unlikely, as the reaction neither in the dark nor under oxygen alters the product pattern.



Scheme 4.

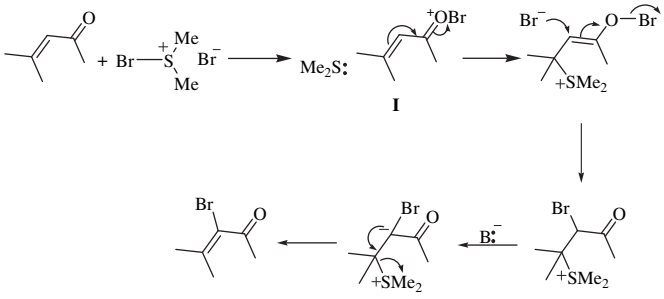
3.4. Preparation of α-bromo enones

The same group (Chow et al.) also found that BDMS can be used for the preparation of α-bromo enones from the corresponding α,β-unsaturated ketones[15] These α-bromo enones are important from a synthetic point of view as they serve as precursors for the synthesis of both natural[16] and un-natural products.[17] Although several methods for the preparation of α-bromo enones involving various reagents such as Br_2/Et_3N[16] or $Br_2/NaHCO_3$,[18] PhSeBr/pyridine,[19] and DMD/NaBr, followed by dehydration,[20] organic ammonium tribromides,[21] etc. have been described in the literature, most of these have some limitations such as the direct use of hazardous molecular bromine or other toxic reagents or expensive catalysts. The reaction of BDMS with conjugated enones at 0 °C gives α-bromo-β-sulfonium carbonyl compounds, which on subsequent treatment with aqueous K_2CO_3 give α-bromo enones in excellent yields, as depicted in Scheme 5.



Scheme 5.

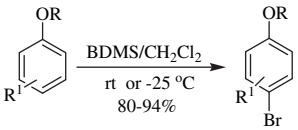
Despite the advantages of BDMS over the direct use of molecular bromine, it also has some limitations such as its ineffectiveness in reacting with maleic anhydride, whereas Br_2 readily reacts in carbon tetrachloride. Mechanistically, it may be conjectured that the addition takes place by bromonium ion-initiated electrophilic addition to the conjugated double bond or dimethyl sulfide-initiated nucleophilic attack at the β-carbon, similar to a Michael-type 1,4-addition. Logistically, the attack of bromonium ion on the double bond of the enone is not likely, due to the electron deficiency in the double bonds of enones. Similarly, dimethyl sulfide attack is a rare occurrence and the possibility is much less. Again, the possibility of a radical mechanism was ruled out, as there was no effect of the presence of air on the pattern of the addition product. Chow et al. proposed that the most preferable mechanistic pathway for this transformation is an electrophilic attack of the bromonium ion at the carbonyl oxygen to give the intermediate **I**. The schematic illustration of the addition of BDMS to an enone is shown in Scheme 6.



Scheme 6.

3.5. Regioselective *para*-halogenation

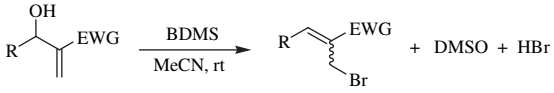
The regioselective halogenation of activated aromatics is one of the most widely used aromatic electrophilic substitution reactions in organic synthesis. Conventionally, it gives a mixture of products, i.e., *ortho*/*para* and the *ortho* isomer frequently exceeds the *para*. As a consequence, isolation of selectively *para*-halogenated aromatics is an enduring challenge in organic synthesis. Interestingly, BDMS as well as its chloro analogue was found to be an efficient regioselective halogenating agent for electron-rich aromatics such as phenols, anisole, diphenyl ether and *N*-alkyl anilines,[22] as shown in Scheme 7. The observed high *para* selectivity is a consequence of the transfer of halogens going through a 'late' arenium ion-like transition state and of the bulky nature of the halogenating agents. However, BDMS fails to halogenate *para*-substituted activated aromatics.



Scheme 7.

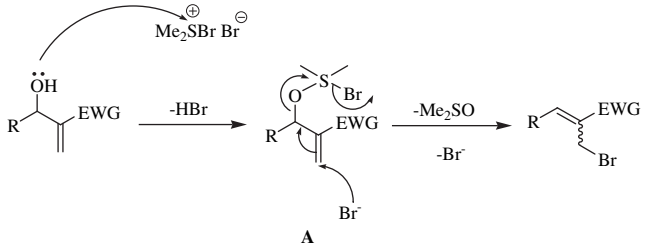
3.6. Preparation of *Z*- and *E*-allyl bromides from Baylis–Hillmann adducts

Das et al. have reported the virtue of BDMS for the preparation of stereoselective (*Z*)- and (*E*)-allyl bromides from the Baylis–Hillman adducts in MeCN (Scheme 8).[23] The allyl halides prepared from the reaction of Baylis–Hillmann adducts are used for the synthesis of various natural and biologically active molecules and their analogues such as α-methylidene-γ-butyrolactones,[24a] α-alkylidene-β-lactams[24b] and flavonoids.[24c] Conventionally, this transformation is achieved by using different halogen-containing reagents including strong acids such as HBr/H_2SO_4.[24a] Interestingly, BDMS was found to be a superior reagent for this transformation, providing 83–99% yields from different Baylis–Hillmann adducts containing COOMe, COOEt and CN functional groups. The allyl bromides were formed with excellent stereoselectivities. When the electron-withdrawing group (EWG) is an ester moiety such as COOMe or COOEt, the *Z* isomer is the major product, but, in the case of a CN group, the *E* isomer predominates.



Scheme 8.

The probable mechanism is shown in Scheme 9. First, the electron pair of the OH group attacks the S atom of BDMS to form the species **A**, which, on subsequent attack by Br^-, followed by isomerization with concomitant detachment of the C(3)–O bond, gives the desired allyl bromide.



Scheme 9.

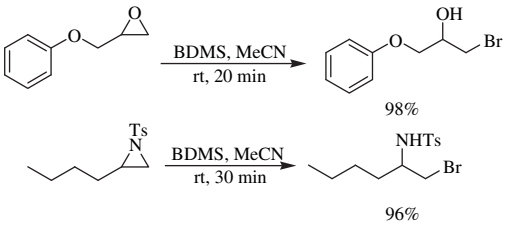
3.7. Preparation of halohydrins and bromo amines by ring opening of epoxides and aziridines

The vicinal halohydrins and haloamines are useful precursors in the synthesis of halogenated marine natural products and other bioactive molecules.[25] The conventional method to prepare these products is by the ring opening of epoxides and aziridines with different reagents. Due to the large number of applications of these products, over the years several methods have been reported in the literature for the ring opening of epoxides, e.g., with halogens,[26] hydrogen halides[27] and metal halides,[28] as well as for the ring opening of aziridines with metal halides.[28b,29] Recently, Das et al. revealed that BDMS can be used for the effective ring opening of epoxides and aziridines at room temperature (Scheme 10).[30] The conversions are highly regioselective and provided excellent yields.

Bicyclic epoxides and aziridines react with BDMS to afford the corresponding halohydrin or haloamine with a trans orientation.

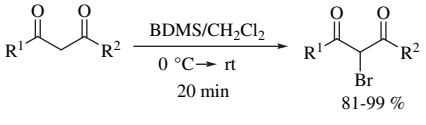
3.8. Regioselective α-bromination of β-keto esters and 1,3-diketones

The regioselective α-bromination of β-keto esters and 1,3-diketones is a useful transformation in organic synthesis.[31] These



Scheme 10.

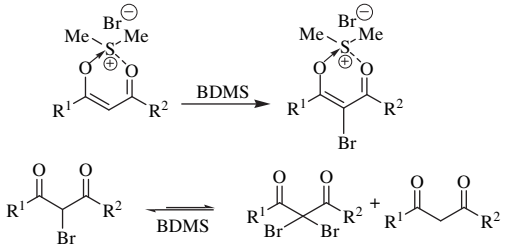
brominated products serve as valuable building blocks for the synthesis of both natural and un-natural products.[32] Conventionally, molecular bromine in combination with a base such as NaH[32a] or Et_3N[33] or NBS/NaH[34] or NBS in combination with various Lewis acids or additives [35] are used to carry out this transformation. The chemoselective α-monobromination of β-keto esters and 1,3-diketones is a challenging task, since some of the monobrominated products are reported to be unstable and undergo disproportionations to dibromo and debrominated products. Recently, we have disclosed the potential of BDMS for the regioselective α-bromination of β-keto esters and 1,3-diketones, as shown in Scheme 11.[36] The probable mechanism is depicted in Scheme 12.



R^1 = Me, Ph, 4-$NO_2C_6H_4$

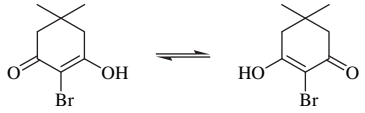
R^2 = OMe, OEt, O^{t}Bu

Scheme 11.



Scheme 12.

Interestingly, dimedone provided exclusively the monobrominated product at room temperature, which is sometimes difficult to achieve by some of the reported methods. The proton attached to the α-brominated carbon atom was not found in the ^{1}H NMR spectrum and, in the IR spectrum, we did not observe any carbonyl peak for this product. From the single-crystal XRD, we have confirmed that, in the solid state, it exists as an enol and exhibits intermolecular hydrogen bonding. In the solution state, it could undergo rapid keto–enol tautomerization, as shown in Scheme 13, for which we do not observe the proton signal for the α-hydrogen associated with the brominated carbon.

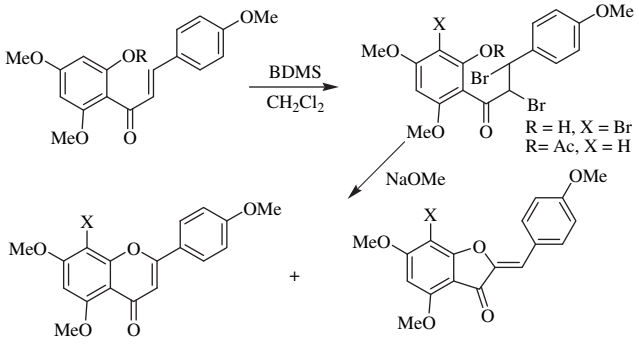


Scheme 13.

The key features of this method are its operational simplicity, high chemoselectivity, excellent yields and mild reaction conditions, as well as the avoidance of column chromatographic separations. A wide range of β-keto esters and 1,3-diketones can be transformed into the monobrominated products within 20–30 min, without any added base or other Lewis acids or additives, using this potent reagent.

3.9. Synthesis of flavones and aurones

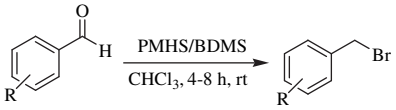
Flavones and aurones are structurally isomeric compounds and are widely distributed in nature.[37a] The syntheses of these compounds have gained considerable attention in recent years, due to their biological activities, as well as their medicinal properties.[37b] Recently, Khan et al. revealed that BDMS is an efficient brominating agent for the bromination of 2′-acetoxy chalcones. These dibromo derivatives can be further cyclized under basic condition for the synthesis of flavones and aurones.[37c] Interestingly, the process is regioselective and provides flavones as the major product. In addition, it is possible to prepare brominated flavones and aurones when the hydroxyl group of the chalcone is free, as shown in Scheme 14.



Scheme 14.

3.10. Synthesis of benzyl bromides from aromatic aldehydes in presence of polymethylhydrosiloxane

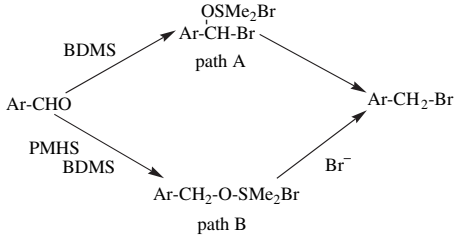
Polymethylhydrosiloxane (PMHS) is an important reducing agent in organic synthesis. BDMS in combination with PMHS was found to be a good combination for the one-pot synthesis of benzyl bromides from the corresponding aromatic aldehydes (Scheme 15).[37d] Interestingly, the author has revealed that, for the reductive bromination of aromatic aldehydes, the combination of PMHS/BDMS was found to be better than the combination of PMHS/NBS.



R = H, Me, OMe, Br, Cl, NO_2

Scheme 15.

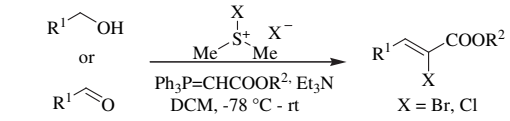
Although the exact mechanistic pathway is not clear, it is believed that the transformation might follow either path A or path B, as shown in Scheme 16.



Scheme 16.

3.11. One-pot synthesis of α-haloacrylates

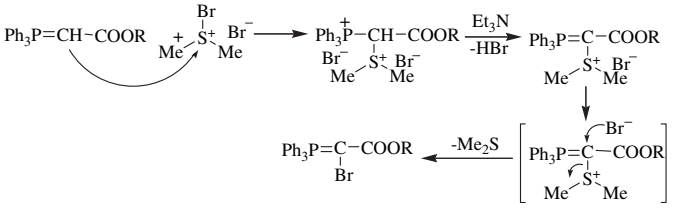
Recently Jiang et al. have disclosed the novel use of BDMS for the one-pot synthesis of α-haloacrylates.[37e] It was found that halodimethylsulfonium halides (BDMS and CDMS) are effective for the one-pot synthesis of α-haloacrylates. It is noteworthy that the conventional method for the preparation of these α-haloacrylates involves the Wittig reaction of an α-halo phosphonium ylide with the corresponding aldehydes. Moreover, the methods for the preparation of the α-halo phosphonium ylide are quite limited and sometimes involve the use of expensive/hazardous brominating reagents or harsh reaction conditions and unavoidable side reactions. Interestingly, BDMS as well as CDMS act as novel reagents in this transformation, as shown in Scheme 17.



R^1 = Ph, 4-$NO_2C_6H_4$, 4-ClC_6H_4, $C_6H_4CH_2CH_2$, 2-naphthyl; R^2 = Me, Et

Scheme 17.

The mechanistic aspect of this transformation is quite interesting. The author has ruled out the Wittig olefination–bromination pathway and has strongly suggested that a rapid in situ α-bromo ylide might be involved in the process, as shown in Scheme 18.



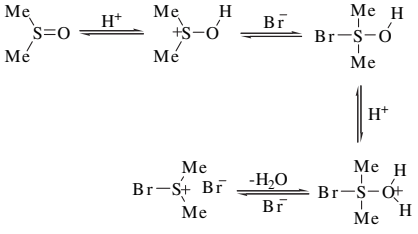
Scheme 18.

The key features of this transformation are that it is one-pot, high yielding and gives high *Z*/*E* ratios.

4. In situ-generated BDMS and its application

As mentioned in the previous section, the reagent BDMS can also be prepared in situ from a combination of aqueous HBr and DMSO. In this section, the application of in situ-generated BDMS will be demonstrated for various organic transformations.

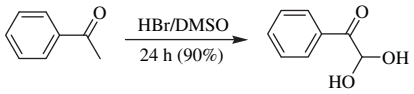
The mechanism shown in Scheme 19 accounts for the formation of BDMS in situ from DMSO and HBr.[38]



Scheme 19.

4.1. Oxidation of acetophenone to glyoxal hydrate by in situ-generated BDMS

Floyd et al.[39] achieved the oxidation of acetophenone into glyoxal hydrate using BDMS, generated in situ from aqueous hydrobromic acid in DMSO, as shown in Scheme 20. This method is a novel route for the functionalization of acetophenones. In this oxidation, electrophilic aromatic bromination was observed as a side reaction along with the desired conversion.



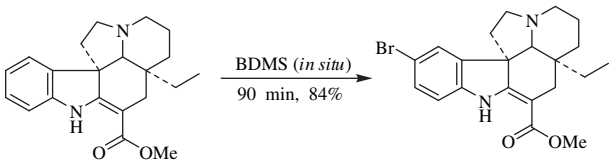
Scheme 20.

4.2. Aromatic ring bromination by in situ BDMS

Interestingly, Fletcher and Pan reported the bromination of aromatic amines[40] with concomitant amino alkylation using a combination of ethyl bromide and DMSO, as depicted in Scheme 21.

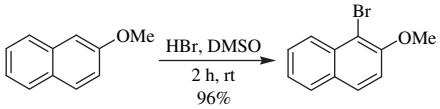
Scheme 21.

Similarly, Megyeri and Keve found that indole alkaloids could also be brominated using BDMS (Scheme 22).[41]



Scheme 22.

Due to the enormous synthetic utility of bromo-organics, bromination is one of the most important transformations in organic synthesis. In continuation of the use of BDMS in various transformations, Majetich et al. demonstrated that BDMS generated in situ by treating DMSO with aqueous HBr is a milder and a more selective reagent for electrophilic aromatic bromination than elemental bromine (Scheme 23).[10c]



Scheme 23.

The effects of other co-solvents for the bromination of 2-methoxynaphthalene with aqueous hydrobromic acid and dimethyl sulfoxide are summarized in Table 1.

Table 1
Effects of different solvents for the bromination of 2-methoxynaphthalene with aqueous HBr

Solvent	Reaction conditions	Yield (%)	Reaction completion
DMSO	2 h (rt)	96	Complete
Acetonitrile	32 h (rt)	84	Trace unreacted SM[a]
THF	1 h (reflux)	Trace	Only unreacted SM[a]
THF	24 h (reflux)	99	Complete
THF/AcOH (3:1)	2 h (rt)	50	~50% complete
AcOH/DMSO	<5 min	96	Complete

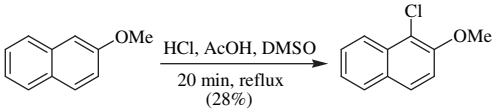
[a] SM=starting material.

Bromination is slow in acetonitrile and very sluggish in THF; only a trace of brominated product was obtained in THF after 1 h in

reflux conditions. The use of acetic acid as a co-solvent, however, greatly enhances the reaction rate. This observation reflects the ionic nature of the electrophilic reagent BDMS, which is better solvated and stabilized in a polar medium.

Activated arenes such as aniline or *N*,*N*-dimethylaniline undergo monobromination without any side products. In contrast, molecular bromine provided benzylic brominated products for substrates such as *o*-cresol. Although BDMS offers a wealth of advantages, it also suffers from some limitations, e.g., acid-sensitive functionalities such as acetals or ketals did not survive under the experimental conditions and deactivated arenes containing electron-withdrawing substituents such as carboxylic acids, halogens, nitro groups, aldehydes and ketones without any α-protons did not react, even under harsh conditions.

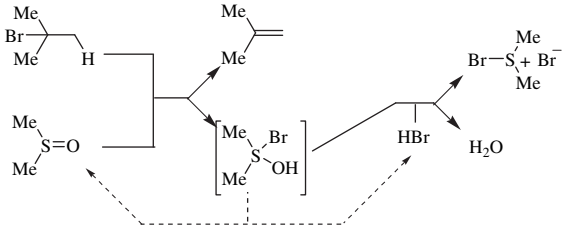
Next, Majetich et al.[10c] treated 2-methoxynaphthalene with aqueous hydrochloric acid along with acetic acid and DMSO (Scheme 24) to see whether aryl chlorides could be prepared by generating CDMS in situ. Unfortunately, chlorination was not observed at room temperature and gave a poor yield of 1-chloro-2-methoxynaphthalene in reflux conditions.



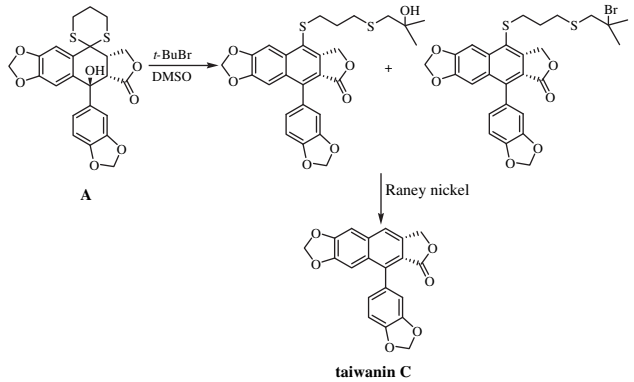
Scheme 24.

4.3. In situ BDMS and its novel application in total synthesis

Harrowven et al. have shown[42] the applicability of in situ-generated BDMS for the total synthesis of a natural product, lignan. According to their probable mechanism, *tert*-butyl bromide reacts with DMSO and generates in situ BDMS, as depicted in Scheme 25. Using this combination, a natural product, taiwanin **C**, can be easily synthesized starting from **A** (Scheme 26).



Scheme 25.

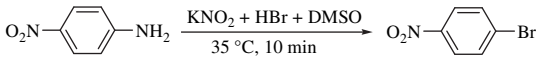


Scheme 26.

The role played by the in situ BDMS generated from *tert*-butyl bromide and dimethyl sulfoxide for initiating the sequential elimination of **A** was crucial to this synthetic programme.

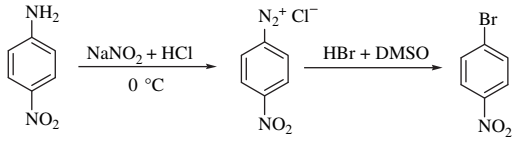
4.4. One-pot transformation of aminoarenes into haloarenes

The halodimethylsulfonium halide, which is readily formed in situ from hydrohalic acid and DMSO, is a good nucleophilic halide. This activated nucleophilic halide rapidly converts aryldiazonium salts prepared in situ using the same hydrohalic acid and nitrite ion into aryl chlorides, bromides or iodides in good yields (Scheme 27).[43] The combined action of KNO_2 and 48% hydrobromic acid in DMSO is required for the direct transformation of aromatic amines into aryl bromides. The molar ratio of HBr, KBr and aromatic amine should be 4:4:1. More than 4 equiv of HBr results in dibrominated products and, with a stoichiometric amount of HBr, the reaction does not proceed to completion and the starting material remains; as a result, the percentage yield becomes low. Solvents like H_2O, DMF, THF, HMPA, hexane and benzene does not give the desired product under the same experimental conditions. DMSO has two roles in this reaction: firstly, it reacts with HBr to form BDMS and, secondly it readily dissolves nitrite ion.



Scheme 27.

To prove that the reaction proceeds via an aryldiazonium salt, Baik et al.[43] prepared the diazonium salt by the general method using $NaNO_2$ and HCl and treated the product with a mixed solution of HBr and DMSO, as shown in Scheme 28, to obtain *p*-bromonitrobenzene.



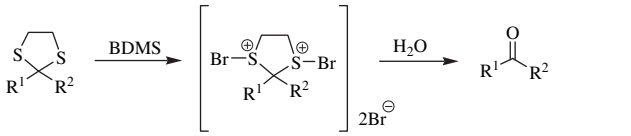
Scheme 28.

Substituted compounds with electron-donating or -withdrawing groups or sterically hindered aromatic amines were smoothly transformed into the corresponding aromatic halides. These workers also carried out the reaction with copper halide. It is worthy of note that the addition of 0.2 equiv of CuBr increased the yield and reduced the reaction time.

5. Application of BDMS in protection, deprotection chemistry

5.1. Deprotection of dithioacetals

The importance of dithioacetals as a protecting group for carbonyl compounds is well recognized in the literature.[44a] Several methods have been developed for the deprotection of dithioacetals to the parent carbonyl compounds. The deprotection of dithioacetals is generally carried out using the heavy metal salt $HgCl_2$.[44b] Due to its toxicity as well as the environmental concerns, the use of $HgCl_2$ is not recommended in modern chemistry. Therefore, Olah et al. replaced the conventional reagent by BDMS for the cleavage of dithioacetals into their corresponding carbonyl compounds.[44c] Two equivalents of BDMS reacts with 1 mmol of the dithioacetals under reflux conditions in dichloromethane, followed by hydrolysis to regenerate the parent carbonyl compounds. BDMS is considered as a storage agent of bromonium ion, and thus the 'soft' electrophile Br^+ can combine with the 'soft' sulfur atoms of the dithioacetals to give a bis-sulfonium ion intermediate (**A**), which can be finally hydrolyzed to regenerate the parent carbonyl compounds, as shown in Scheme 29.



A

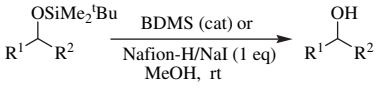
R^1 = *n*-Bu, R^2 = Me 65%
R^1 = Ph, R^2 = H 75%

Scheme 29.

This protocol is equally applicable to both dithioacetals of aliphatic and aromatic aldehydes and ketones. It is gratifying to note that, in contrast to this protocol, molecular bromine in a strongly acidic medium provided moderate-to-poor yields for the same transformation. Aromatic ring bromination does not take place under these experimental conditions.

5.2. Deprotection of *tert*-butyldimethylsilyl ethers

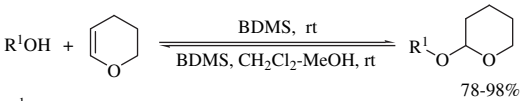
tert-Butyldimethylsilyl is one of the most popular protecting groups for alcohols (forming the trialkylsilyl ethers), because of its stability under varying reaction conditions. Conventionally, tetrabutylammonium fluoride (TBAF) is used as a convenient reagent for the deprotection of *tert*-butyldimethylsilyl ethers.[45] Vankar et al. reported that catalytic amounts of BDMS, or Nafion-H along with NaI (1 equiv) in methanol cleave a variety of *tert*-butyldimethylsilyl ethers readily in high yields (Scheme 30).[46] Chemoselectively, alkyl *tert*-butyldimethylsilyl ethers can be cleaved in the presence of phenolic *tert*-butyldimethylsilyl ethers using this protocol.



Scheme 30.

5.3. Tetrahydropyranylation/depyranylation of alcohols and phenols

To the best of our knowledge, the catalytic activity of BDMS for these reactions was unexplored, until we disclosed its application for tetrahydropyranylation and depyranylation.[5] Tetrahydropyranyl (THP) is one of the most useful protecting groups, due to its low cost and stability towards strongly basic reaction conditions. Tetrahydropyranylation has been performed with a variety of reagents or catalysts. In continuation of our efforts to explore new reagents in organic synthesis, we demonstrated that BDMS is an effective catalyst for the protection of hydroxyl compounds as their tetrahydropyranyl ethers and the same reagent is also useful for depyranylation (Scheme 31). This protocol is applicable to a wide range of alcohols and phenols. The notable advantages of this protocol are excellent yields, no aqueous work-up and the process is rapid. Additional advantages of this procedure are the mild reaction conditions, high selectivity, costeffectiveness, no solvent requirement in case of protection and compatibility with the presence of other protecting groups. Mechanistically, it is proposed that the reagent BDMS generates HBr in situ in the presence of alcohol, and the HBr could be the true catalyst for this transformation.

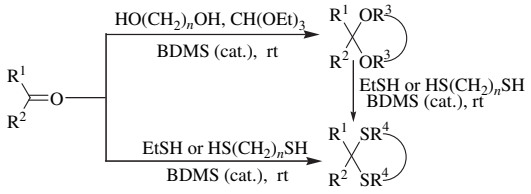


R^1= alkyl, aryl, sugar residue, nucleoside residue

Scheme 31.

5.4. Thioacetalization, acetalization and transthioacetalization

In continuation of our efforts towards the development of new synthetic methodologies using BDMS, we have demonstrated the catalytic activity as well as the effectiveness of this reagent for thioacetalization and acetalization as well as transthioacetalization of carbonyl compounds. A wide variety of carbonyl compounds can be masked in an effective manner in high yields using a catalytic amount of BDMS, as shown in Scheme 32.[47]

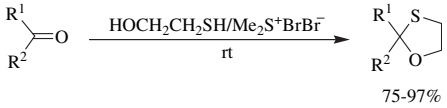


R^1 = aryl/alkyl; R^2 = H/alkyl; R^3 = Me, -$(CH_2)_n$-, n = 2,3
R^1 = aryl/alkyl; R^2 = H/alkyl/aryl; R^4 = Et, -$(CH_2)_n$-, n = 2,3

Scheme 32.

5.5. Oxathioacetalization of carbonyl compounds

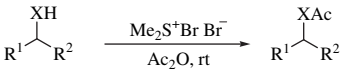
BDMS has also been used as a catalyst for the oxathioacetalization of carbonyl compounds (Scheme 33).[48] A wide variety of aldehydes and ketones can be transformed into the corresponding oxathioacetals in the presence of catalytic amounts of BDMS in high yields. The results obtained using this reagent clearly showed that BDMS is a more efficient and cheaper catalyst than most of the earlier reported catalysts for this transformation. Even a large-scale reaction can also be performed using this protocol and the pure products can be isolated just by distillation of the crude reaction mixture, avoiding any aqueous work-up and column chromatography.



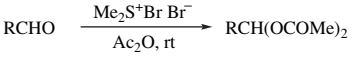
Scheme 33.

5.6. Acylation of alcohols, phenols, amines, thiols and aldehydes

Subsequently, we have also noted[49] that, in the presence of catalytic amounts of BDMS, alcohols, phenols, amines, thiols and thiophenols undergo acylation with a quantitative amount of acetic anhydride under solvent-free conditions at room temperature (Scheme 34). Acylation of both aliphatic and aromatic aldehydes can also be accomplished at room temperature using the same catalyst.



X= O, NH, S
R^1 = alkyl, aryl, sugar residue, nucleoside residue
R^2 = H, alkyl, aryl

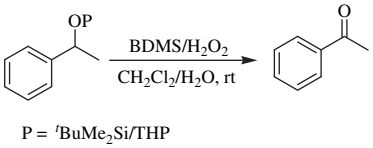


R = alkyl, aryl

Scheme 34.

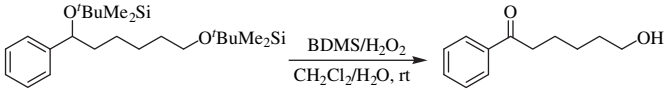
5.7. Oxidative deprotection of *tert*-butyldimethylsilyl and THP ethers to carbonyl compounds

In continuation of our work on the application of BDMS, we have very recently observed that hydrogen peroxide in combination with a catalytic amount of BDMS is an effective combination for the oxidative deprotection of *tert*-butyldimethylsilyl and THP ethers into their corresponding carbonyl compounds (Scheme 35).[50] BDMS exhibits a very important role in this transformation and it is proposed that an in situ-generated bromine radical is responsible for the oxidation involved.



Scheme 35.

An interesting feature of this reagent in this transformation is that it exhibits chemoselectivity, as shown in Scheme 36.

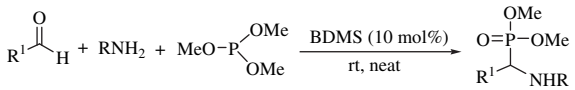


Scheme 36.

6. Catalytic activity of bromodimethylsulfonium bromide

6.1. Synthesis of α-aminophosphonates

Organic phosphonates are biologically potent molecules. In recent years, the syntheses of these molecules have attracted much attention, due to their diverse applications such as inhibitors of synthase,[51] HIV protease[52] and PTPases,[53] and as antibiotics,[54] enzyme inhibitors,[53] and surrogates of α-amino carboxylic acids.[55] α-Aminophosphonates are also important for the synthesis of phosphonopeptides.[56] The usual methods for the synthesis of these compounds are the Kabachnik–Fields method[57] or methods using lanthanide triflates [58] as well as Lewis acid-catalyzed[59] condensation of amines with aldehydes followed by the addition of phosphite to the resulting imine. BDMS was found to be an efficient and effective catalyst for the one-pot synthesis of α-aminophosphonates under solvent-free conditions in good-to-excellent yields (Scheme 37).[60] The method is applicable for aromatic as well as α,β-unsaturated aldehydes and the products are obtained in very good yields. BDMS was found to be more effective than the other acid catalysts such as $ZrCl_4$,[61] $AlCl_3$,[59b] $InCl_3$,[59c] etc. in terms of environmental compatibility, yields, simple work-up and short reaction times.



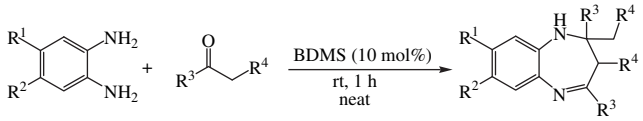
R^1 = 4-$OMeC_6H_4$, R = Ph, 95%

R^1 = 4-MeC_6H_4, R = Ph, 90%

Scheme 37.

6.2. Synthesis of 1,5-benzodiazepines

The synthesis of benzodiazepines has gained considerable attention in recent years, due to their medicinal properties such as analgesic, anti-anxiety, antidepressant and anti-inflammatory agents.[62] BDMS is an efficient catalyst for the solvent-free synthesis of 1,5-benzodiazepines by condensation of *o*-phenylenediamine with enolizable ketones,[63] as shown in Scheme 38. The reaction takes place at room temperature and provides very good yields. It is noteworthy that BDMS exhibits better catalytic activity for this transformation than other catalysts such as $InCl_3$[64] and $CeCl_3 \cdot 7H_2O$.[65] Interestingly, no brominated side products were observed under the experimental conditions.



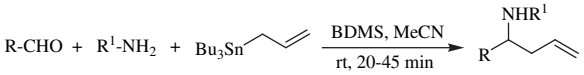
$R^1 = R^2$ = Me, R^3 = Ph, R^4 = H, 86%

R^1 = Me, R^2 = H, R^3 = Me, R^4 = $CHMe_2$, 95%

Scheme 38.

6.3. Synthesis of homoallylic amines

Recently, the reaction of imines with allylorganometallics in the presence of a catalyst has gained considerable attention for the synthesis of homoallylic amines.[66] Various Lewis acids such as $TiCl_4$ or $BF_3 \cdot OEt_2$[67] have been employed for this reaction. Das et al. demonstrated that BDMS catalyzes the multicomponent reaction of aldehydes, amines and allyltributylstannane, affording the corresponding homoallylic amines in excellent yields in a short reaction time[68] (Scheme 39).



R = Ph, R^1 = Ph, 90%; R = Ph, R^1 = 4-ClC_6H_4, 92%

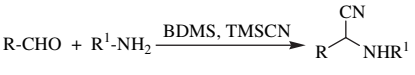
Scheme 39.

In situ imines formed from the reaction of aldehydes and amines in the presence of a catalytic amount of BDMS undergo a facile reaction with allyltributylstannane and provides the homoallylic amines in excellent yields within 20–45 min at room temperature. The key features of this method are its high selectivity for aldehydes, as ketones do not form products under the reaction conditions and the use of acid-sensitive aldehydes such as furfuraldehyde and sterically hindered aldehydes such as 1-naphthaldehyde also provides the corresponding homoallylic amines.

Mechanistically, BDMS catalyzes the conversion with the rapid formation of imines along with its simultaneous transformation into Me_2SO and HBr. The nucleophilic addition of allyltributylstannane to these imines in the presence of HBr followed by subsequent hydrolysis afforded the homoallylic amines. Again, Me_2SO reacts with HBr to regenerate the catalyst BDMS.

6.4. Synthesis of α-amino nitriles

Further, Das et al. reported[69] that BDMS is an effective catalyst for the efficient one-pot synthesis of α-amino nitriles from the three-component condensation of carbonyl compounds, amines and trimethylsilyl (TMS) cyanide, as shown in Scheme 40. The reaction takes place in a short reaction time with high yields.

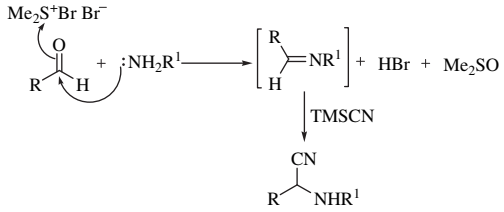


R = Ph, 4-$OMeC_6H_4$ etc.

R^1 = Ph, Me_2CH

Scheme 40.

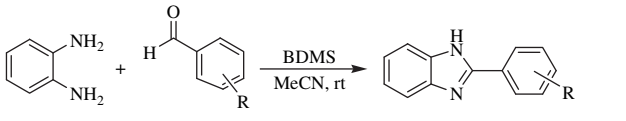
The mechanism of the reaction, which was proposed by Das et al. proceeds via the initial formation of an imine by reaction between an aldehyde and amine in the presence of the catalyst.[69] The imine is subsequently attacked by TMSCN to provide the α-amino nitrile and this step may be catalyzed by in situ-generated HBr (Scheme 41).



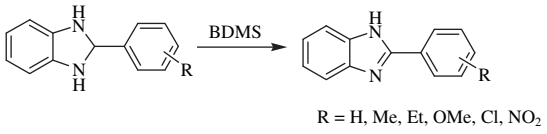
Scheme 41.

6.5. Synthesis of benzimidazoles

The benzimidazole ring is an important pharmacophore in modern drug discovery.[70] Benzimidazole derivatives exhibit significant activity against several viruses such as HIV,[71] influenza[72] and human cytomegalovirus (HCMV).[71a] In addition, benzimidazoles are very important intermediates in organic reactions.[73] Therefore, the preparation of benzimidazoles has gained considerable attention in recent years.[74] Medicinal chemists classify them as 'privileged sub-structures' for drug design. Very recently, Das et al. have reported the BDMS-mediated synthesis of benzimidazoles by the treatment of *o*-phenylenediamine with aldehydes (Scheme 42).[74d] It is believed that the reagent BDMS is responsible for oxidative dehydrogenation of the cyclic intermediate formed from the reaction of *o*-phenylenediamine and aldehydes to achieve the desired benzimidazoles, as shown in Scheme 43.



Scheme 42.



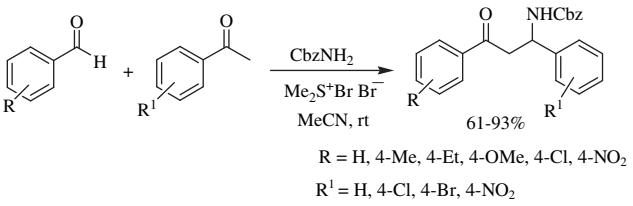
Scheme 43.

Due to its ready accessibility, availability and cost efficiency as well as the highly efficient catalytic activity of BDMS, it has emerged as a versatile reagent in modern organic synthesis.

6.6. One-pot synthesis of β-amino ketones

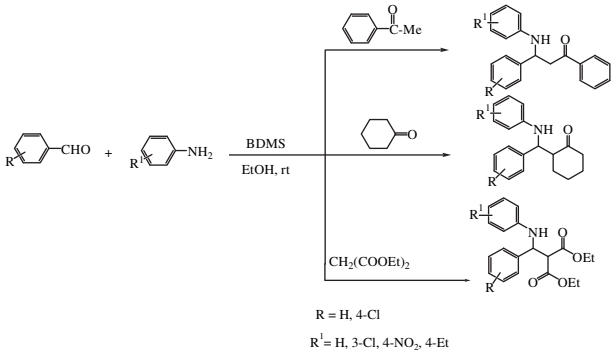
Recently, BDMS has been introduced as a potent catalyst for the one-pot, three-component synthesis of Cbz-protected β-amino ketones from a mixture of aldehydes, ketones and benzyl carbamate, as shown in Scheme 44.[74e]

A wide range of aromatic aldehydes reacts under the given conditions to afford the corresponding protected β-amino ketones. In the case of acetophenone derivatives such as propiophenone, the reaction shows very good-to-excellent diastereoselectivity, yielding the trans isomer as the major product.



Scheme 44.

Consequently, we have demonstrated that BDMS is an effective catalyst for the Mannich-type reactions of a variety of in situ-generated aldimines using aldehydes and anilines, with enolizable ketones or diethyl malonate, in a three-component reaction to afford the corresponding β-amino carbonyl compounds (Scheme 45).[74f]



Scheme 45.

The method is reasonably faster, more cost effective and simpler than the most of the existing methods. The efficacy of BDMS can be ascertained from the data shown in Table 2. The salient features of this protocol are (a) the simplicity of the procedure, (b) the avoidance of column chromatography and (c) the high yields and good diastereoselectivities.

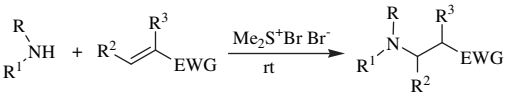
Table 2
Comparison of BDMS with different catalysts for the Mannich reaction of benzaldehyde, aniline and acetophenone

Entry	Catalyst	Reaction conditions	Reaction time (h)	Yield (%)
1	—	EtOH, rt	48	NR[a]
2	$FeCl_3$	EtOH, rt	24	NR[a]
3	$NbCl_5$	EtOH, rt	12	95
4	$Yb(OPf)_3$	PhMe/$C_6F_5CF_3$, 60 °C	12	98
5	Silica/sulfuric acid	EtOH, rt	12	92
6	[$NaBAr^F_4$]	H_2O, 30 °C	48	81
7	BDMS	EtOH, rt	0.5	96

[a] No reaction.

6.7. Michael addition of amines to electron-deficient alkenes

The conjugate addition of amines to electron-deficient alkenes is an important and widely used transformation in organic synthesis. It provides an easy route to β-amino acid derivatives as well as for the synthesis of heterocycles containing a β-amino carbonyl unit.[75] Over the years, numerous methods have been developed using a variety of reagents such as $SnCl_4/FeCl_3$,[76] $InCl_3$,[77] $CeCl_3\cdot 7H_2O/NaI$,[78] $Yb(OTf)_3$,[79] $LiClO_4$,[80] $ZrClO_4\cdot 8H_2O$/montmorillonite,[81] CAN,[82] H_3BO_3,[83] Borax,[84] β-cyclodextrin,[85] etc. Very recently, our group has demonstrated the potential of BDMS for aza-Michael additions of amines to electron-deficient alkenes, as shown in Scheme 46.[86] It is worthy of note that, in

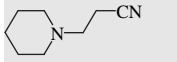
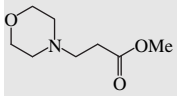


R = H/ alkyl; R^1= alkyl/ benzyl; R^2= H; R^3= H/ Me

Scheme 46.

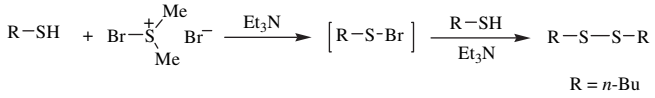
contrast to most of the reported catalysts for the Michael addition of amines to electron-deficient alkenes, BDMS was found to be superior in terms of its easy accessibility, efficiency, simplicity of the procedure and yields obtained (Table 3).

Table 3
Comparison of BDMS with different catalysts for the Michael addition of amines to electron-deficient alkenes

Product	Catalyst (mol %)	Time min/[h]	Yield (%)
	$LiClO_4$ (100)	[1]	80
	$ZrClO_4 \cdot 8H_2O$/montmorillonite (0.075 g/mmol)	15	94
	CAN (10)	20	96
	H_3BO_3 (10)	[1.5]	95
	Borax (10)	[2]	90
	β-Cyclodextrin (100)	[6]	84
	BDMS (5)	5	99
	$ZrClO_4 \cdot 8H_2O$/montmorillonite (0.075 g/mmol)	35	76
	H_3BO_3 (10)	[3]	85
	Borax (10)	[3]	92
	BDMS (5)	5	97

6.8. Oxidation of thiols into disulfides

The conversion of thiols into the corresponding disulfides (oxidative S–S coupling) is an important reaction in organic synthesis. This oxidation is generally carried out using a variety of oxidants such as manganese dioxide,[87] nickel peroxide,[88] chromium peroxide,[89] sodium perborate,[90] etc. Olah et al. demonstrated that BDMS efficiently oxidized thiols into the corresponding disulfides,[3] as shown in Scheme 47. The reaction takes place in the presence of triethylamine at room temperature, affording good yields. This method for the preparation of disulfides is milder and efficient in comparison to the other methods reported in the literature.

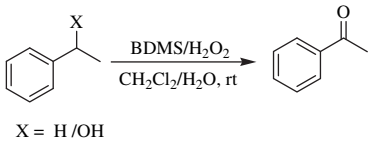


Scheme 47.

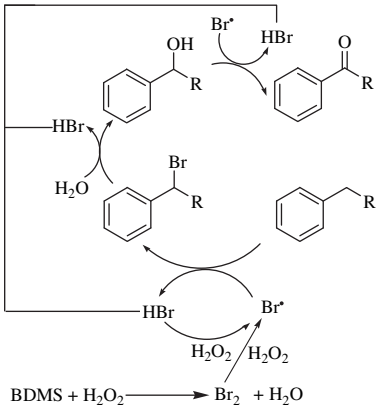
Aromatic as well as aliphatic thiols react with BDMS in the presence of triethylamine at room temperature to provide the corresponding disulfides instantaneously in high yields. The advantage of this method is that the byproducts, dimethyl sulfide and triethylamine hydrobromide, can be removed from the reaction mixture by a simple aqueous work-up.

6.9. Benzylic C–H and O–H oxidation

BDMS was found to be a highly efficient catalytic oxidizing agent in combination with hydrogen peroxide. A wide variety of alkyl arenes and benzylic alcohols undergo C–H and O–H oxidation at room temperature and in good yields (Scheme 48).[91] It is assumed that the one-pot process proceeds via an in situ generation of a Br radical (Scheme 49). This radical reacts with



Scheme 48.



Scheme 49.

alkyl arenes and benzylic bromination takes place. Subsequently, hydrolysis of this benzylic bromide to the corresponding alcohol and a final oxidation by the Br radical gives the desired carbonyl compounds.

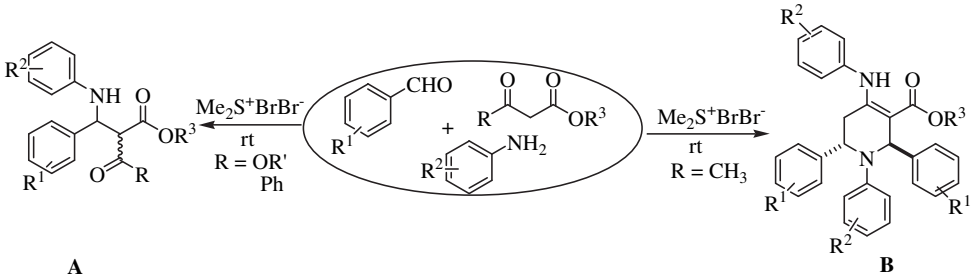
In addition, the reagent BDMS exhibits chemoselectivity, e.g., secondary benzylic alcohols can be oxidized in the presence of primary aliphatic alcohols. The BDMS-catalyzed benzylic C–H oxidation was found to be milder and more effective than the existing methods.

6.10. Synthesis of highly functionalized piperidines

Recently we have revealed one interesting multicomponent reaction using BDMS as catalyst as shown in Scheme 50.[92] This protocol demonstrates the competitive effect of 1,3-dicarbonyl compounds for choosing either the path of Mannich-type product **A** or the highly functionalized piperidines **B** in presence of catalytic amount of BDMS. The combination of aromatic aldehydes, amines and 1,3-dicarbonyl compounds prefers the formation of Mannich-type product **A** when R is a non-enolizable carbon or an alkoxy group, whereas in case of R=CH_3 the same combination yielded highly functionalized piperidines **B** in the presence of catalytic amount of BDMS.

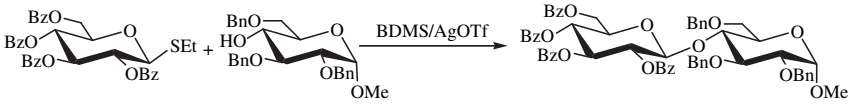
6.11. Synthesis of oligosaccharides by activation of thioglycosides

Bromodimethylsulfonium bromide (BDMS) in combination with silver triflate found to be a very efficient thiophilic promoter system, capable of activating both 'disarmed' and 'armed' thioglycosides for glycosidic bond formation (Scheme 51).[93] The thioglycosides are one of the most enduring and widely used donors for glycosylation due to their stability, accessibility, and compatibility. The sulfur atom in a thioglycoside is a soft nucleophile, and is therefore able to react selectively with soft electrophiles. Interestingly, BDMS alone cannot activate thioglycosides at all except in conjunction with silver triflate (AgOTf).



R^1 =H, Cl, Me, OMe, NO_2; R^2 = H, OMe, Br; R^3= Me, Et, ^{t}Bu

Scheme 50.



Scheme 51.

7. Conclusions and future perspectives

In summary, BDMS can be considered to be a very versatile and useful reagent in organic synthesis. From this report, it is clear that BDMS is a unique reagent, which can act either as a source of molecular bromine or bromonium ions or bromine radicals as well as a nucleophilic bromide ion. In addition, this reagent has the ability to generate dry HBr in the reaction medium, which can be utilized in a wide variety of organic transformations. Due to its fascinating properties, BDMS plays a vital role in different organic transformations. Depending upon the reaction conditions or the nature of the substrate, it is able to behave in a different way. Although a few publications have already been reported, the efficacy and versatility of this reagent still remain to be explored. The small number of publications employing BDMS indicates that the dawn of its use in organic synthesis has only just begun. It is expected that BDMS will emerge as a powerful, cheap and highly useful reagent in organic synthesis.

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Biographical sketch

Dr. **Md. Lokman Hakim Choudhury** was born on 31st December, 1978 at Rangia, Assam, India. After completion of his graduation from Bajali College at Gauhati University, he joined the Indian Institute of Technology Guwahati, for his M.Sc degree in Chemistry in 2001. Subsequently, he started his doctoral work under the supervision of Professor Khan in the same institute and obtained his Ph.D. degree on March 12, 2007. He took up a position as a Lecturer in the Department of Basic Sciences and Social Sciences, North-Eastern Hill University in January 8, 2007. He has also been awarded a prestigious Royal Society Incoming Fellowship (2007–08) for his postdoctoral research work at the School of Chemistry in the University of Manchester, UK. Recently, he has moved to the Indian Institute of Technology Patna as Assistant Professor. His current research interests are the development of new synthetic methodologies using both homogeneous and heterogeneous catalysts, green chemistry, domino reactions and click chemistry.

Dr. **Tasneem Parvin** was born on April 1, 1983 at Cooch Behar, West Bengal, India. After obtaining her B.Sc Degree with a second position from North Bengal University in West Bengal, she joined the Indian Institute of Technology Guwahati, in 2004 for her Master's degree in chemistry. After completing her Master's degree, she started her doctoral work under the supervision of Professor Khan in 28th July 2006. She obtained her Ph.D. degree on 10th July 2009. Her current research interests include multicomponent reactions, development of new synthetic methodologies and green chemistry.

Professor **Abu T. Khan** was born on 20th November 1961 in West Bengal, India. After obtaining his Master's Degree in Chemistry from Kalyani University in 1985, he started his doctoral work under the guidance of Professor K.C. Majumdar at the same university and received his Ph.D. degree in 1990 on 'Phase Transfer Catalysed Alkylation and [3,4] Sigmatropic Rearrangement.' Subsequently, he joined as a Research Associate in the School of Chemistry, University of Hyderabad under the supervision of Professor Goverdhan Mehta on December 1989 and then continued until May 1992. During his postdoctoral tenure, he worked on total synthesis of natural products. In March 1992, he was awarded an Alexander von Humboldt Fellowship to carry out his postdoctoral research work in Germany. After finishing a German language course at the Goethe Institute in Murnau, he started his research work with Professor R.R. Schmidt at the University of Konstanz from 1st November 1992, where he worked on the total synthesis of natural products and carbohydrate chemistry. After returning to India, he joined the Natural Products Chemistry Division at Regional Research Laboratory Jorhat as a Scientist Fellow in 1995. Later, he moved to the Indian Institute of Technology Guwahati, on 23rd December 1996, as an Assistant Professor, from where he started his independent research career. He has also served as a Reader in Chemistry, Visva Bharati University in West Bengal from January to April, 2002 by taking a short leave from IITG. Presently, he is holding a position of Professor in Chemistry and his current research interests include work on the synthesis of bioactive natural products and carbohydrate and heterocyclic chemistry other than the development of synthetic methodologies.