JOC*Note*

A Mild and Regioselective Method for α-Bromination of β-Keto Esters and 1,3-Diketones Using Bromodimethylsulfonium Bromide (BDMS)

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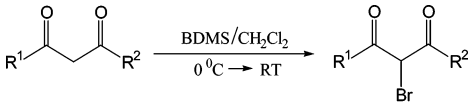

R^1 = alkyl/ Ph, R^2 = OR / Me/ Ph, R = alkyl

Bromodimethylsulfonium bromide has been found to be an effective and regioselective reagent for α-monobromination of β-keto esters and 1,3-diketones. A wide variety of β-keto esters and 1,3-diketones undergo chemoselective α-monobromination with excellent yields at 0−5 °C or room temperature. The notable advantages of this protocol are no need of chromatographic separation, use of less hazardous reagent than molecular bromine, and no added base, Lewis acid, or other catalyst.

The regioselective α-bromination of β-keto esters and 1,3-diketones is a useful transformation in organic synthesis.[1] These brominated products serve as valuable building blocks for the synthesis of both natural and non-natural products.[2] Over the years, several methods have been developed for the bromination of 1,3-dicarbonyl compounds.[1] Conventionally, molecular bromine,[3] bromine/NaH,[2a] NBS/Et_3N,[2d] and NBS/NaH[4] are used to access these compounds. In addition, other reagents such as $CuBr_2$ with [hydroxy(tosyloxy)iodo]benzene[2c] or NBS/Mg-$(ClO_4)_2$[5] or NaOBr in acetone/acetic acid[6] or NBS in various combinations such as silica-supported $NaHSO_4$[7] or Amberlyst-15[8] or sulfonic acid functionalized silica[9] or in ionic liquids[10] are also utilized for similar transformation. Though several methods in the literature provide good yields, most of them suffer from limitations; for example, molecular bromine is hazardous and difficult to handle, the use of Lewis acid as an additive or strong bases may be required, and sometimes the reaction needs to be performed under dry and inert atmospheric conditions. From the literature it is apparent that the chemoselective α-monobromination of unsubstituted β-ketoesters or 1,3-diketones is a very challenging task since some of the monobrominated products are reported to be unstable and to undergo disproportionations to dibromo and debrominated products.[11] In continuation of our effort in the field of new synthetic methodologies using bromodimethylsulfonium bromide in various organic transformations,[12] we were in search of a new and improved synthetic protocol for chemo- and regioselective α-monobromination of β-keto esters and 1,3-diketones that could be applied to a wide range of substituted and unsubstituted β-keto esters and 1,3-diketones. So far, BDMS has been utilized for the transformations of alcohols to the corresponding bromides,[13] oxidation of thiols to disulfides,[14] deprotection of dithioacetals,[15] and preparation of α-bromoenones from the corresponding enones.[16] Recently, we have demonstrated that the peroxo vanadium mediated oxidation of bromide ion to bromonium ion can be utilized for selective α-monobromination of β-keto esters and 1,3-diketones.[17] Interestingly, we have noted by our earlier method that some of the substrates did not provide monobrominated product exclusively. However, by employing bromodimethylsulfonium bromide, it is possible to prepare selectively monobrominated products. In addition, it offers a wealth of advantages in comparison with the earlier reported methods, e.g., the reagent BDMS is readily accessible, can be considered a convenient storage of molecular bromine, is less hazardous and easy to handle, and facilitates maintaining the stoichiometric ratio while carrying out the reactions. In this note, we report that BDMS is a convenient and valuable reagent for highly selective α-bromination of β-keto esters and 1,3-diketones at 0−5 °C or room temperature under mild reaction conditions without using any base or Lewis acid or any other additive, as shown in Scheme 1.

For the present study, the catalyst bromodimethylsulfonium bromide (BDMS) was prepared by following the literature procedure.[15] In the preliminary experiment, when methyl

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(2) (a) Stotter, P. L.; Hill. K. A. *Tetrahedron Lett.* **1972**, *13*, 4067. (b) Yoshida, J.; Yano, S.; Ozawa, T.; Kawabata, N. *Tetrahedron Lett.* **1984**, *25*, 2817. (c) Coats, S. J.; Wasserman, H. H. *Tetrahedron Lett.* **1995**, *36*, 7735. (d) Bateson, J. H.; Quinn, A. M.; Southgate, R. *J. Chem. Soc., Chem. Commun.* **1986**, 1151.
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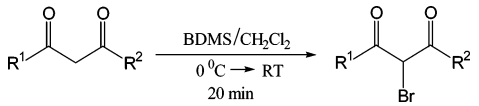
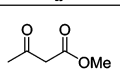
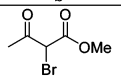
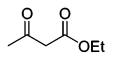
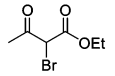
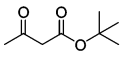
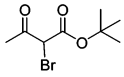
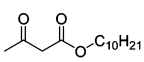
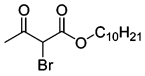
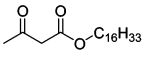
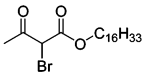
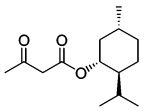
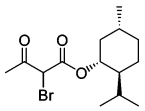
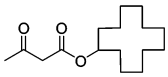
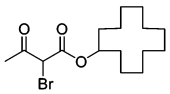
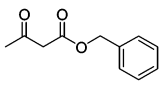
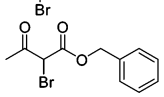
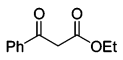
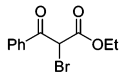
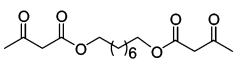
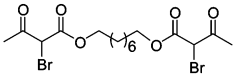
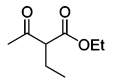
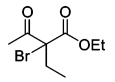
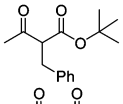
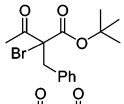
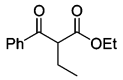
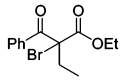
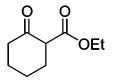
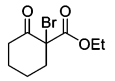
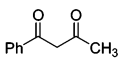
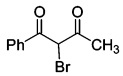
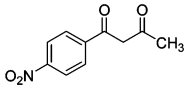
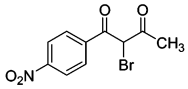
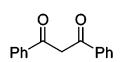
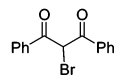
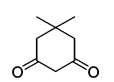
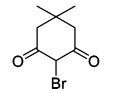
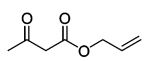
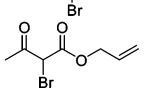
SCHEME 1. Selective α-Bromination of β-Keto Esters and 1,3-Diketones



acetoacetate (1 mmol) was treated with bromodimethylsulfonium bromide (1.25 mmol) in dichloromethane (5 mL) at 0−5 °C, it provided exclusively monobrominated product within 20 min in 85% yield. The product **1b** was characterized by recording ^{1}H and ^{13}C NMR spectra and elemental analysis. Interestingly, we did not observe any detectable amount of dibrominated product under the experimental conditions while recording the ^{1}H NMR spectrum of the crude product. Encouraged by this result, we tried to apply this protocol to a wide range of β-keto esters. Similarly, other unsubstituted β-keto esters (Table 1, entries **2a** and **3a**) underwent α-bromination smoothly under similar conditions and afforded exclusively monobrominated product in excellent yields. For further investigation, a wide variety of β-keto esters (Table 1, entries **4a**−**8a** and **10a**) were prepared by transesterification of methyl acetoacetate with their corresponding alcohols using a silica-supported perchloric acid method.[18] By following the identical reaction procedure, various substrates **4a**−**9a** were converted to the desired α-monobrominated products in very good yields. Next, the di-keto ester of octanediol (**10a)** was treated with 2.5 equiv of BDMS, and the desired monobrominated product **10b** was found in very good yield**.** The notable advantages of this protocol over the other existing methods are that the conversion takes place within a very short time without using any catalyst and there is no need of chromatographic separation, as it gives full conversion of the starting material with a single product. NMR spectra of all the products were recorded from crude product just after aqueous workup without any further purifications and showed high purity without detectable byproducts. To explore further, monosubstituted β-keto esters (entries **11a**−**13a**) were prepared by alkylation of β-keto esters using K_2CO_3 as base by following a standard procedure. Subsequently, the substrates **11a**−**13a** were treated with BDMS following the same experimental procedure and provided the monobrominated products **11b**−**13b**, respectively, in good yields at room temperature. As there is no probability for dibromination, we performed the reactions at room temperature instead of ice-bath temperature. Similarly, a cyclic β-keto ester (entry **14a**) underwent α-bromination smoothly in good yield at room temperature. Likewise, various 1,3-diketones (Table 1, entries **15a**−**17a**) provided the desired α-monobrominated products **15b**−**17b** exclusively with very good yields under the given experimental conditions.

Interestingly, dimedone (entry **18a**) provided exclusive monobrominated product at room temperature, which is sometimes difficult to achieve by some of the reported methods.[9] Surprisingly, we could not find the proton attached with the α-brominated carbon atom of compound **18b** in the ^{1}H NMR spectrum. We observed only two signals at 1.12 (s) and 2.48 (s), respectively. Also, in the IR spectrum, we did not observe any carbonyl peak of this product. Therefore, to further confirm the structure of compound **18b**, whether the product is mono- or dibrominated, the product was recrystallized from ethyl acetate/hexane (7:3) and a single-crystal XRD was recorded. Interestingly, we found that in solid state it exists in enol form as shown

TABLE 1. α-Bromination of β-Keto Esters and 1,3-Diketones[a]

Entry	Substrate a	Product[a] b	% Yield[b]
1			85
2			84
3			91
4			95
5			90
6			93
7			92
8			94
9			94
10			97[d]
11			89[c]
12			96[c]
13			95[c]
14			99[c]
15			97
16			86
17			98
18			91[c,e]
19			81

[a] Reaction conditions: β-keto ester/1,3-diketone (1 mmol), BDMS (0.278 g, 1.25 mmol), 0 °C to rt, 20−30 min. [b] Reactions were carried out at 0 °C. [c] Reactions were performed at room temperature. [d] Bromodimethyl sulfonium bromide (2.5 equiv) was used. [e] Reaction time was 30 min.

(18) Khan, A. T.; Goswami, P.; Kalpana, K.; Choudhury, L. H. Unpublished work.

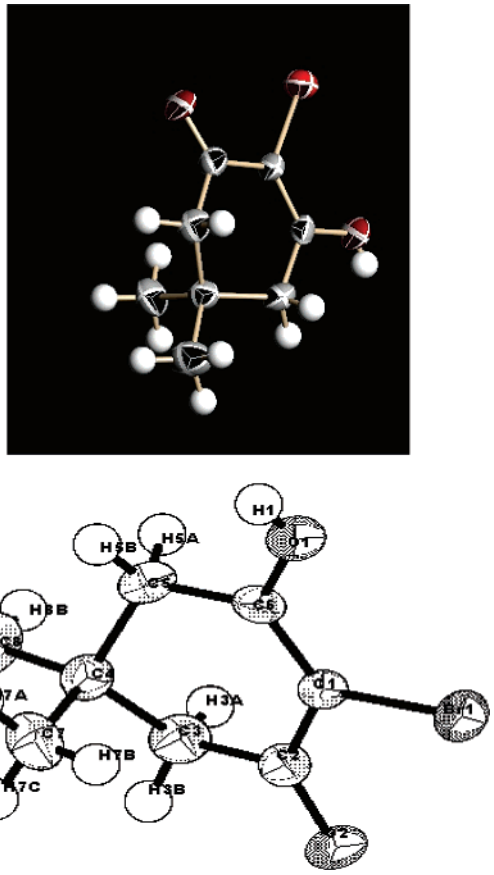
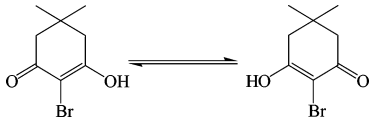


FIGURE 1. ORTEP plot of α-monobromo dimedone with atom numbering scheme.

SCHEME 2. Rapid Keto−Enol Tautomerization in Solution



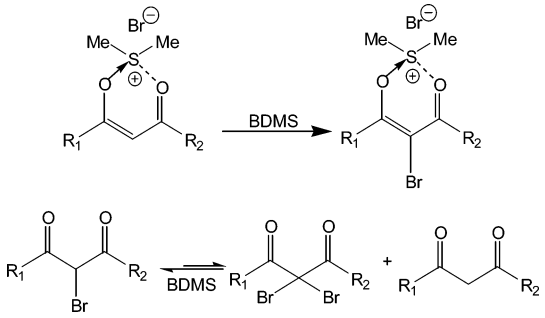
in the ORTEP diagram of Figure 1, which shows intermolecular hydrogen bonding of O−H of enol and ketonic CO of the other unit. We believe that in solution state it undergoes rapid keto−enol tautomerization as shown in Scheme 2, for which we do not observe the proton signal for the α-hydrogen associated with the brominated carbon.

Next, to exemplify further the applicability of this protocol, the substrate **19a** was treated under the experimental conditions. Interestingly, the allylic double bond survives under the given conditions and provided the desired product **19b** in good yields.

A probable mechanism is depicted in Scheme 3. We believe that bromodimethylsulfonium bromide facilitates the enol formation of *β*-keto esters or 1,3-diketones. In addition, bromodimethylsulfonium ion may also bind with the enol form of the monobrominated product, which provides extra stability of the monobrominated product and as a result makes the process sluggish for further bromination or disproportionation.

In conclusion, we have devised a simple and efficient synthetic protocol for highly selective α-monobromination of *β*-keto esters and 1,3-diketones using the versatile reagent bromodimethylsulfonium bromide. The notable advantages of this protocol are mild, clean, and simple reaction conditions; very good yields; no need of chromatographic separations; and

SCHEME 3. Probable Mechanism for Selective Monobromination



no need of any base or Lewis acid as an additive, which is invariably required by NBS methods. Furthermore, this method is also expected to have valuable application in organic synthesis because of the low cost, easy accessibility, and less hazardous nature of the reagent.

Experimental Section

Preparation of Bromodimethylsulfonium Bromide (BDMS).[15] Dimethyl sulfide (1.83 mL, 25 mmol) was taken in 5 mL of dry dichloromethane into a 150 mL standard joint conical flask. Then, 1.3 mL of bromine (25 mmol) was dissolved in 5 mL of dry dichloromethane and added slowly into the above solution at ice-bath temperature over a period of 5 min. During the addition, light orange crystals of bromodimethylsulfonium bromide begin to separate out. After the addition of bromine was completed, the crystals of bromodimethylsulfonium bromide were collected by filtration. The solid material was then washed with dry hexane and dried under vacuum. The crystalline product was obtained as 4.3 g in 77% yield, mp 80 °C.

General Procedure for α-Bromination of *β*-Keto Esters and 1,3-Diketones. Bromodimethylsulfonium bromide (BDMS) (1.25 mmol, 0.278 g) was added to a stirred solution of *β*-keto ester or 1,3 diketone (1 mmol) in CH_2Cl_2 (5 mL) at 0−5 °C or room temperature. After 20 min, the reaction mixture was washed with water (10 mL × 2) and extracted with CH_2Cl_2 (10 mL × 2). The organic layers were combined and dried over anhydrous Na_2SO_4, and solvents were removed by evaporation in a rotary evaporator to get the crude product. All products were characterized without any further purification.

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Supporting Information Available: Experimental details and analytical data of all products and ^1H and ^{13}C NMR spectra of unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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