



REGULAR ARTICLE

Facile NBS/DMSO mediated dibromination of olefins including selected natural products and glycols

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MS received 7 June 2021; revised 31 August 2021; accepted 12 September 2021

Abstract. A highly chemo- and diastereoselective *vic*-dibromination of olefins has been developed. The process employs a readily available N-Bromosuccinimide (NBS)/DMSO reagent system as a bromine source. High substrate scope, simple reaction conditions, application to natural products and glycols makes the process very attractive.

Keywords. Dibromination; olefins; natural products; glycols; regio- and chemoselectivity.

1. Introduction

The usefulness of vicinal dibromoalkanes as an expedient reactive intermediate in organic synthesis needs no endorsement.¹ Whether it is a preparation of alkynes,² cycloalkanes³ or reaction partners for palladium catalysed coupling reactions,⁴ vicinal dibromoalkanes have always taken the mothers place. In a total or diversity-oriented synthesis of natural products, dibromination of C-C double bond can be used either as a protecting group for late-stage functionalization or structural modifications. Vicinal dibromination of olefins is well documented. The use of molecular bromine itself or bromine carrying reagents as bromine source is well exploited.^{1,5} Further conceptualising the enzyme-mediated oxidative halogenation processes; several oxidative dibromination strategies for olefins have been developed.⁷ These involve *in situ* generations of brominating reagent using oxidants like hydrogen peroxide, molecular oxygen, persulfates, select fluor, hypervalent iodine, etc. Despite these advances, researchers are still in search of new reagent systems which are environment friendly, cost-effective, high yielding with broad substrate scope and most importantly user friendly as

most of the literature methods are devoid of all these features.¹

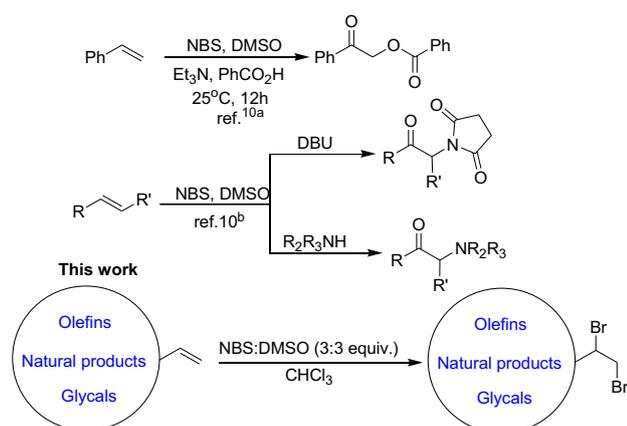
Towards olefin functionalisation, N-bromosuccinamide/dimethylsulphoxide (NBS/DMSO) reagent system has emerged as a useful tool. For example, it has been exploited under different reaction conditions for oxo-acyloxylation and oxo-amination of alkenes (Scheme 1).⁷ To the best of our knowledge, the application of the NBS/DMSO reagent system for the bromination of olefins is not documented. Herein, we describe the highly regio- and stereoselective *vic*-bromination of olefins, some selected natural products and glycols using the NBS/DMSO reagent system.

2. Experimental

We began with the reaction of styrene (**1**) with NBS. Initially, **1** (1 equiv.) and NBS (2 equiv.) were allowed to stir in DMSO (3 mL) under nitrogen at room temperature. Instantaneous generation of yellow colour and its decolouration prompted us to check the reaction progress. To our delight, the formation of two products was observed through TLC. The spectroscopic analysis confirmed the formation of vicinal

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Supplementary Information: The online version contains supplementary material available at <https://doi.org/10.1007/s12039-021-02003-3>.



Scheme 1. Previous applications of NBS/DMSO system to olefins and the current work.

dibromostyrene (**2**) and bromohydrin **2'** (Table 1). ^1H NMR and ^{13}C NMR of both the compounds were in full agreement with the literature. In order to get vicinal dibromostyrene (**2**) as the sole product, the reaction was carried out under various conditions.

The results of our standardisation are summarised in Table 1. We found that no reaction occurred using NBS in polar solvents like DCM, CCl_4 , CHCl_3 , CH_3CN , etc. making the role of DMSO in this reaction inevitable. In this connection, we realised use of DMSO in combination with other solvents. We

observed the use of 2 equivs. each of NBS and DMSO in DCM leads to the formation of **2** in 70% yield. Using 3 equiv. of NBS and 2 equiv. of DMSO yielded **2** in 80% yield. Further standardisation proved that use of 3 equivs. each of NBS and DMSO in dry DCM yielded **2** as sole products (Table 1, entry 9).

Having established the optimised reaction conditions, we next examined the scope of various styrenes.

A series of substituted styrenes were allowed to react with NBS. Styrenes with electron-donating and electron-withdrawing groups, ortho-, meta- and para-substituted were checked for their reactivities (Figure 1, entries 3–7). In all cases, the corresponding vicinal dibromo derivatives were obtained in good to high yield (Figure 1). The nature and position of the substituent hardly had any effect on the reactivity and yield of the reaction. Due to the fact that NBS promotes allylic/benzylic bromination, we selected 4-methoxy allyl benzene to prove the nature of bromination using NBS/DMSO reagent system under the standard conditions. Vicinal dibromide **8** in 99% yield was obtained without allylic/benzylic bromination proving the regioselectivity of the reagent system. Thus, different types of allyl derivatives including N-allyl (amide), O-allyl (both ester and ether), C-allyl (cycloalkyl) were allowed to react with NBS/DMSO reagent system under the optimised reaction conditions (entries 8–13, Figure 1). All sorts of allyl derivatives yielded

Table 1. Optimization of reaction conditions for dibromination of styrene (1).

Entry	Solvent ^a	NBS (equiv.) ^c	t (min.)	Yield % ^d
1	DMSO	2	3	40
2	CCl_4	2	60	0
3	DCM	2	60	0
4	CH_3CN	2	60	0
5	DMF	2	30	30
6	CHCl_3	2	60	0
7	DCM/DMSO ^b (2 equiv.)	2	10	70
8	DCM/DMSO (2 equiv.)	3	5	80
9	DCM/DMSO (3 equiv.)	3	5	95
10	DCM/DMSO (3 equiv.)	4	5	95
11	DCM/DMSO (4 equiv.)	4	5	90

^aIn all cases 3 mL of anhydrous solvent was used per equiv. of substrate.

^bHighly anhydrous DMSO purchased from sigma Aldrich was used

^cFreshly crystallized NBS (with respect to 1 equiv. of substrate) was used.

^dYields after column chromatography.

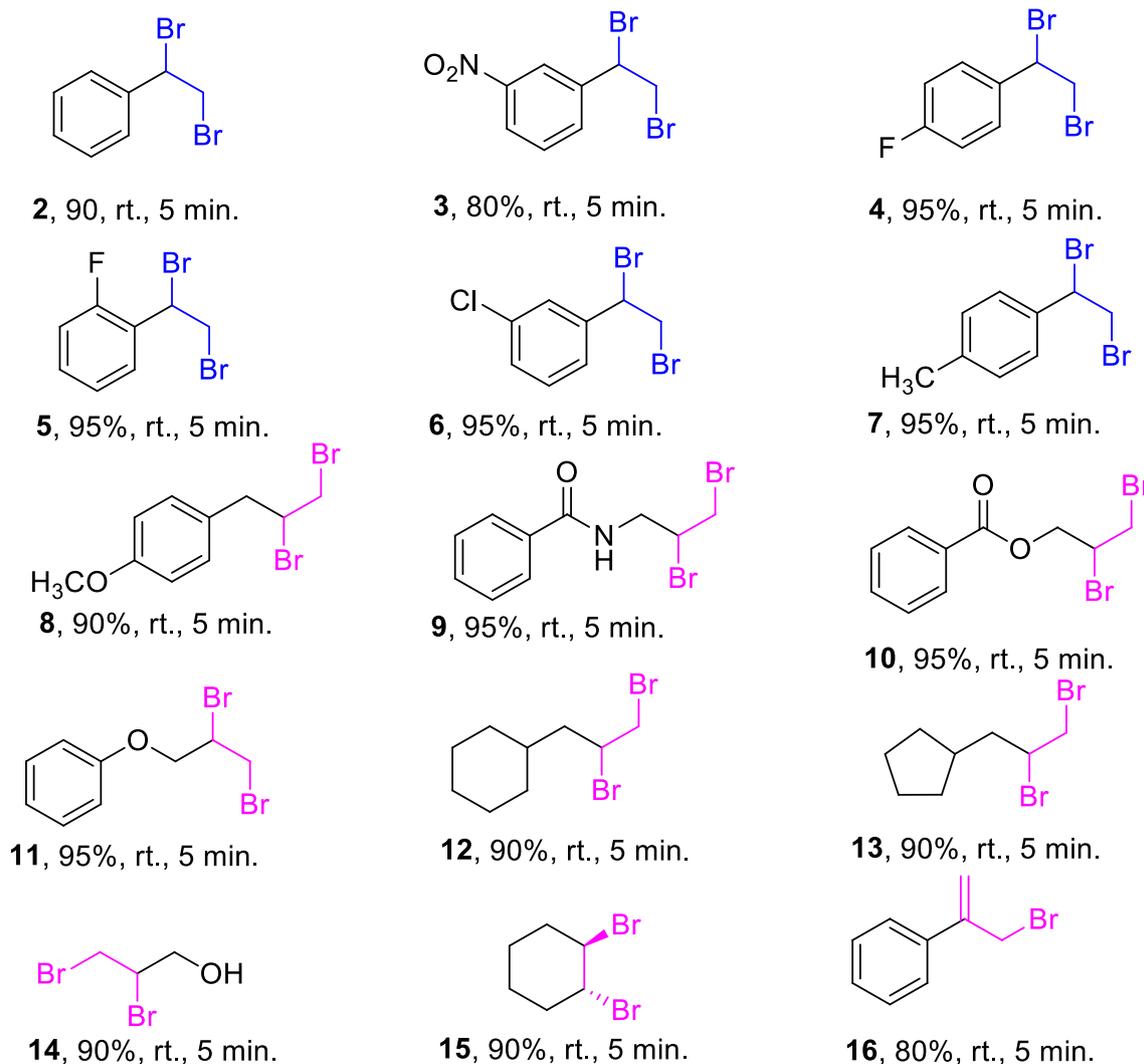


Figure 1. Substrate scope of the vic-dibromination of olefins.

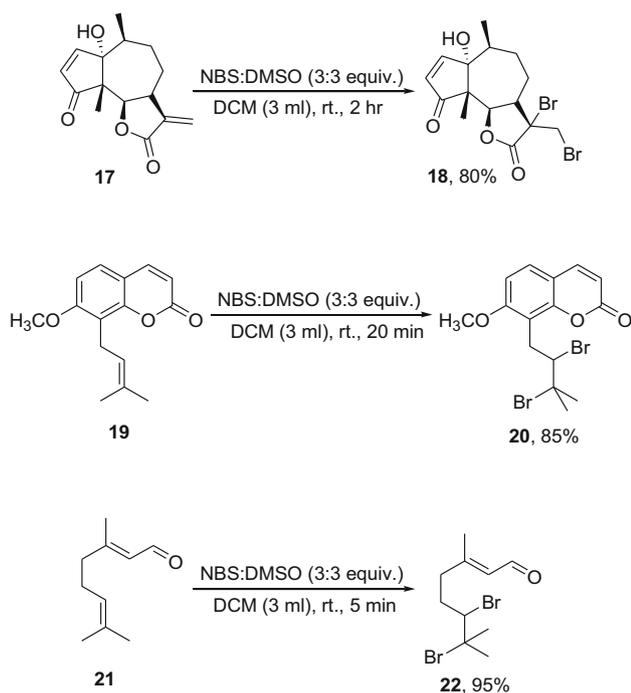
vicinal dibromo products in excellent yield. Furthermore, the reaction of simple allyl alcohol afforded the formation of 2,3-dibromopropan-1-ol (**14**) in 90% yield. It is noteworthy that reaction of cyclohexene yielded *trans*-1,2-dibromocyclohexane (**15**) in 90% yield with high diastereoselectivity which under HBr/DMSO reagent system yielded the product in not more than 16% yield with poor selectivity.¹ However, in the case of alpha-methylstyrene allylic bromination predominated over vicinal dibromination leading to the formation of **16** in 80% yield.

To impart more drug-like properties in biologically significant natural products, selective halogenation has always played a crucial role. It is either used to enhance the bioactivity through structural modifications or study the role of unsaturation in comprehensive SAR studies. We were attracted to test the applicability of NBS/DMSO reagent system for the bromination of some of the important natural products. Initially, selective

dibromination of a sesquiterpene lactone parthenein⁸ (**17**) was achieved in 80% yield under the standardised reaction conditions in 2 h without affecting ring A having α,β -unsaturation, thus proving the chemoselectivity of the reagent system. Similarly, an O-methylated coumarin, osthol⁹ (**19**) afforded the corresponding dibromo product in 85% yield in 20 min without disturbing lactone moiety or aromatic ring further supporting the chemoselectivity of the reagent system. The bromination of terpenoid citral (**21**) also proceeded smoothly and selectively to afford the dibromo product **22** in high yield (Scheme 2).

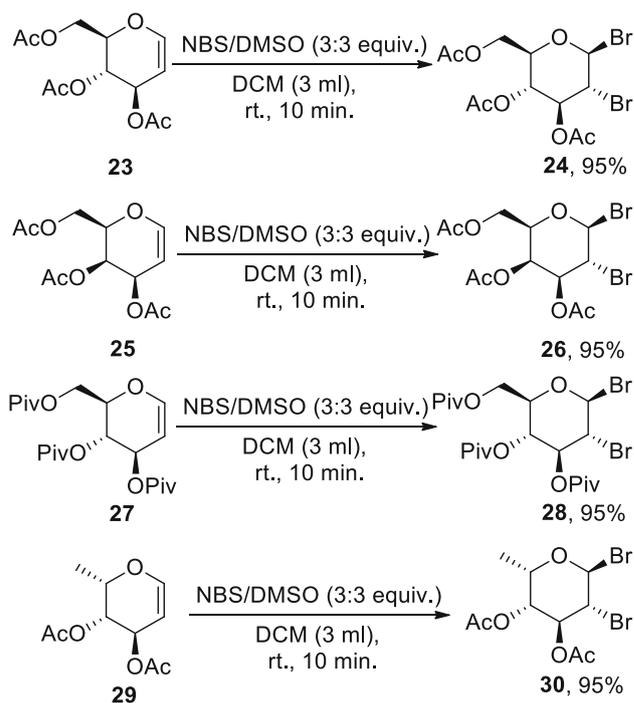
3. Results and Discussion

In carbohydrate chemistry, halogenated sugars represent one of the most common and important class of chiral auxiliaries.¹⁰ This can be attributed to their



Scheme 2. Dibromination of some selected natural products.

potential as unparalleled starting material for the generation of amino-, deoxy sugars and deoxy nucleosides which are not easily accessible. The polarity of C-X bonds renders them susceptible to nucleophilic attack by a varied number of nucleophiles. This has also imparted in them the property to serve as glycosyl donors in various glycosylation reactions. Anomeric halogenation has also been exploited in the generation of the corresponding anomeric carbanions and radicals. Due to their huge synthetic potential, the preparation of 1,2-dihalogeno sugars has always remained a field of interest for carbohydrate chemists. Among the various sugar halogens, bromo sugars have been most extensively used. Despite various methods, bromine addition to glycals makes the most common way for the preparation of 1,2-dibromo sugars. However, lack of stereoselectivity is the main disadvantage of the process as the addition process may lead to the formation of four possible diastereomeric products often difficult to separate.^{11a,b} Owing to the mildness of the NBS/DMSO reagent system, we were interested to investigate the dibromination of tri-*O*-acetyl-D-glucal (**23**). Thus, **23** was allowed to react with NBS/DMSO under optimised reaction conditions. We were delighted to obtain 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy- β -glucopyranosylbromide (**24**) in 99% yield with 100% diastereoselectivity (α/β -selectivity as well as *cis/trans* selectivity). The structure of **24** was confirmed through spectroscopic analysis and was in full



Scheme 3. Reaction of glycals with NBS/DMSO reagent system.

agreement with the literature reports.¹² High diastereoselectivity of the reaction in **23** prompted us to study the dibromination of tri-*O*-acetyl-D-galactal (**25**) using NBS. Here, 1,2-dibromo derivative **26** was obtained as the sole product without the formation of even traces of the other three possible isomers. Similar results were obtained with tri-*O*-pivaloyl-D-glucal (**27**) which yielded the dibromo derivative **28** as the only product.¹⁵ Reaction of deoxy sugar 3,4-di-*O*-acetyl-L-rhamninal (**29**) with NBS/DMSO reagent combination gave the expected product **30** with 100% diastereoselectivity (Scheme 3).

Although the mechanism of the reaction has not been completely studied, however on the basis of our experimental observations, we believe that in the present bromination reaction, the interaction of NBS/DMSO generates bromine *in-situ* leading to the formation of bromonium ion and consequent ring-opening by the nucleophilic bromide ion.

4. Conclusions

In summary, we have developed an operationally simple NBS/DMSO mediated dibromination strategy for olefins. The process is highly regio-, stereo- and chemoselective. Broad substrate scope and applicability to functionally dense natural products make the process highly useful. Further, the efficacy of the

reagent system towards selective dibromination of glycals is worth noting.

Supplementary Information (SI)

^1H and ^{13}C NMR data and other supplementary information are available at www.ias.ac.in/chemsci.

Acknowledgement

The authors are highly thankful to director CSIR-IIIM (Indian Institute of Integrative Medicine) for the necessary facilities. SKY is highly obliged to DST-India for a research grant under the INSPIRE Faculty scheme. (IIIM-Publication number of the current study is IIIM/1828/2015).

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