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Bromodimethylsulfonium bromide: A useful reagent for acylation of alcohols, phenols, amines, thiols, thiophenols and 1,1-diacylation of aldehydes under solvent free conditions

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Dedicated to A.C. Ghosh, Former Director, RRL-Jorhat, Assam on the occasion of his 65th birthday.

Abstract

Various alcohols and phenols, amines, thiols and thiophenols can be transformed easily to the corresponding acetate derivatives, on treating with two equivalent amount of acetic anhydride in the presence of 5 mol% bromodimethylsulfonium bromide pre-catalyst at room temperature in good yields. In addition, various aldehydes can also be converted to the corresponding *gem*-diacetates in good yields by employing 10 mol% of the same pre-catalyst using four equivalent amount of acetic anhydride. Some of the important features are: good yields, mild reaction conditions, no-aqueous work-up and chromatographic separation for a large-scale reaction, compatible with the substrates having other protecting groups and applicable to the carbohydrates and nucleosides. Interestingly, neither alkyl bromide formation from the corresponding alcohol nor bromination of the substrates took place under the experimental conditions.

Keywords: Acylation; Acetic anhydride; Alcohols and phenols; Amines; Thiols; Aldehydes; Catalytic synthetic protocol

1. Introduction

The acylation of alcohols and phenols, amines and thiols is one of the most useful and versatile transformations in organic synthesis [1]. Among them, the conversion of hydroxyl or amino group into the corresponding acetate is essential due to its medicinal value, e.g. the preparation of paracetamol from 4-aminophenol as well as for confirmation of the presence of hydroxyl or amino group in a compound. In addition, the protection of hydroxyl functionality as acetate is preferred due to its ease of introduction, stable under mild acidic reaction conditions and also ease of removal by mild alkaline hydrolysis. The acetylation of alcohols and phenols or amines is usually performed with acid anhydrides or acetyl chloride in the presence of amine bases such as triethylamine or pyridine or pyridine along with 4-(dimethylamino)pyridine (DMAP), which acts as a co-catalyst, or 4-pyrrolidinopyridine (PPY) [2]. Sometimes tributylphosphine (Bu_3P) is also employed as a less basic catalyst for acylation reactions particularly for the base sensitive substrates [3]. In the literature, several methods have been developed for the preparation of acetate from the corresponding alcohol or phenol or thiol using various metal salts, such as $CoCl_2$ [4], $ZnCl_2$ [5], $RuCl_3$ [6], $TiCl_4$–$AgClO_4$ [7], $LiClO_4$ [8], $Mg(ClO_4)_2$ [9], $Zn(ClO_4)_2{\cdot}6H_2O$ [10] and some triflates such as $Sc(OTf)_3$ [11], Me_3SiOTf [12], $In(OTf)_3$ [13], $Cu(OTf)_2$ [14], $Ce(OTf)_3$ [15] and $Bi(OTf)_3$ [16] as catalysts or stoichiometric reagents. Recently, it was reported that I_2 is also a useful catalyst for acetylation of alcohols under solvent

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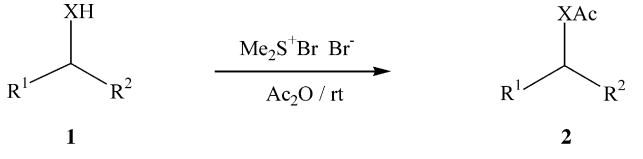

1 **2**

X = O / NH / S

R^1 = alkyl / aryl / sugar residue/ nucleoside residue;
R^2 = H, alkyl, aryl

Scheme 1.

free conditions [17]. Though perchlorates [8–10] have been found to be effective catalysts for this transformation, but there is a serious drawback such as some of the perchlorates are highly explosive [18]. In addition, $Mg(ClO_4)_2$ should be anhydrous in order to obtain better yields [9]. The other methods based on triflates [11–16] or $RuCl_3$ [6] have some disadvantages: (i) the reagents are expensive and some of them difficult to handle [12], (ii) long reaction times, (iii) dry reaction conditions [4] and (iv) invariably aqueous work-up and chromatographic separation procedure. Although numerous methods are known in the literature in order to obtain good yields of the acetylated products, still there is a great demand for mild and effective catalyst, which can be used for acetylation reaction to a wide variety of substrates. In continuation of our research programme to develop better and newer synthetic methodologies [19], we realized that bromodimethylsulfonium bromide, which can generate HBr in the reaction medium on reaction with alcohol [20], might be a very useful pre-catalyst for the acetylation reactions. The pre-catalyst, bromodimethylsulfonium bromide, has been utilized so far for the transformations of alcohols to the corresponding bromides [20], oxidation of thiols to the disulfides [21], deprotection of dithioacetals [22] and preparation of α-bromoenones from the corresponding enones [23]. Very recently, we have demonstrated tetrahydropyranylation/depyranylation of alcohols and phenols [24] as well as acetalization and thioacetalization of carbonyl compounds [25], and also oxathioacetalization of carbonyl compounds [26] using the same pre-catalyst. These successful results further encouraged us to study whether the same pre-catalyst could be implemented further for acylation reactions or not. In this paper, we wish to report the acetylation of alcohols and phenols, amines, thiols and thiophenols by employing acetic anhydride in the presence of a catalytic amount of bromodimethylsulfonium bromide as pre-catalyst under solvent free conditions, as shown in Scheme 1.

2. Result and discussion

For our present study, firstly bromodimethylsulfonium bromide was prepared according to the literature procedure [23]. Then, we attempted the acylation reaction of cetyl alcohol (**1a**) with acetic anhydride in the presence of 5 mol% of bromodimethylsulfonium bromide at room temperature. We have noticed that the reaction was completed within 20 min and the pure acetate derivative of cetyl alcohol (**2a**) was obtained in 96% yield as a gummy liquid. The product was characterized by recording IR, ^{1}H NMR spectra and elemental analysis and is agreeable with the acetate. Next, we examined that benzoyl, benzyl, tosyl and *tert*-butyldimethylsilyl ether protected alcohols **1b–e** were converted smoothly to the corresponding acetates **2b–e** in good yields without affecting the protecting groups by following identical reaction conditions. All the products were characterized by recording IR, ^{1}H NMR spectra and elemental analyses. Likewise, various benzylic alcohols (**1f–k**), secondary alcohol (**1l**), allyl alcohol (**1m**) and 1,4-butynediol (**1n**) were also provided the corresponding acetate derivatives **2f–n** in good yields. It is interesting to mention that neither alkyl bromide formation from the corresponding alcohols nor HBr addition took place at the double bond or even at the triple bond during the experimental conditions. It was observed that the alkyl TBS ether did not survive during acetylation by employing $Ce(OTf)_3$ [15] as catalyst. However, our protocol has some advantage because the TBS group was unaffected during the reaction conditions. Moreover, a tertiary alcohol (**1o**) as well as a sterically hindered tertiary alcohol adamantanol (**1p**) was smoothly converted to the corresponding acetate derivatives **2o** and **2p**, respectively, without the formation of elimination product. The product **2o** was also confirmed by recording ^{13}C NMR spectrum as well as ^{1}H NMR spectrum. We have noticed that the present method is more efficient in terms of reaction timing as compared to the ruthenium(III) chloride method [6] particularly for the preparation of **2p**. After that we wanted to investigate the versatility of the reagent for acetylation of phenolic compounds. By using our protocol, the phenolic compounds **1q** and **1r** were transformed smoothly to the corresponding acetate derivatives **2q** and **2r**. Again, we have observed that 4-nitrophenol (entry **1r**) was converted to the acetate derivatives much faster as compared to the earlier reported procedure [6]. Remarkably, an alcohol containing isopropylidene group **1s** can also be acetylated under identical conditions without cleavage of the isopropylidene group. Next, we intended to further study whether the present methodology could be extended for acetylation of carbohydrates and nucleosides. We have found that various carbohydrate molecules, such as **1t–v** and thymidine (**1w**) were converted to the corresponding acetate derivatives **2t–w** in good yields under identical reaction conditions. Importantly, thio- and methoxyl group at the anomeric position were unaffected during experimental conditions. The reaction times and yields of the products are summarized in the Table 1. All the acetylated products were characterized by recording IR, ^{1}H NMR spectra and elemental analyses, and in full agreement with the expected products. By using our protocol, aliphatic and aromatic amines (entry **1x–y**) as well as thiols (entry **1z** and **1a′**) were transformed to the corresponding acetate derivatives **2x–a′** in good yields by employing the same pre-catalyst.