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Bismuth compounds in organic synthesis. Bismuth nitrate catalyzed chemoselective synthesis of acylals from aromatic aldehydes.

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Abstract—Aromatic aldehydes are smoothly converted into the corresponding acylals in good yields in the presence of 3–10 mol% $Bi(NO_3)_3 \cdot 5H_2O$. Ketones are not affected under the reaction conditions. The relatively non-toxic nature of the catalyst, its ease of handling, easy availability and low cost make this procedure especially attractive for large-scale synthesis.

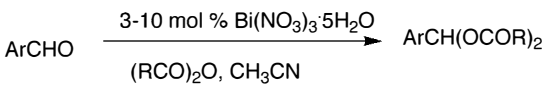
Keywords: Bismuth nitrate, Acylals, Environment-friendly, Anhydrides.

1. Introduction

Acylals (geminal diesters) are frequently used as protecting groups for aldehydes because they are stable to neutral and basic conditions.[1] In addition, the acylal functionality can be converted into other useful functional groups by reaction with appropriate nucleophiles.[2] For example, recently a novel synthesis of chiral allylic esters has been developed using palladium-catalyzed asymmetric allylic alkylation of *gem*-diesters.[3] The synthesis of homoallyl acetates by allylation of 1,1-diacetates has also been reported.[4] We have reported the use of bismuth triflate, $Bi(CF_3SO_3)_3 \cdot 4H_2O$ as a highly efficient and relatively non-toxic catalyst for the synthesis of acylals.[5] Although bismuth compounds are attractive due to their remarkably low toxicity,[6] low cost and ease of handling, one drawback of bismuth triflate is that it is not yet commercially available and must be synthesized in the laboratory. Our continued work with bismuth compounds has led to the discovery of bismuth nitrate pentahydrate, $Bi(NO_3)_3 \cdot 5H_2O$, an inexpensive, easy-to-handle, commercially available solid as a versatile catalyst for the chemoselective formation of acylals from aromatic aldehydes. The most commonly used reagent for acylal formation is acetic anhydride which results in the formation of 1,1-diacetates. Some examples of the reagents and catalysts that have been developed for this purpose include LiOTf,[7] ceric ammonium nitrate,[8] $InCl_3$,[9] H_2NSO_3H,[10] $LiBF_4$,[11] H_2SO_4,[12] PCl_3,[13] NBS,[14] I_2,[15] TMSCl-NaI,[16] anhydrous ferrous sulfate[17] and $FeCl_3$.[18] Several inorganic heterogeneous catalysts have also been developed as catalysts for synthesis of acylals.[19] Lewis acids such as $Cu(OTf)_2$ (2.5 mol%)[20] and $Sc(OTf)_3$ (2 mol%)[21] are also efficient for this conversion. Many of these reagents are highly corrosive and difficult to handle while some Lewis acid catalysts such as copper and scandium triflate are rather expensive and moisture sensitive. Some procedures require the use of a large excess (5–8 equiv.) of acetic anhydride to effect acylal formation.[7] Further, there are very few reports in the literature on formation of acylals using other anhydrides.[11] Given the synthetic utility of acylals, newer reagents that are inexpensive, non-toxic, chemoselective and effective for acylal formation with a variety of anhydrides would provide a valuable addition to the literature.

2. Results and discussion

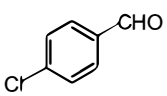
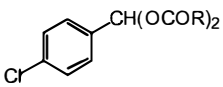
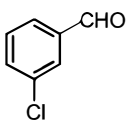
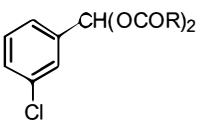
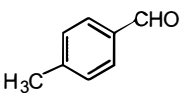
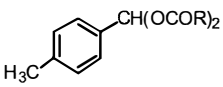
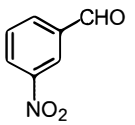
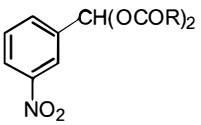
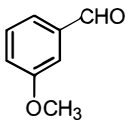
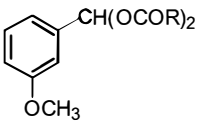
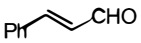
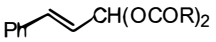
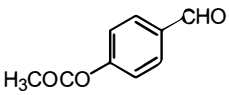
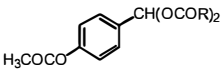
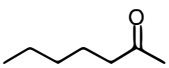
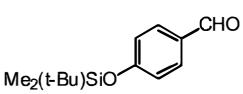
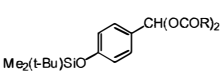
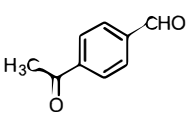
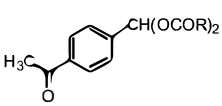
We now report that bismuth nitrate, $Bi(NO_3)_3 \cdot 5H_2O$ is an efficient catalyst for the chemoselective conversion of aromatic aldehydes to a variety of acylals (Scheme 1 and Table 1).



Scheme 1.

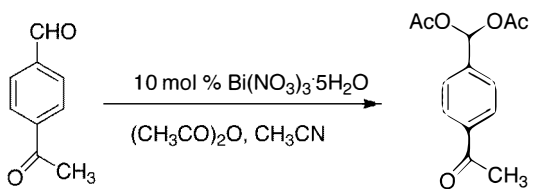
The experimental procedure for the synthesis of the acylals is simple and involves stirring the aldehyde and the corresponding anhydride as a solution in acetonitrile. The product is isolated by extraction with a relatively non-toxic and industry-friendly solvent, ethyl acetate. A wide variety of aromatic aldehydes (Table 1, entries 1–6) underwent

Table 1. Formation of acylals using $Bi(NO_3)_3{\cdot}5H_2O$ in CH_3CN

Entry[a]	Substrate	Anhydride $(RCO)_2O$	Time	Product	Yield[b]	^{13}C NMR data ($CDCl_3$)
1[18]	PhCHO	R=CH_3	1.5 h	$PhCH(OCOR)_2$	87	(R=CH_3) δ 20.5, 89.4, 126.4, 128,4, 129.5, 135.3, 168.5
		R=CH_3	6 h		80[c]	
		R=*n*-Pr	16 h		91	(R=*n*-Pr) δ 13.4, 18.1 35.8, 89.3, 126.5, 128.4, 129.5, 135.7, 171.3
		R=*i*Pr	4 h		68	(R=*i*-Pr) δ 18.4, 18.6, 39.7, 89.3, 126.3, 128.4, 129.3, 135.7, 174.6
2[26]		R=CH_3	3 h		76[c]	(R=CH_3) δ 20.5, 89.0, 128.1, 128.7, 133.9, 135.6, 168.6
		R=*n*-Pr	4 h		80	(R=*n*-Pr) δ 13.3, 18.1, 35.7, 88.7, 127.9, 128.7, 134.2, 135.4, 171.2
		R=*i*Pr	15 h		82	(R=*i*-Pr) δ 18.4, 18.6, 39.7, 85.7, 127.9, 128.6, 134.3, 135.3, 174.6
3[26]		R=CH_3	4 h		86	δ 20.7, 88.7, 124.9, 126.7, 129.8, 129.8, 134.4, 137.3, 168.5
4[26]		R=CH_3	2.5 h		79	δ 20.8, 21.2, 89.7, 126.5, 129.2, 132.5, 139.7, 168.7
		R=CH_3	14 h		77[d]	
5[26]		R=CH_3	2.5 h		85[e]	δ 20.6, 88.2, 121.7, 124.4, 129.7, 132.8, 137.4, 148.1, 168.5
6[7]		R=CH_3	15 h		57	δ 20.5, 54.9, 89.2, 111.9, 115.0, 118.6, 129.5, 136.7, 159.5, 168.5
7[18]		R=CH_3	6 h		82[c]	
		R=CH_3	18 h		94[d]	
8[26]		R=CH_3	16 h		91	δ 20.7, 20.9, 88.9, 121.7, 127.9, 132.9, 151.4, 168.5, 169.1
9		R=CH_3	[f]	NR		
10[7]		R=CH_3	14 h		59[c]	δ −4.5, 18.1, 20.8, 25.5, 89.6, 120.0, 128.0, 128.2, 156.8, 168.7
11[5]		R=CH_3	19 h		91	

[a] Superscript against the entry # refers to literature reference for the product.
[b] Refers to yield of isolated product. Yields are not optimized. Unless otherwise mentioned, the purity was estimated to be >98% by ^1H and ^{13}C NMR spectroscopy.
[c] Reaction was carried out with 5.0 mol% $Bi(NO_3)_3{\cdot}5H_2O$.
[d] Reaction was carried out with 3.0 mol% $Bi(NO_3)_3{\cdot}5H_2O$.
[e] Reaction carried out under solvent-free conditions at reflux temperatures. Based on ^1H NMR analysis, the crude product contained 4% aldehyde.
[f] No reaction occurred even under reflux conditions.

smooth reaction to give the corresponding acylal in good yield. Phenolic ester groups which are fairly unstable at low and high pH were stable to the reaction conditions (entry 8). In contrast to aromatic aldehydes, the results with saturated aliphatic aldehydes were less promising. Aliphatic aldehydes reacted sluggishly even under solvent-free conditions, and even after 12 h, 50% of unreacted starting material remained. Acylal formation employing acetic anhydride was attempted with several aldehydes including heptanal, hexanal and phenylpropionaldehyde. In all cases, the product mixture consisted of the expected acylal, unreacted starting material and several unidentifiable by-products. NMR analysis of the crude product in each case indicated that the side products were not consistent with the self-aldol condensation of these aldehydes. The spectra were also not consistent with the enol acetates that would form from the elimination of the expected acylal. Although *t*-butyldimethylsilyl (TBDMS) groups are relatively acid-sensitive, under the reaction conditions a moderate yield of the acylal from the TBDMS protected phenol (entry 10) was obtained. Deprotection of the TBDMS occurred to the extent of 15%. The pure acylal was obtained by column chromatography. In contrast, THP ethers proved unstable to the reaction conditions. When the THP ether of *p*-hydroxybenzaldehyde was subjected to the reaction conditions, acylal formation occurred but significant deprotection of the THP ether was also observed. Ketones proved completely resistant to acylal synthesis with acetic anhydride: no diacetate formed even under reflux conditions. The chemoselectivity of this method was demonstrated using acetylbenzaldehyde (entry 11). Smooth conversion of the aldehyde to the corresponding diacetate was observed while the ketone functionality remained unaffected (Scheme 2).

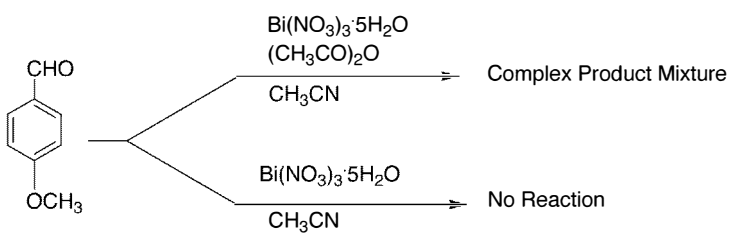


Scheme 2.

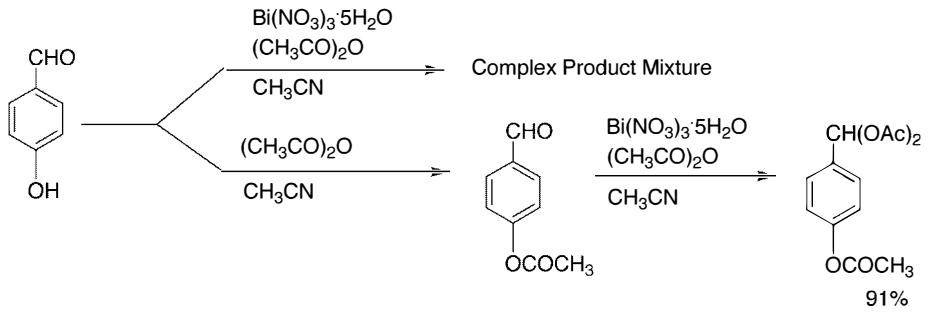
The formation of acylals from aromatic aldehydes bearing activating groups such as OCH_3 and OH proved troublesome. When *p*-anisaldehyde (*p*-methoxybenzaldehyde) was subjected to the reaction conditions with acetic anhydride, the resulting product mixture was found to be complex (Scheme 3). ^1H NMR analysis of the product mixture indicated that in addition to the expected acylal, at least three other compounds were present (^1H NMR indicated the presence of methoxy groups, δ 3–4). A control experiment in which a solution of *p*-anisaldehyde in CH_3CN was stirred with bismuth nitrate indicated that the starting aldehyde is stable to bismuth nitrate.

This observation suggested that the complex mixture results from reaction of the corresponding acylal product. It was not possible to get a pure sample of the acylal by column chromatography. In order to test whether the side-products arose as a result of activation of the acylal product by the electron-releasing *p*-methoxy group, the reaction was also attempted with *m*-methoxybenzaldehyde (at the *meta* position, the −I effect of the OCH_3 group would be operative but not the +R effect). In this case, it was possible to obtain the corresponding acylal in a 57% yield (unoptimized) after column chromatographic purification. When the pure acylal from *m*-methoxybenzaldehyde was subjected to the reaction conditions with acetic anhydride, nitration products were formed to the extent of 5–10%. It has also been reported in the literature that toluene can be nitrated by $Bi(NO_3)_3{\cdot}5H_2O$ impregnated on K10 montmorillonite in the presence of acetic anhydride.[22] However, the authors found that the nitration was quite solvent sensitive and no nitration occurred in acetonitrile. It is speculated that acetyl nitrate is an intermediate. We attempted the acylal formation reaction with *p*-tolualdehyde using both 3 and 10 mol% $Bi(NO_3)_3{\cdot}5H_2O$ as the catalyst. In both cases, in addition to the expected acylal, side products formed to the extent of 10–20%. NMR analysis of the crude product indicated that the use of 10 mol% $Bi(NO_3)_3{\cdot}5H_2O$ gave rise to more impurities than when 3 mol% $Bi(NO_3)_3{\cdot}5H_2O$ was used. While the side-products were not isolated, the spectral data of the crude material is consistent with formation of nitration products. The pure acylal was isolated by column chromatography. In contrast, it was not possible to obtain the acylal from *p*-hydroxybenzaldehyde in good yield. The product mixture was found to be very complex indicating that the OH group activates the ring toward substitution reactions. However, in the absence of bismuth nitrate, reaction of *p*-hydroxybenzaldehyde with acetic anhydride gave a good yield of *p*-acetoxybenzaldehyde (entry 8). When *p*-acetoxybenzaldehyde was subjected to the reaction conditions, smooth conversion to the acylal occurred. These results are consistent with the hypothesis that once the ring is no longer activated, ring substitution reactions do not occur and the acylal can be obtained in good yields (Scheme 4).

The reaction also worked with other acid anhydrides including butyric anhydride and isobutyric anhydride while most literature methods for acylal formation employ only acetic anhydride. It was difficult to separate the unreacted butyric and isobutyric anhydrides from the corresponding acylal product. The hydrolysis of higher



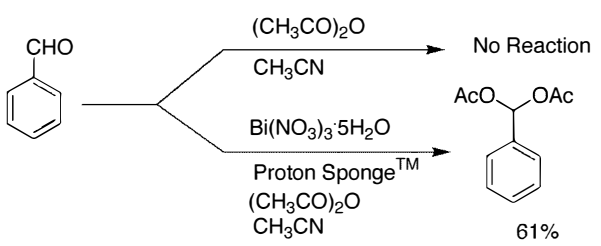
Scheme 3.



Scheme 4.

anhydrides with aqueous Na_2CO_3 is also considerably slower than the hydrolysis of acetic anhydride due to solubility problems. A practical solution to this problem was found by using methanol/aqueous Na_2CO_3 in the work-up. Pivalic anhydride and benzoic anhydride proved too unreactive at room temperature and significant reaction was not observed at higher temperatures. When bismuth nitrate is heated, it undergoes decomposition accompanied by the formation of a brown gas (NO_2). Therefore, all reactions were carried out at room temperature with the exception of entry 5.

While detailed mechanistic studies were not conducted, a few other points merit comment and are summarized in Scheme 5. No acylal formation was observed in the absence of bismuth nitrate. The possibility that the reaction is catalyzed by nitric acid released from bismuth nitrate pentahydrate in CH_3CN was considered. A suspension of bismuth nitrate in water as well as CH_3CN is acidic (pH=2). However, the reaction of benzaldehyde with acetic anhydride using 0.6 equiv. of HNO_3 did not afford the desired acylal in good yield. When the amount of HNO_3 was increased to 1.2 equiv. the starting aldehyde was recovered unchanged. The reaction of benzaldehyde with acetic anhydride catalyzed by bismuth nitrate in the presence of proton-sponge® (*N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalenediamine)[23] was also carried out. Although the reaction was slow, the desired product was formed in 61% yield after chromatographic purification. The lower yield resulted primarily from the small-scale of this experiment and the difficulty in separating the proton-sponge® from the acylal product. Although this result does suggest that the reaction is catalyzed by bismuth(III) acting as a Lewis acid, protic acid catalysis cannot be completely ruled out. In contrast, studies using bismuth bromide as a catalyst for deprotection of oximes as well as for synthesis of cyclic ethers using intramolecular etherification reactions of δ-trialkylsilyloxy aldehydes and ketones suggest that its main role is to generate HBr, which is the active catalyst.[24]



Scheme 5.

From our studies it is also evident that it is difficult to control the amount of nitric acid in the solution and hence bismuth nitrate is a more convenient reagent than nitric acid to catalyze this reaction. In the presence of water, bismuth nitrate is converted to bismuth subnitrate, $BiONO_3$. Bismuth subnitrate is commercially available and hence the reaction was also attempted with bismuth subnitrate. The reaction of benzaldehyde with acetic anhydride catalyzed by bismuth subnitrate was only 50% complete in 2 h.

3. Conclusions

In summary, a new catalytic method employing bismuth nitrate catalysis has been developed for the conversion of aromatic aldehydes to acylals with a variety of anhydrides. Advantages of this method include: (1) the use of an inexpensive, air-stable, commercially available and relatively non-toxic catalyst and (2) the observed chemoselectivity.

4. Experimental

4.1. General

NMR spectra were recorded on a JEOL Eclipse NMR spectrometer at 270 MHz (^{1}H) and 67.5 MHz (^{13}C) in $CDCl_3$ as the solvent. Flash chromatography was performed on Merck Silica gel (230–400 Mesh).[25] Reaction progress was monitored by TLC, GC analysis or by NMR spectroscopy. Thin layer chromatography was performed on aluminum backed silica gel plates. Spots were visualized under UV light or by spraying the plate with phosphomolybdic acid followed by heating. GC analysis was carried out on a Varian CP 3800 Gas Chromatograph. Although all the products have been previously reported in the literature, the ^{13}C spectral data for many of the acylals is not available. Hence, ^{13}C NMR data for selected acylals is reported in Table 1. Reagent grade acetonitrile was used for all reactions. The TBDMS ether from *p*-hydroxybenzaldehyde (entry 10, Table 1) was prepared by treatment of *p*-hydroxybenzaldehyde with *tert*-butyldimethylsilyl chloride in the presence of DMAP and triethylamine.

4.1.1. Representative procedure for formation of acylal using acetic anhydride. A solution of *p*-tolualdehyde (1.00 g, 8.32 mmol) in reagent grade CH_3CN (5 mL) was stirred as acetic anhydride (2.36 mL, 24.96 mmol, 3 equiv.) and $Bi(NO_3)_3{\cdot}5H_2O$ (0.404 g, 0.832 mmol, 10 mol%) were

added. The resulting mixture was stirred under N_2 at room temperature for 2.5 h and then aqueous saturated Na_2CO_3 solution (20 mL) was added. The resulting mixture was stirred for 20 min and then extracted with EtOAc (3×25 mL). The combined organic layers were washed with saturated NaCl solution (20 mL) and dried (Na_2SO_4). The solvents were removed on a rotary evaporator to yield 1.71 g of the crude product. A portion of the product (1.66 g) was purified by flash column chromatography on 70 g of silica gel (ethyl acetate/hexane, 1:9 as the eluent) to yield 1.43 g (overall yield 79%) of the acylal which was characterized by ^1H and ^{13}C NMR spectroscopy.

4.1.2. Representative procedure for formation of acylal using higher anhydrides. A solution of *p*-chlorobenzaldehyde (1.00 g, 7.11 mmol) in reagent grade CH_3CN (5 mL) was stirred as isobutyric anhydride (3.54 mL, 21.3 mmol, 3 equiv.) and $Bi(NO_3)_3{\cdot}5H_2O$ (0.345 g, 0.71 mmol, 10 mol%) were added. The resulting mixture was stirred under N_2 at room temperature for 15 h and then CH_3OH/aqueous Na_2CO_3/H_2O (1:1:1, v/v/v) was added. The mixture was then stirred for 30 min and then extracted with EtOAc (3×25 mL). The combined organic layers were washed with saturated NaCl solution (15 mL) and dried (Na_2SO_4). The solvents were removed on a rotary evaporator and the product was then placed under high vacuum at 40 °C (oil bath) to yield 1.74 g (82%) of the desired acylal which was characterized by ^1H and ^{13}C NMR spectroscopy.

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