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Carbon Tetrabromide/Sodium Triphenylphosphine-*m*-sulfonate (TPPMS) as an Efficient and Easily Recoverable Catalyst for Acetalization and Tetrahydropyranylation Reactions

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Abstract: A solid complex, conveniently prepared from carbon tetrabromide and sodium triphenylphosphine-*m*-sulfonate (TPPMS), can be used as an easily recoverable catalyst for the selective acetalization of aldehydes and tetrahydropyranylation of alcohols. The catalyst can be recovered by simple precipitation with ether and can be reused at least 7 times without loss of catalytic activity.

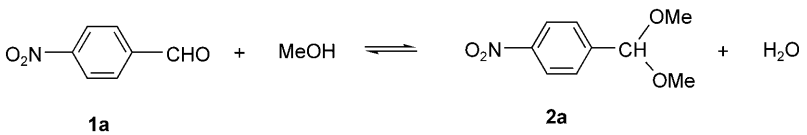
Keywords: acetalization; carbon tetrabromide; organocatalysts; sodium triphenylphosphine-*m*-sulfonate; tetrahydropyranylation

Introduction

Carbon tetrabromide (CBr_4) has been used as organocatalyst for a variety of organic transformations. For example, it catalyzes the hydrolysis of acetals in acetonitrile/water solution,[1] the hydrolysis of tetrahydropyranyl ethers in methanol,[2] the cleavage of trityl ethers in methanol,[3] the deprotection of trialkylsilyl esters,[4] as well as selectively β-(trimethylsilyl)ethoxymethyl ethers.[5] It also serves as the catalyst for esterification[4,6,7] and epoxide ring opening.[8] More recently, carbon tetrabromide has been found to mediate the formation of carbon-sulfur bond[9] and thioureas.[10] As a catalyst, CBr_4 offers the advantages that the reaction conditions are generally mild, and the reactions are often chemo-[11] as well as regioselective.[8] On the other hand, CBr_4 is an irritant and a toxic substance (IVN-MUS LD_{50}: 56 mg kg^{-1}) and may cause damage to liver and kidney.[12] Its release into the environment would be hazardous. Because of the ready solubility of CBr_4 in many organic solvents, the separation and recovery of CBr_4 from the reaction mixture usually require chromatography.[1–10] In here, we describe a catalytic system of CBr_4 which is stable, functions under mild conditions, is easily recoverable from the reaction mixture, and reusable for acetalization and tetrahydropyranylation reactions.

Results and Discussion

Since CBr_4 was able to catalyze the hydrolysis of acetals,[1] we reasoned that it can also be used for the formation of acetals from aldehydes and alcohols. Using *p*-nitrobenzaldehyde (**1a**) in methanol at 25 °C for 12 h as the standard conditions, the catalytic formation of the acetal **2a** (Scheme 1) with CBr_4 was indeed found to be effective, giving a yield of 88% (Table 1, entry 1). It is more effective than the commonly used *p*-toluenesulfonic acid (PTSA) which gave **2a** in 67% yield under the same conditions (entry 2). Interestingly, the use of triphenylphosphine (TPP)/CBr_4, a reagent usually used for the Corey–Fuchs[13] and



1a 2a

Scheme 1. Acetalization of *p*-nitrobenzaldehyde with methanol.

Table 1. Acetalization of *p*-nitrobenzaldehyde according to Scheme 1.

Entry	Catalyst used	Yield [%]of **2a**[a]
1	CBr_4	88
2	PTSA	67
3	TPP/CBr_4	90
4	TPPMS/CBr_4 (**3**)	>95
5	TPPMS	0
6	TPPMSO	0
7	TPPMS/HBr	60
8	TPPMSO/HBr	33
9	TPPMSO/CBr_4	86

[a] The yield was based on the ^{1}H NMR spectra of crude reaction mixtures.

Appel[14] reactions, was equally effective in catalyzing the acetalization (entry 3).

We have recently developed the use sodium triphenylphosphine-*m*-sulfonate (TPPMS) as a replacement of triphenylphosphine in the Wittig reaction.[15] The advantage of using TPPMS is that it and its oxidation product, sodium triphenylphosphine-*m*-sulfonate oxide (TPPMSO), can be easily separated and recovered from the reaction mixture by precipitation with a non-polar solvent, without the need for tedious chromatography as is usually required for the removal of triphenylphosphine oxide. We therefore examined the possibility of using TPPMS/CBr_4 as a catalyst for the acetalization reaction.

A mixture of TPPMS and carbon tetrabromide (1:1 molar ratio) was stirred at room temperature in methanol for several hours, then the reaction mixture was concentrated and ether was added to precipitate the TPPMS/CBr_4 complex (**3**) as a white solid. As we can see from Table 1, the complex **3** was able to catalyze the acetalization effectively giving >95% yield of **2a** (entry 4). The catalytic activity was not due to TPPMS, as the compound itself or its oxidation product TPPMSO, was devoid of activity (entries 5 and 6). Since CBr_4 may react with methanol to give HBr, we examined the catalytic activities of TPPMS/HBr and TPPMSO/HBr as well. Both were found to be active but not as efficient as **3** (compare entries 7 and 8 with entry 4). Finally, we also examined the complex TPPMSO/CBr_4 (**4**) and found that it also had catalytic activity (entry 9) but again not as effective as **3**.

A useful property of the complex **3** is that it is soluble in relatively polar organic solvents such as methanol but can be easily and quantitatively recovered from the reaction mixture by simply adding a non-polar organic solvent such as ether. This is illustrated in Figure 1. In Tube A, complex **3** was dissolved in methanol (sudan red 7B was added to aid viewing). By adding ether to the solution, **3** precipitated from the solution (Tube B). After filtration, the solid **3** (Tube D) can be separated from the filtrate (Tube C)

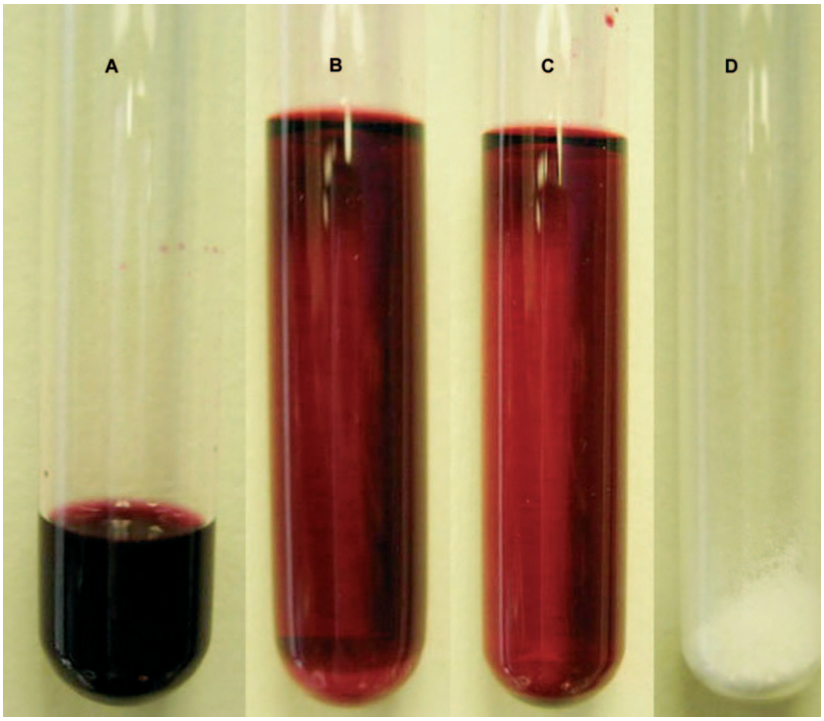


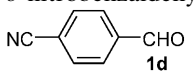
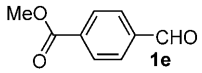
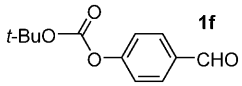
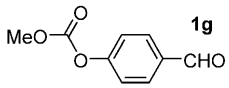
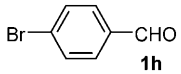
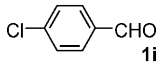
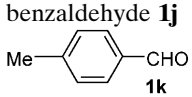
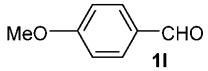
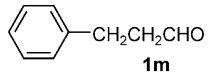
Figure 1. Recovery of complex **3**. Tube A) complex **3** (50 mg), sudan red 7B (3 mg) and MeOH (1 mL); Tube B) addition of Et_2O (3 mL); Tube C) filtrate obtained from filtration of B; Tube D) recovered **3** (47 mg) after washing with Et_2O (3×5 mL) and drying.

Table 2. Recycle of **3** for acetalization of *p*-nitrobenzaldehyde according to Scheme 1.[a]

Cycle	1	2	3	4	5	6	7
Yield	>95	>95	93	90	93	93	92

[a] The yield was based on the ^{1}H NMR spectra of crude reaction mixtures.

Table 3. Acetalization of various aldehydes with methanol.

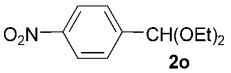
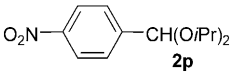
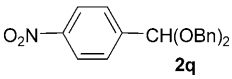
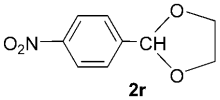
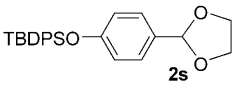
Entry	Aldehyde (**1**)	Isolated yield [%] of **2**
1	*p*-nitrobenzaldehyde **1a**	98
2	m-nitrobenzaldehyde **1b**	96
3	*o*-nitrobenzaldehyde **1c**	96
4	 **1d**	90
5	 **1e**	91
6	 **1f**	90[a]
7	 **1g**	81[a]
8	 **1h**	91
9	 **1i**	89
10	benzaldehyde **1j**	84
11	 **1k**	78
12	 **1l**	47 (77)
13	 **1m**	93
14	$CH_3(CH_2)_{10}CHO$ **1n**	92

[a] 2 mol% catalyst was used.

and recovered quantitatively. In the acetalization reaction, the separation and recovery of the catalyst **3** was therefore simply carried out by precipitation with ether after completion of the reaction (see Experimental Section). The recovered catalyst **3** can be reused without loss of catalytic activity. We demonstrated this with the acetalization of *p*-nitrobenzaldehyde with methanol using recovered **3** for seven cycles without diminished yield (Table 2).

The complex **3** was able to catalyze the acetalization of both aryl and aliphatic aldehydes with methanol as indicated in Table 3. The reaction conditions are usually quite mild, simply stirring of the solution

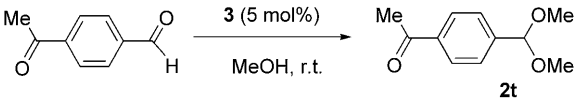
Table 4. Acetalization of benzaldehydes with various alcohols using **3** as catalyst.

Entry	ROH	Product	Yield [%]
1	EtOH	 **2o**	96
2	*i*-PrOH/DCM	 **2p**	91
3	BnOH/DCM	 **2q**	95
4	$(CH_2OH)_2$/DCM	 **2r**	95
5	$(CH_2OH)_2$/DCM	 **2s**	82[a]

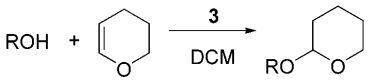
[a] 60 °C.

at room temperature overnight. In the case of *p*-methoxybenzaldehyde, the lower yield (entry 12) obtained was probably due to the equilibrium influenced by the methoxy substituent. Indeed, by adding a dehydrating agent ($MgSO_4$) to the reaction mixture, a higher yield (77%) of the acetal was obtained. Aliphatic aldehydes gave good yields of the corresponding acetals even without the need of a dehydrating agent. The ester function was stable to the acetalization conditions. Thus, aldehydes **1e** (entry 5) was efficiently acetalized. For aldehyde **1g** (entry 7), the methyl carbonate function was stable to the acetalization conditions but a lower amount of catalyst (2 mol%) was used, otherwise, cleavage of the carbonate function was observed. Interestingly, the *tert*-butoxycarbonyl function also survived the acid conditions at 2 mol% catalyst (entry 6). As expected,[4] trialkylsilyl ethers such as *t*-butyldimethylsilyl ether were cleaved under the reaction conditions. On the other hand, the more bulky *tert*-butyldiphenylsiloxy group was relatively stable (see below).

Acetalizations with alcohols other than methanol were also catalyzed by compound **3** (Table 4). In the case of higher boiling alcohols, a stoichiometric amount of the alcohol was used and the reaction was conducted in dichloromethane as the solvent (Table 4, entries 2–5). The product acetals were formed in good yields. In the case of *p*-*tert*-butyldiphenylsiloxybenzaldehyde (entry 5), the acetal **2s** was formed in good yield without cleavage of the silyl group. The catalytic system **3** showed remarkable chemoselectivity in acetalizing aldehydes only. Simple ketones such as benzophenone, acetophenone and cyclohexanone were completely unreactive with methanol and 5 mol% of **3** and no acetal was observed even after 48 h at room temperature or reflux for 8 h. Thus, 4-acetylbenzalde-



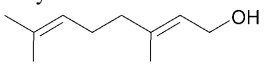
Scheme 2. Selective acetalization.



Scheme 3. Tetrahydropyanylation of alcohols.

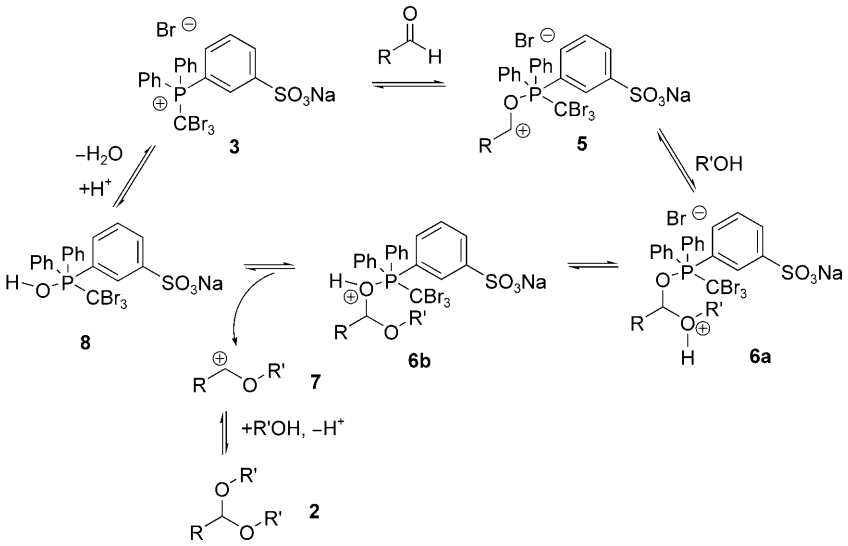
hyde was selectively acetalized with methanol using 5 mol% of **3** to give the acetal **2t** in quantitative yield (Scheme 2). Only a few of the acetalization methods reported the chemoselective protection of aldehydes in the presence of ketone function.[16,17j]

Table 5. Tetrahydropyranylation of alcohols according to Scheme 3.

Entry	ROH used	Yield [%]
1	4-nitrophenol	89
2	4-bromophenol	91
3	phenol	93
4	4-cresol	94
5	2-naphthol	87
6	1-hexanol	92
7	1-octanol	94
8	3-phenyl-1-propanol	95
9	cinnamyl alcohol	95
10	2-octanol	84
11	cyclohexanol	91
12	trityl alcohol	80
13		90

Tetrahydropyranylation is widely used to protect alcohols because they are stable enough to strong basic media, oxidative conditions, reduction with hydrides, and many reactive organometallic reagents such as Grignard reagents or lithium alkyls. On the other hand, tetrahydropyranyl ethers are easily deprotected under acidic conditions. The complex **3** was shown to be an effective catalyst for the tetrahydropyranylation of various alcohols at room temperature in dichloromethane (Scheme 3 and Table 5). As shown in Table 5, primary, secondary, benzylic, allylic alcohols and phenols with different substituents were converted to the corresponding THP ethers with good yields. The tertiary trityl alcohol was also converted to the THP ether in good yield (entry 12). The mild reaction conditions did not isomerize double bonds during the reaction (entries 9 and 13). The separation and recovery of catalyst **3** was conveniently achieved with the precipitation/filtration sequence initiated by the addition of diethyl ether.

The exact structure of complex **3** has not been firmly established. In the case of triphenylphosphine/CBr_4, it was generally assumed that a phosphonium intermediate was formed, involving the cleavage of the C–Br bond.[13,14] Using that as analogy, a plausible mechanism for the catalytic action of **3** is illustrated in Scheme 4. The aldehyde is activated by coordination with the phosphonium intermediate **3** to give the pentacovalent intermediate **5**. Recently, phosphonium salts have been proposed as novel metal-free Lewis acid catalysts by virtue of the hypervalent intereaction through the formation of pentacoordinate intermediates.[17] Addition of alcohol to **5** gives the hemiacetals **6**. Dissociation of **6** gives the cationic intermediate **7** and the phosphorus compound **8**. Reaction of **7** with another alcohol gives the acetal **2** with the release of



Scheme 4. Mechanism for the catalyzed acetalization reaction by **3**.

a proton whereas **8** acquires a proton to regenerate **3**. In the catalytic cycle, aldehyde is converted to the acetal with the formation of a water molecule. A similar mechanism can be suggested for the tetrahydropyranylation of alcohols.

Conclusions

In conclusion, we have demonstrated that the TPPMS/CBr_4 complex **3** is a highly efficient catalyst for the synthesis of both cyclic and acyclic acetals from a range of aldehydes in high yields. The synthesis proceeds at room temperature without the requirement of inert or anhydrous reaction conditions. The catalyst **3** is stable and can be kept readily. It is easily separable from the substrate and product and can be recovered and reused without loss of catalytic activity for at least 7 cycles. The catalyst also works for the tetrahydropyranylation of various alcohols.

Experimental Section

Preparation of the TPPMS/CBr_4 Complex 3

A mixture of TPPMS (728 mg, 2 mmol) and carbon tetrabromide (663 mg, 2 mmol) was stirred at room temperature in methanol (10 mL). After 4 h, the reaction mixture was concentrated and ether was added. After filtration, the TPPMS/CBr_4 complex **3** was obtained as a white solid; yield: 1 g (70%). ^{1}H NMR (400 MHz, CD_3OD): $\delta = 8.10$–8.07 (m, 2H), 7.82–7.77 (m, 1H), 7.69–7.63 (m, 7H), 7.58–7.54 (m, 4H); ^{31}P NMR (81 MHz, CD_3OD): $\delta = 32.7$ (s, 1P); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 146.1$, 146.0, 133.5, 133.4, 132.9, 132.8, 132.8, 132.0, 131.9, 131.8, 131.5, 130.4, 130.0, 129.9, 129.3, 129.2, 129.1, 129.0, 129.0, 128.9.

Standard Conditions to Assess the Catalytic Activity of Various Catalysts According to Scheme 1 (Table 1)

The catalyst (5 mol%) and *p*-nitrobenzaldehyde (0.2 mmol) were added to methanol (1 mL). The reaction mixture was stirred at room temperature for 12 h. Ether (3 mL) was added and the mixture was filtered. The filtrate was evaporated to give the crude product. The yields were based on the ^{1}H NMR spectra of the crude products.

Typical Procedure for Acetalization

(a): The TPPMS/CBr_4 complex **3** (5 mol%) and the appropriate aldehyde (0.2 mmol) were added to the appropriate alcohols (1 mL, for methanol or ethanol). The reaction mixture was stirred at room temperature overnight. Ether (3 mL) was added and the solid TPPMS/CBr_4 complex **3** was recovered by filtration. The liquid filtrate was evaporated to give the corresponding acetal products, usually in good purity. In some cases, further purification by chromatography may be required to purify the product from the unreacted aldehyde.

(b): In the case of high boiling alcohols, the TPPMS/CBr_4 complex **3** (5 mol%) and the appropriate aldehyde (0.2 mmol) were added to dichloromethane (1 mL). The appropriate alcohol (0.24 mmol, 1.2 equiv.) was added and the reaction mixture was stirred at room temperature overnight. The mixture was worked up in the same manner as above to recover **3** and to obtain the acetal.

Recycling Study

The catalyst **3** (5 mol%) and *p*-nitrobenzaldehyde (30 mg, 0.2 mmol) was added to methanol (1 mL). The reaction mixture was stirred at room temperature for 12 h. Ether (3 mL) was added and the mixture was filtered. The solid recovered was dissolved in methanol (1 mL) for the next round of acetalization. Seven cycles were done and the yields were 95%, 95%, 93%, 90%, 93%, 93%, 92% based on ^{1}H NMR spectra.

Typical Procedure for Tetrahydropyranylation

To a solution of 3,4-dihydro-2*H*-pyran (0.3 mmol) and the appropriate alcohols or phenols (0.2 mmol) in DCM (1 mL), the TPPMS/CBr_4 complex **3** (5 mol%) was added. The mixture was stirred overnight at room temperature. To the mixture, ether (3 mL) was added. The TPPMS/CBr_4 complex **3** was recovered by filtration. The liquid filtrate was evaporated to give the corresponding products, usually in good purity. Column chromatography may be necessary in some case to give pure product.

The acetals and the tetrahydropyranyl ethers are all known compounds: They were properly characterized and found to be in agreement with literature reports.[18]

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