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Utilization of hexabromoacetone for protection of alcohols and aldehydes and deprotection of acetals, ketals, and oximes under UV irradiation

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Abstract Hexabromoacetone (HBA) was efficiently used for the protection of alcohols and aldehydes and deprotection of benzaldehyde dimethyl acetal, solketal, and other acetals and ketals. In only 10 min, the protection of glycerol yielded 90% of solketal and protection of benzaldehyde gave 95% of benzaldehyde dimethyl acetal. The deprotection of benzaldehyde dimethyl acetal under UV irradiation gave over 90% yield of benzaldehyde within 15 s using only 2.5 mol% of HBA. HBA was also successfully used for deoximation. Solvent was found to play an important role in the efficiency of HBA for these reactions.

Keywords Hexabromoacetone · Glycerol · Solketal · Diol · Aldehyde · Ketal · Acetal · Protection · Deprotection · Oxime

Introduction

Conversion from one functional group to another is not always straightforward. Occasionally, when there are two or more functional groups in the same molecule, protection of one or more functional groups may be necessary in order to chemoselectively perform a reaction at the desired part of the molecule. The process does add additional steps to the synthesis, and even though there have been attempts to avoid protection and subsequent deprotection steps [1–4], it is arguably still the method that is more commonly used. Despite having many established methods for

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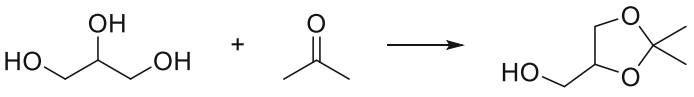
protection and deprotection [5], researchers still try to find a more selective, convenient, rapid, and economical method. Depending on the reaction performed, functional groups that are normally required to protect are hydroxyl, amine, carbonyl, carboxylic acid, phosphate, and terminal alkyne. Hydroxyl and carbonyl compounds are the main focus here.

When the compound that is being worked on has a hydroxyl group and there is a need to carry out a transformation on another functional group in the molecule, such as oxidation, acylation, halogenation with phosphorus or hydrogen halides, and dehydration, then this hydroxyl group likely requires to be protected [5]. Hydroxyl compounds are normally protected by converting them to ethers or esters, while 1,2- and 1,3-diols can be protected by making cyclic acetals and ketals. Among various cyclic acetals and ketals that have been reported, the formation of acetonide (isopropylidene ketal) is the most commonly used protection for 1,2- and 1,3-diols. The use of acetone, which is cheap, readily available and easy to remove, and other small molecules also makes this method attractive as a protective group. Because of its advantages and popularity, 33 preparative methods using various reagents and catalysts were listed in the latest edition of *Greene's Protective Groups in Organic Synthesis*, while the classical method is the reaction of diol with acetone using an acid as a catalyst [5].

Acetalization is not only for protection of hydroxyl group but it can also be used for producing fine chemicals. For instance, with the recent popularity of biodiesel, large excess glycerol byproduct is being produced, and one way to convert this excess glycerol to a fine chemical is to make its ketal, called solketal, as shown in Scheme 1. Solketal is a valuable chemical and being utilized as a solvent, plasticizer, surfactant, flavor enhancer, pharmaceutical intermediate, and fuel additive [6]. Latest examples of publications on the production of solketal from glycerol include the use of $Lu(OTf)_3$ [7], a batch process using sulfonic ion exchange resin Lewatit GF101 [8], metal-containing TUD-1 mesoporous silicates as solid acid catalysts [9], β and Y zeolites and KU-2 and Amberlyst 70 cation-exchange resins [10], M-$AlPO_4$/$x$$AlPO_4$ (x = Zn, Cu, Ni, or Co) solid acid catalysts [11], various types of Brønsted solid acid catalysts including various forms of zeolites, Amberlyst-15, cesium salt of phosphotungstic acid (CsHPW), montmorillonite K-10, molybdenum oxide supported on silica (MoO_3/SiO_2) [12], $SnCl_2$ [13], aluminum triflate-grafted MCM-41 [14], and organic–inorganic hybrid catalysts from organic ammonium salt and heteropoly acid [15].

For aldehydes and ketones, they are normally converted to an acetal or ketal [5, 16]. A classical method for making acetals or ketals uses an acid to catalyze, and the mechanism is generally well known. The use of acid is sometimes not compatible with the intended substrate and the reaction generally requires the use of the Dean–Stark apparatus to remove water and shift the equilibrium toward the



Scheme 1 Conversion of glycerol to solketal

product. Many methods have been reported for the preparation of acetals and ketals. Some recent examples are the use of (bromodimethyl)sulfonium bromide [17], various Brønsted acidic imidazolium salts [18, 19], and metal organic frameworks (MOFs) as solid heterogeneous catalysts [20, 21].

After protection of the susceptible group and transformation of the desired group, the next step is deprotection. Traditionally, deprotection of acetal uses acid as a catalyst. Other reagents or catalysts that can be used for the deprotection of acetals and ketals include CF_3COOH [22], PTSA [23], $LiBF_4$ [24], HCO_2H [25], Amberlyst-15 [26], Me_2BBr [27], I_2 [28], hollow mesoporous aluminosilica spheres [29], mesoporous silica-supported Er(III) catalyst [30], zeolite ZSM-5 embedded in the walls of hollow fibers [31], chloral hydrate [32], TiF_4 [33], and silica sulfuric acid and wet SiO_2 [34]. In another interesting example, Williams et al. [35] reported that various aliphatic and aromatic dimethyl and diethyl acetals and dketals can be hydrolyzed when heated at 80 °C in neat water or aqueous medium without a catalyst or additive. Recently, there has been growing interest in multistep cascade reactions, and the conversion of acetal to aldehyde has been a part of several multistep cascade reactions [36–50].

Formation of oximes is another way to protect carbonyl compounds, even though it is not very popular because it still possesses an acidic hydrogen and a quite reactive C=N [5]. They can then be cleaved by oxidation, reduction, or hydrolysis in the presence of another carbonyl compound [5, 51]. Many methods have been reported, and over 60 methods were summarized in *Greene's Protective Groups in Organic Synthesis* [5]. It should be noted that carbonyl compounds are also byproducts for Beckmann rearrangement by various catalysts [52–55]. The latest discoveries that have been reported are the use of $NaClO_2$ in water [56], ruthenium trichloride and *p*-toluenesulfonic acid (PTSA) in a mixture of dimethylacetamide and water for deoximation [57], sodium bromate in the presence of acidic ionic liquid [bmim]HSO_4 [58], *p*-chloroperbenzoic acid [59], mixed iron and copper hexacyanocolbatate [60], sym-collidinium chlorochromate (S-COCC) [61], nano-manganese-catalyst and *N*-hydroxyphthalimide (2-hydroxy-1H-isoindole-1,3-dione) under oxygen pressure [62], and anhydrous $AlCl_3$ supported on nano-silica [63].

Even though hexabromoacetone (HBA) was first reported hundreds of years ago [64], there have been a few reports on its applications. Recently, it has been used for the bromination of alcohols [65–67], as a tribromoacetylating agent for the preparation of tribromoacetamide [68–70], as a mediator in the conversion of carboxylic acids into amides [70], and as a catalyst for the chemoselective *N*-tert-butyloxycarbonylation of amines [71]. To explore its potential applications, HBA was tested for the protection of alcohols, aldehydes, and ketones and deprotection of various acetals and ketals, and it could catalyze the reactions quickly and efficiently. In addition, it was also used for the conversion of oximes back to their corresponding carbonyl compounds.

Experimental

General

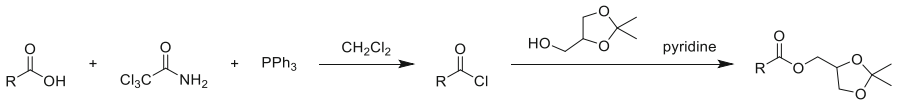
Chemicals and solvents were purchased from standard suppliers and were used without further purification. HBA was both synthesized [72] and obtained from Sigma–Aldrich. Oximes were prepared according to the literature [73]. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Ultrashield 400 Plus NMR spectrometer or a Varian Mercury NMR spectrometer with an Oxford YH400 magnet operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. GC analysis was performed using a Varian CP-3800 Gas Chromatograph equipped with SGE BP1 or BP21 column. A home-made UV reactor consisted of eight UV lamps (6 W, 254 nm, Sylvania G6 W T5) and a fan for ventilation. A magnetic stirrer was placed underneath the UV reactor for stirring the reaction. The reactions under UV irradiation were performed in custom-made quartz tubes for maximum UV transmission. The tubes were placed in the middle of the UV reactor at approximately 7 cm from the nearest UV lamp.

General procedure for preparation of dioxolane derivatives

To a 250-mL round-bottomed flask was added the corresponding carboxylic acid (25 mmol), trichloroacetamide (8.12 g, 50 mmol), triphenylphosphine (13.11 g, 50 mmol), and dichloromethane (100 mL) to give a colorless solution. The mixture was stirred and heated at reflux for 1 h. Then, solketal (3.11 mL, 25 mmol) and pyridine (6.04 mL, 75 mmol) were added to the resulting acid chloride solution and the reaction mixture was heated at reflux until completion as indicated by TLC (approximately 4 h). After completion, the solution was extracted with 10% HCl and sat. aq. $NaHCO_3$, dried over Na_2SO_4 and evaporated. The crude product was purified with a silica gel column eluting with 5% EtOAc/hexane (Scheme 2).

General procedure for protection of glycerol and diols with acetone

To a 25-mL quartz tube was added 1 mmol of glycerol or diol, 0.025 mmol (13 mg) of HBA, and 1 or 2 mL of acetone. The reaction mixture was stirred and irradiated by a home-made UV reactor for the desired time at room temperature. To quantify the product using GC, 1 mmol of naphthalene or biphenyl was added as an internal standard. The sample was diluted with acetone and injected into the GC equipped with a SGE BP21 or BP5 column.



Scheme 2 Procedure for preparation of dioxolane derivatives

General procedure for protection of diols with benzaldehyde

To a 25-mL quartz tube was added 1 mmol of a diol, 2.5 mmol benzaldehyde, 0.025 mmol (13 mg) of HBA, and 2 mL of dichloromethane. The reaction mixture was stirred and irradiated by a home-made UV reactor for 60 min at room temperature. To quantify the product using GC, 1 mmol (128 mg) of naphthalene was added as an internal standard. The sample was diluted with dichloromethane and injected into the GC equipped with a SGE BP5 column.

Representative procedure for protection of benzaldehyde with methanol

To a 25-mL quartz tube was added 1 mmol (106 mg) of benzaldehyde, 0.025 mmol (13 mg) of HBA, and 1 mL of methanol. The reaction mixture was stirred and irradiated by a home-made UV reactor for 10 min at room temperature. To quantify the product using GC, 1 mmol (154 mg) of biphenyl was added as an internal standard. The sample was diluted with methanol and injected into the GC equipped with a SGE BP1 column.

General procedure for protection of other aldehydes and ketones with methanol

To a 25-mL quartz tube was added 1 mmol of an aldehyde or ketone, 0.025 mmol (13 mg) of HBA, and 8 mL of methanol. The reaction mixture was stirred and irradiated by a home-made UV reactor for the desired time at room temperature. To quantify the product using GC, 1 mmol of naphthalene or biphenyl was added as an internal standard. The sample was diluted with methanol and injected into the GC equipped with a SGE BP5 column.

General procedure for protection of other aldehydes with ethylene glycol

To a 25-mL quartz tube was added 1 mmol of an aldehyde, 1.5 mmol ethylene glycol, 0.025 mmol (13 mg) of HBA, and 2 mL of dichloromethane. The reaction mixture was stirred and irradiated by a home-made UV reactor for 30 min at room temperature. To quantify the product using GC, 1 mmol of naphthalene or biphenyl was added as an internal standard. The sample was diluted with dichloromethane and injected into the GC equipped with a SGE BP5 column.

Representative procedure for deprotection of acetals and ketals

To a 25-mL quartz tube was added 1 mmol (152 mg) of benzaldehyde dimethyl acetal, 0.025 mmol (13 mg) of HBA, and 5 mL of solvent. The reaction mixture was stirred and irradiated by a home-made UV reactor for 1 min at room temperature. To quantify the product using GC, 1 mmol (154 mg) of biphenyl was added as an internal standard. The sample was diluted with methanol and injected into the GC equipped with a SGE BP1 column. To obtain an isolated yield, the solvent was evaporated and the crude product was purified using a silica gel column.

Representative procedure for conversion of oximes to ketones

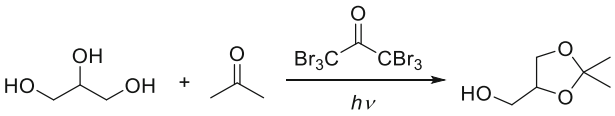
To a 25-mL quartz tube was added 1 mmol (113 mg) of cyclohexanone oxime, 0.2 mmol (106 mg) of HBA, 4 mL of CH_3CN, and 1 mL of water. The reaction mixture was stirred and irradiated by a home-made UV reactor for 2 min at room temperature. To quantify the product using GC, 1 mmol (154 mg) of biphenyl was added as an internal standard. The sample was diluted with methanol and injected into the GC equipped with a SGE BP21 column.

Results and discussion

Protection of glycerol with acetone

For the protection of glycerol with acetone to prepare solketal (Table 1) using 2.5 mol% of HBA as a catalyst under UV irradiation, the yield of solketal was 75% after only 1 min (entry 1) and 87% after 5 min (entry 2). Note that, for the reactions under UV irradiation, quartz test tubes were used in order to maximize the UV light transmitted to the reaction mixture. Increasing the reaction time to 10 and 30 min,

Table 1 Conversion of glycerol to solketal by HBA



Entry	Time (min)	Remaining glycerol (%)[a]	Yield of solketal (%)[a]
1	1	15	75
2	5	8	87
3	10	10	88
4	30	10	85
5[b]	10	12	86
6[c]	10	14	86
7[d]	10	5	90
8[e]	10	99	1
9[f]	10	100	0
10[e,f]	10	100	0

Reaction conditions: 1 mmol glycerol, 1 mL acetone, 0.025 mmol (2.5 mol%) HBA, room temperature

[a]Determined by GC and SGE BP21 column using naphthalene as an internal standard

[b]50 mg of molecular sieves type 4A was added to the reaction mixture

[c]0.050 mmol (5 mol%) HBA was used

[d]2 mL acetone was used

[e]Without HBA

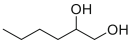
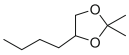
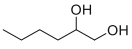
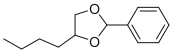
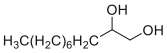
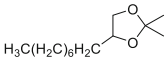
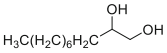
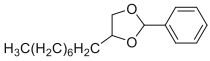
[f]Without UV irradiation

the yields did not change much (entries 3, 4). Reaction conditions were then changed to improve the product yield. Since the formation of acetal generally generates water, to drive equilibrium to the solketal product, a drying agent can be added to absorb water. However, in this case, when 50 mg of molecular sieves type 4A was added to the reaction mixture, the yield of solketal did not improve (entry 5). Doubling the amount of HBA still did not increase the product yield (entry 6) while doubling the amount of acetone only slightly increased the product yield (entry 7). It should be noted that, under UV irradiation and without HBA (entry 8), with HBA and without UV irradiation (entry 9), and without HBA and UV irradiation (entry 10), only trace amounts or no solketal was detected by GC. Overall, HBA was successfully used to catalyze the conversion of glycerol with acetone to solketal and only 2.5 mol% of HBA was used. Using higher amounts of acetone would give higher amounts of solketal product. The results here are much faster than those reported in the literature. For example, a catalyst based on mesostructured cellular foams gave only 72% conversion after 180 min [6], $Ln(OTf)_3$ produced 100% conversion and selectivity but took 1–3 h [7], and $SnCl_2$ gave a yield under 80% after 250 min at 60 °C [13].

Protection of diols

This protection method was then applied for the protection of 1,2-hexanediol and 1,2-decanediol using either acetone or benzaldehyde (Table 2). Protection of both diols with acetone proceeded quickly and the yields were 100% for both diols in 10 min (entries 1, 3). Benzaldehyde acetals of these two diols were also prepared, and after 60 min the yields were 74 and 63% for 1,2-hexanediol and 1,2-decanediol, respectively (entries 2, 4).

Table 2 Protection of other diols by HBA

Entry	Reagent	Protecting agent	Product	Time (min)	Yield (%) [a]
1[b]		Acetone		10	100
2[c]		Benzaldehyde		60	74
3[b]		Acetone		10	100
4[c]		Benzaldehyde		60	63

Reaction conditions: 1 mmol reagent, 0.025 mmol (2.5 mol%) HBA, under UV irradiation, room temperature

[a]Determined by GC and SGE BP5 column using naphthalene or biphenyl as an internal standard

[b]2 mL acetone

[c]2.5 mmol benzaldehyde, 2 mL CH_2Cl_2

Protection of benzaldehyde with methanol

The effect of the amount of methanol for protection of benzaldehyde with methanol

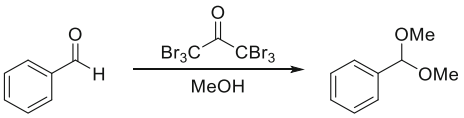
The amount of methanol was varied for the protection of benzaldehyde using HBA as a catalyst. Since this reaction is generally reversible, increasing the amount of methanol should shift the reaction toward the product. As shown in Table 3, when the amount of methanol increased from 0.5 to 16 mL, the amount of benzaldehyde dimethyl acetal did increase. The amount of the product reached a plateau of about 95% after 8 mL of methanol was used. The reactions were performed under UV irradiation for 10 min.

The effect of the amount of HBA for protection of benzaldehyde with methanol

The amount of HBA was also varied from 0.63 to 5 mol% in order to find the optimal amount (Table 4). The reactions were performed under UV irradiation for 10 min using 8 mL of methanol. At 0.63 mol%, only 66% of benzaldehyde dimethyl acetal was formed, indicating that this was too small an amount (entry 1). When the amount of HBA was raised to 1.25–5 mol%, the yields increased to above 90%, but were not over 95% (entries 2–4). This means that using between 1.25 and 2.5 mol% of HBA should be sufficient for this reaction. In addition, for control experiments, when the reactions were performed either without HBA or UV irradiation (entries 5–7), there was no acetal produced at all. This indicates that both HBA and UV irradiation are required.

In summary, protection of benzaldehyde with methanol by HBA produced very high yields of the acetal product in very short times. Higher amounts of methanol used will result in higher yields of the product. The amount of HBA can be reduced

Table 3 The effect of the amount of methanol for protection of benzaldehyde with methanol



Entry	MeOH (mL)	Remaining aldehyde (%)[a]	Yield of acetal (%)[a]
1	0.5	29	71
2	1	15	84
3	2	12	88
4	4	10	89
5	8	4	95
6	16	5	95

Reaction conditions: 1 mmol benzaldehyde, 0.025 mmol (2.5 mol%) HBA, 10 min UV irradiation, room temperature

[a]Determined by GC and SGE BP1 column using biphenyl as an internal standard

Table 4 The effect of the amount of HBA for protection of benzaldehyde with methanol

Entry	HBA (mol%)	Remaining aldehyde (%)[a]	Yield of acetal (%)[a]
1	0.63	33	66
2	1.25	9	91
3	2.5	4	95
4	5.0	10	90
5[b]	2.5	100	0
6	0	100	0
7[b]	0	100	0

Reaction conditions: 1 mmol benzaldehyde, 8 mL MeOH, 10 min UV irradiation, room temperature

[a]Determined by GC and SGE BP1 column using biphenyl as an internal standard

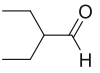
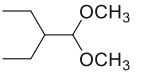
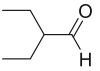
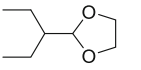
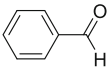
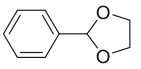
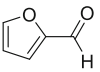
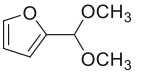
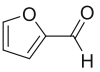
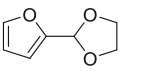
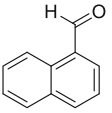
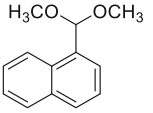
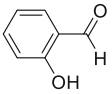
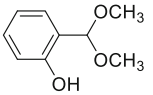
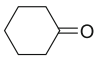
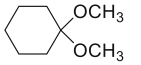
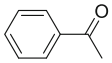
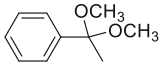
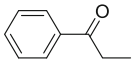
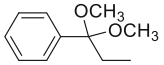
[b]Without UV irradiation

to as low as 1.25 mol% and the reaction can still produce high yields of the product. HBA-catalyzed protection of benzaldehyde with methanol is much faster than other recent methods in the literature. For instance, when Brønsted acidic imidazolium salts were used, it took 24 h to obtain yields of 98% [18] while MOFs-catalyzed reaction also took 24 h to produce 94% yield [20].

Protection of other aldehydes and ketones

This method was subsequently applied for the protection of other aldehydes and ketones using either methanol or ethylene glycol as a protecting agent into the corresponding dimethyl acetals or ketals (Table 5). Protection of an aliphatic aldehyde 2-ethylbutyraldehyde with methanol produced 95% of the acetal product in 10 min (entry 1), while protection with ethylene glycol (1.5 equivalent) in 2 mL dichloromethane took a longer time and gave 89% of the corresponding product in 30 min (entry 2). While the protection of benzaldehyde with methanol explained above gave up to 95% of product in 10 min, protection with ethylene glycol produced the lower yield at 60% in 30 min (entry 3). 2-Furaldehyde was readily protected with methanol and the yield was 97% in just 10 min (entry 4). However, with ethylene glycol, the yield was surprisingly low at 39% in 30 min (entry 5). The other two aldehydes tested were 1-naphthaldehyde and 2-hydroxybenzaldehyde, and protection with methanol gave the corresponding acetals at 83 and 76% in 60 min, respectively (entries 6, 7). This method was also tested with ketones, and for a cyclic aliphatic ketone, cyclohexanone, protection with methanol gave 68% of the ketal product in 10 min (entry 8). Protection of aromatic ketones were much more difficult and the yields for the protection of acetophenone and propiophenone with methanol were only 11 and 10% in 60 min, respectively. Therefore, more optimization is needed to provide better yields for the protection of ketones.

Table 5 Protection of other aldehydes and ketones by HBA

Entry	Reagent	Protecting agent	Product	Time (min)	Yield (%) [a]
1[b]		CH_3OH		10	95
2[c]		$HOCH_2CH_2OH$		30	89
3[c]		$HOCH_2CH_2OH$		30	60
4[b]		CH_3OH		10	97
5[c]		$HOCH_2CH_2OH$		30	39
6[b]		CH_3OH		60	83
7[b]		CH_3OH		60	76
8[b]		CH_3OH		10	68
9[b]		CH_3OH		60	11
10[b]		CH_3OH		60	10

Reaction conditions: 1 mmol reagent, 0.025 mmol (2.5 mol%) HBA, under UV irradiation, room temperature

[a]Determined by GC and SGE BP5 column using naphthalene or biphenyl as an internal standard

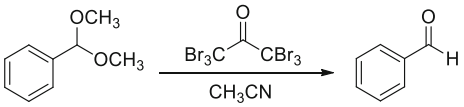
[b]8 mL MeOH

[c]1.5 mmol $HOCH_2CH_2OH$, 2 mL CH_2Cl_2

Deprotection of acetals and ketals

To demonstrate that HBA can deprotect acetals or ketals and is truly responsible for the deprotection and to investigate reaction parameters including the reaction time, molar ratio of HBA to substrate, and the amount of solvent (reaction concentration), various experiments were performed using the commercially available benzaldehyde dimethyl acetal as a model compound. Benzaldehyde dimethyl acetal was converted to benzaldehyde only when HBA was present under UV irradiation

Table 6 Controlled experiments for the deprotection of benzaldehyde dimethyl acetal by HBA



Entry	HBA (mmol)	UV irradiation (min)	Remaining acetal (%)[a]	Yield of Benzaldehyde (%)[a]
1[b]	0	0	100	0
2	0	5	101	0
3[b]	0.025	0	100	0
4	0.025	5	3	97

Reaction conditions: 1 mmol benzaldehyde dimethyl acetal, 0.025 mmol (2.5 mol%) HBA (if applicable), 5 mL CH_3CN, 5 min reaction time

[a]Determined by GC and SGE BP1 column using biphenyl as an internal standard

[b]The reaction tube was wrapped with aluminum foil

(Table 6). The protection of benzaldehyde dimethyl acetal was found to be very fast. To investigate this, the reaction was quenched with sat.aq. $NaHCO_3$ after 0.25, 0.5, 1, and 5 min, and the amounts of benzaldehyde dimethyl acetal and benzaldehyde were quantified by GC. Within 15 s, the yield was already over 90% (Fig. 1), which is remarkably much faster than other methods. For example, when silica sulfuric acid and wet SiO_2 was used, the reaction time was 60 min and must perform at 60–70 °C [34] and, in the case of I_2, it took 5–45 min [28].

Reaction conditions: 1 mmol benzaldehyde dimethyl acetal, 0.025 mmol (2.5 mol%) HBA, 5 mL CH_3CN, under UV irradiation. The amounts of the

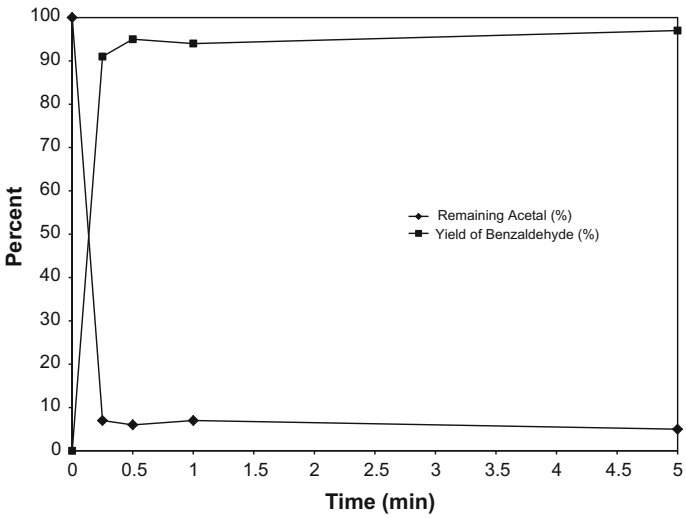


Fig. 1 Time-course investigation of the deprotection of benzaldehyde dimethyl acetal by HBA

substrate and product were determined by GC and SGE BP1 column using biphenyl as an internal standard.

In addition, HBA is also very efficient in the deprotection of benzaldehyde dimethyl acetal. When the amount of HBA was reduced to 1 mol%, the yield of benzaldehyde was 92% in 1 min. However, in 15 s, the yield of benzaldehyde was only 9%. Therefore, there is a tradeoff between the amount of HBA used and the reaction time. Higher amounts of HBA would take less time and vice versa. The effect of the amount of solvent, however, is more pronounced. Increasing the volume of CH_3CN also increases the yield of the product (Fig. 2). This could be because methanol produced from the reaction is more diluted in higher amounts of solvent and, therefore, the competing reverse reaction is much slower, giving higher amounts of product.

Reaction conditions: 1 mmol benzaldehyde dimethyl acetal, 0.0125 mmol (1.25 mol%) HBA, 1 min UV irradiation. The amounts of the substrate and product were determined by GC and SGE BP1 column using biphenyl as an internal standard.

Changing the solvent used in the reaction also changed the effectiveness of HBA as shown in Table 7. Chlorinated solvents gave the highest yields of benzaldehyde (entries 1, 2). Further investigation found that benzaldehyde dimethyl acetal is not very stable in this type of solvent. Upon irradiation under UV light in either 1,2-dichloroethane (DCE) or CH_2Cl_2 without HBA, benzaldehyde dimethyl acetal was converted to benzaldehyde, though at a lower rate than with HBA (62, 35% yield of benzaldehyde in 1,2-dichloroethane and CH_2Cl_2, respectively, after 5 min). Without UV irradiation, 11% of benzaldehyde was formed in 1,2-dichloroethane and a trace amount of benzaldehyde was formed in CH_2Cl_2 after 5 min. Acetonitrile was also a good solvent, giving 94% of benzaldehyde (entry 3). Acetone, THF, diethyl ether,

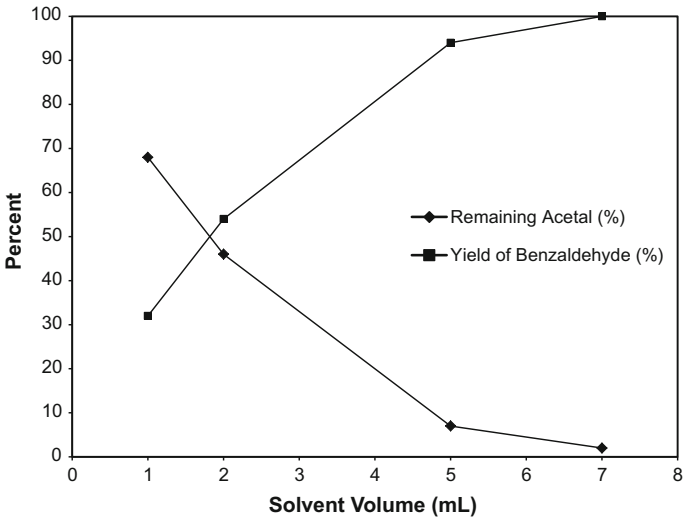
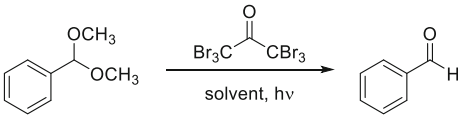


Fig. 2 The effect of the amount of solvent on the deprotection of benzaldehyde dimethyl acetal by HBA

Table 7 The effect of solvent on the deprotection of benzaldehyde dimethyl acetal by HBA



Entry	Solvent	Acetal (%)[a]	Yield (%)[a]
1	DCE	0	98
2	CH_2Cl_2	1	97
3	CH_3CN	6	94
4	Acetone	11	88
5	THF	1	86
6	Et_2O	13	63
7	Benzene	30	63
8	Hexane	21	58
9	MeOH	95	0
10[b]	EtOH	2	17

Reaction conditions: 1 mmol benzaldehyde dimethyl acetal, 0.025 mmol (2.5 mol%) HBA, 5 mL solvent, 1 min UV irradiation, room temperature

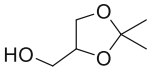
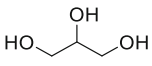
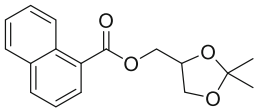
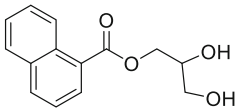
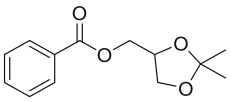
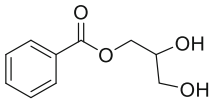
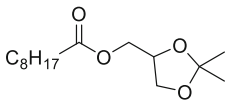
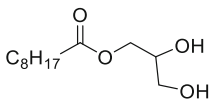
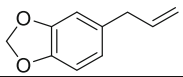
[a]Determined by GC and SGE BP1 column using biphenyl as an internal standard

[b]Major product was benzaldehyde diethyl acetal at 80% yield

benzene, and hexane gave less yield of benzaldehyde (entries 4–8). Using methanol as a solvent, no benzaldehyde product was formed (entry 9), indicating that the reverse reaction was dominating. In addition, when ethanol was used as a solvent (entry 10), transetherification occurred and benzaldehyde diethyl acetal was obtained as a major product (80%). In summary, reactions performed in solvents with higher relative polarity produced higher yields than solvents with lower relative polarity.

To further explore the potential of HBA for the deprotection of acetals and ketals, HBA was also successfully used to deprotect other acetals and ketals as shown in Table 8. For the deprotection of solketal, the reaction tooka much longer time than that of benzaldehyde dimethyl acetal. Methanol was found to be the best solvent. At first, several modifications of the reaction conditions were tried including raising the amount of HBA, variation of the amount of solvent, and increasing reaction time, but the yield of glycerol did not improve. When the product was prepared for verification using ^{1}H NMR, evaporation under reduced pressure was needed to evaporate the solvent. It was found that there was no solketal left. Sun et al. [28] also stated that, because of equilibrium between the substrate and the product, they had to raise the temperature to complete the reaction. However, in this case, after simple evaporation under reduced pressure, a quantitative yield of glycerol was obtained (entry 1). HBA could also cleave solketal that had been esterified to 1-naphthoic acid, benzoic acid, and nonanoic acid giving the corresponding product in high yields (entries 2–4). In addition, 1-naphthoic acid was not detected from the

Table 8 Deprotection of acetals and ketals by HBA

Entry	Reagent	Product	Yield (%)
1			100[a]
2			96[b]
3			90[b]
4			98[b]
5		No reaction[c]	–

Reaction conditions: 1 mmol substrate, 10 mol% HBA, 5 mL MeOH, 30 min UV irradiation, room temperature, and followed by evaporation under reduced pressure

[a]2.5 mol% HBA, determined by GC and SGE BP21 column using naphthalene as an internal standard

[b]Isolated yield

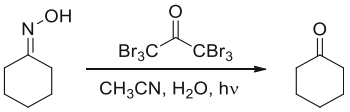
[c]Checked by ^{1}H NMR spectroscopy

reaction indicating that the ester bond was not cleaved. However, dioxolanes of safrole was not cleaved (entry 5) and bromine addition products were not detected.

Conversion of oximes to ketones

To investigate the scope of substrates that can be deprotected by HBA, this reagent was tested for deoximation. Like the reactions above, in addition to HBA, the solvent also plays an important role. In the conversion of cyclohexanone oxime to cyclohexanone, when CH_3CN, 1,2-dichloroethane, diethyl ether, and methanol were used, only a trace amount of cyclohexanone was detected. When water is used together with CH_3CN, the yield was much better. Several publications also used water in combination with other solvents and found that it is a crucial factor [74–77]. It was also found that, for this reaction, the reaction time is much longer and the amount of HBA required is more than that of the deprotection of acetals and ketals. After varying the ratio of CH_3CN and water, 4 mL CH_3CN and 1 mL water was a suitable ratio. As shown in Table 9, when 20 mol% of HBA was used, the yield of cyclohexanone was 51% after 2 h (entry 1). Increasing the reaction time did not improve the yield by much (entries 2, 3). However, when the amount of substrate is lower (lower substrate concentration), the yield is much higher (entry 4), but raising the amount of HBA did not improve the yield (entry 5). It appeared that

Table 9 Conversion of cyclohexanone oxime to cyclohexanone by HBA



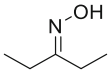
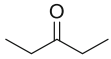
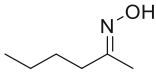
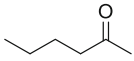
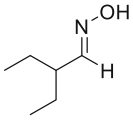
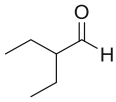
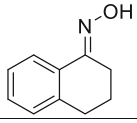
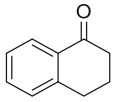
Entry	Oxime (mmol)	HBA (mol%)	UV irradiation time (h)	Oxime (%)[a]	Yield (%)[a]
1	1	20	2	32	51
2	1	20	4	39	60
3	1	20	14	27	59
4	0.25	20	4	13	87
5	0.25	80	2	7	78
6[b]	0.20	20 × 2	1 × 2	5	91
7	1	–	2	91	6

Reaction conditions: 4 mL CH_3CN, 1 mL H_2O, room temperature

[a]Determined by GC and SGE BP21 column using biphenyl as an internal standard

[b]HBA was added in 2 portions at the specified amount and the reaction was stirred for 1 h for each portion

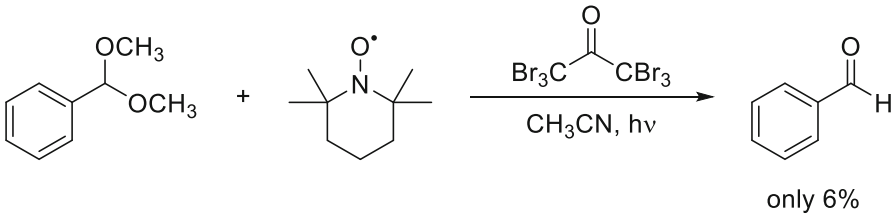
Table 10 Conversion of oximes to ketones by HBA

Entry	Reagent	Product	Oxime (%)[a]	Yield (%)[a]
1			2	92
2			13	87
3			9	91
4			88	12

Reaction conditions: 0.40 mmol oxime, 20 mol% HBA added twice (total 40 mol%, second addition after 1 h stirring), UV irradiation, room temperature, 2 h total, 8 mL CH_3CN and 2 mL H_2O

[a]Determined by GC and SGE BP1 column using naphthalene as an internal standard

HBA became ineffective after some period of time. Therefore, HBA was added in 2 portions and the yield of cyclohexanone dramatically increased to 91% (entry 6). As a controlled reaction, cyclohexanone oxime was irradiated for 2 h without HBA and only 6% of ketone was formed. In comparison to some recently reported methods



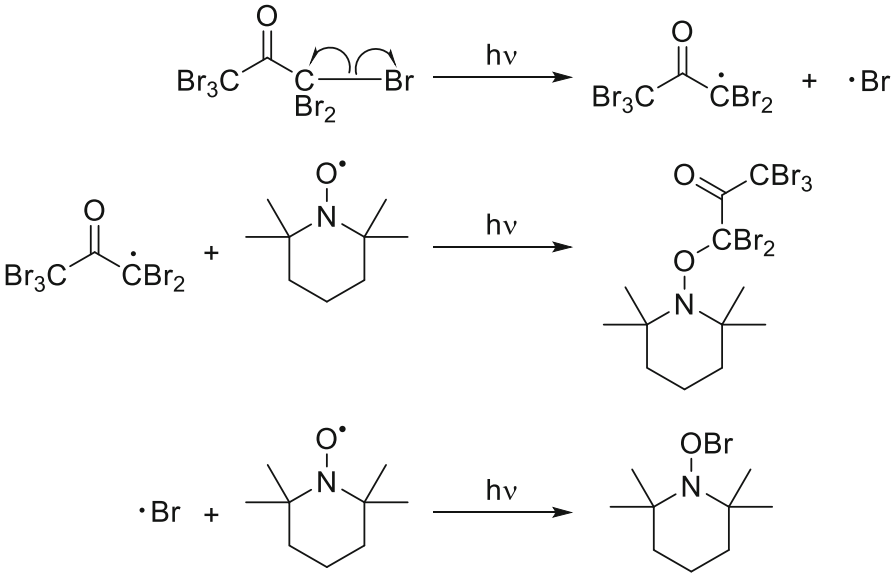
Scheme 3 Using TEMPO as a radical trap for the deprotection of benzaldehyde dimethyl acetal by HBA

for the oxidation of oxime into ketone [60, 62, 78, 79], our method produces the ketone product in very high yield in a short time, uses relatively mild condition, and is also metal-free.

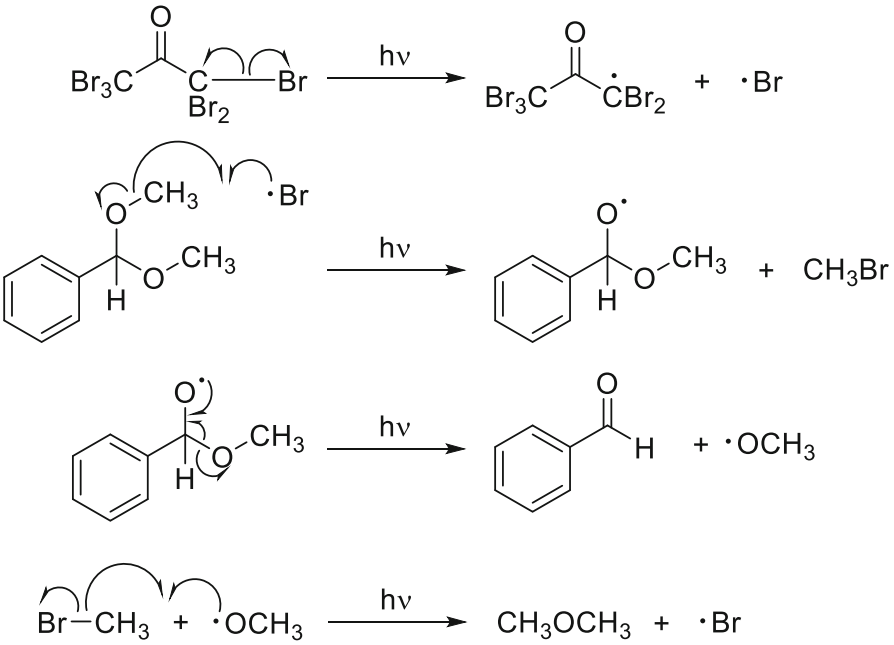
In addition to cyclohexanone oxime, HBA was tested for the conversion of other oximes using the above method, as shown in Table 10. HBA could effectively convert 3-pentanone oxime, 2-hexanone oxime, and 2-ethylbutyraldehyde oxime to the corresponding carbonyl compounds (entries 1–3). However, for α-tetralone oxime, only a small amount of product was obtained (entry 4).

Mechanism investigation

Since UV irradiation was required for the reactions, they were expected to take place via radical intermediates. 2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO) radical was used as a radical trap for the reaction in Scheme 3. While the reaction without TEMPO was nearly complete within 5 min, when TEMPO was added, only



Scheme 4 TEMPO captures the radicals generated from HBA



Scheme 5 Proposed mechanism for deprotection of benzaldehyde dimethyl acetal

6% of benzaldehyde product was formed, reaffirming that radical intermediates were formed after UV irradiation and trapped by TEMPO, inhibiting the reaction (Scheme 4). In Table 1, molecular sieves were added to the reaction, but the yield did not improve at all. Therefore, it is possible that water is not generated by this method. Based on all this information, we proposed the mechanism for deprotection of benzaldehyde dimethyl acetal in Scheme 5.

Conclusions

In summary, HBA was efficiently used for the protection of glycerol, diols, and aldehydes and it was also effective as a deprotecting agent of benzaldehyde dimethyl acetal, solketal, and some other acetals and ketals. In most cases, the reaction was very fast and a very small amount of HBA was needed. HBA was also effectively used for deoximation. The solvent was found to have an impact on the efficiency of HBA, and it is crucial to choose the right solvent or solvent combination for each type of substrate and reaction.

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