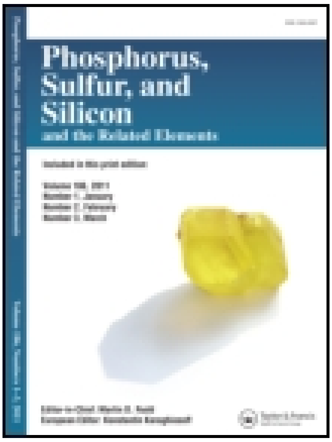

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1,3-Dibromo-5,5-dimethylhydantoin (DBH) as a Mild and Efficient Catalyst for Chemoselective Thioacetalization of Carbonyl Compounds and Dethioacetalization Under Mild Conditions

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1,3-DIBROMO-5,5-DIMETHYLHYDANTOIN (DBH) AS A MILD AND EFFICIENT CATALYST FOR CHEMOSELECTIVE THIOACETALIZATION OF CARBONYL COMPOUNDS AND DETHIOACETALIZATION UNDER MILD CONDITIONS

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Hydantoin bromide is an effective catalyst for chemoselective thioacetalization of aldehydes in the presence of ketones under neutral conditions. In addition, a simple and efficient procedure for the deprotection of 1,3-dithianes and 1,3-dithiolanes of aromatic, aliphatic, and α,β-unsaturated aldehydes and ketones in solvent-free conditions to the corresponding parent carbonyl compounds was successfully carried out with hydantoin bromide in excellent yields.

Supplemental materials are available for this article. Go to the publisher's online edition of **Phosphorus, Sulfur, and Silicon and the Related Elements** ***to view the free supplemental file.***

Keywords Carbonyl compounds; DBH; deprotection; thioacetalization

INTRODUCTION

The protection of functional groups and their regeneration constitute important and essential processes in the synthesis of polyfunctional molecules and complex natural products.[1,2] Thioacetals are relatively stable toward a wide variety of reagents and are also useful in organic synthesis as acyl carbanion equivalents in C—C bond-forming reactions.[3,4] They

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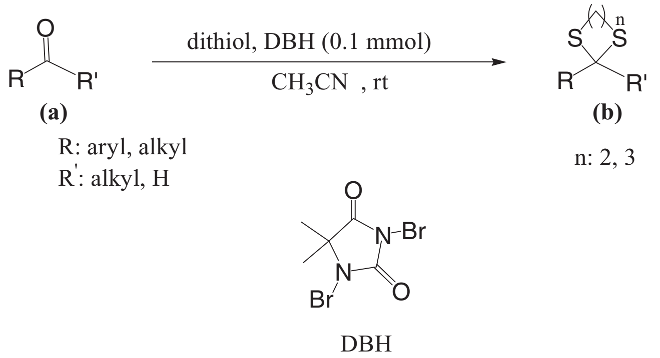
are usually prepared by the condensation of carbonyl compounds with thiols or dithiols using a strong protic acid such as HCl[5] or Lewis acids such as $BF_3.OEt_2$[6] or $ZnCl_2$[7] as catalysts. Other Lewis acids include $AlCl_3$,[8] WCl_6,[3] $InCl_3$,[9] P_2O_5/SiO_2,[10] and [bmim]HSO_4.[11] A number of milder procedures employing lithium salts,[12] $NiCl_2$,[13] trichloroisocyanuric acid,[14] NBS,[15] I_2,[16] microwave,[17] HBF_4-SiO_2,[18] $Y(OTf)_3$,[19] $VO(OTf)_2$,[20] $ScCl_3$,[21] and silica-functionalized sulfonic acid[22] have also been reported for this purpose. The regeneration of parent carbonyl compounds is not always a facile and straightforward process, and therefore development of dethioacetalization protocols has engaged the attention of organic chemists over the years.[23–26] Among the various reagents employed for this purpose are dimethylsulfoxide in the presence of iodine[27] or t-butyl chloride,[28] *N*-halosuccinimide,[29] dinitrogen tetroxide complexes of iron(III) and copper(II) nitrates,[30] 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ),[31] tellurium tetrachloride,[32] dimethylsulfoxide,[33] *N*-fluoro-2,4,6-trimethylpyridinium triflate-water,[34] photosensitized oxygenation reactions,[35] trichloroisocyanuric acid,[36] SiO_2Cl/DMSO,[37] *N,N*′-diiodo-*N,N*′-1,2-ethanediyl-bis(*p*-toluenesulphonamide),[38] zirconium sulfonyl phosphonate,[39] *m*-$ClC_6H_4CO_3H/CF_3CO_2H$,[40] SeO_2,[41] $HgCl_2$,[42] $Hg(NO_3)_2.3H_2O$,[43] and oxone/KBr.[44] Unfortunately, many of these protocols suffer from the drawbacks such as a requirement for stoichiometric amounts of catalysts, long reaction times, the use of expensive reagents and/or chlorinated organic solvents, harsh reaction conditions, difficult workup, and in some instances, strong acidic reagents.

RESULTS AND DISCUSSION

In this communication, we wish to report a mild and highly chemoselective procedure for the conversion of aldehydes in the presence of ketones into 1,3-dithiolanes and 1,3-dithianes using a catalytic amount of 1,3-dibromo-5,5-dimethylhydantoin (DBH) under almost neutral reaction conditions (Scheme 1).



Scheme 1

First the reaction of benzaldehyde, with 1,2-ethanedithiol in the presence of 1,3-dibromo-5,5-dimethylhydantoin (DBH) (0.1 mmol) at room temperature using different solvents such as CH_2Cl_2, $CHCl_3$, CCl_4, CH_3CN, and EtOH were carried out (Table I). The results show that CH_3CN is a better solvent.

To test the generality and versatility of this procedure in the thioacetalization, we examined a number of aromatic, aliphatic, and α,β-unsaturated aldehydes and ketones using

Table I Solvent effect on the reaction of benzaldehyde and 1,2-ethanedithiol by DBH[a] at room temperature

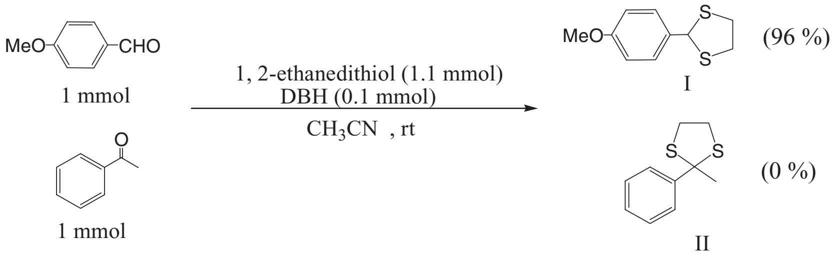
Entry	Solvent	Time (min.)	Yield (%)[b]
1	CH_2Cl_2	45	92
2	$CHCl_3$	65	80
3	CCl_4	90	85
4	CH_3CN	35	98
5	EtOH	35	90

[a] 0.1 mmol.

[b] Isolated yield.

optimized conditions (Table II). As shown in Table II, various types of aromatic aldehydes with electron-donating and electron-withdrawing groups were cleanly and rapidly converted to the corresponding dithianes and dithiolanes in the presence of catalysts. However, aromatic and aliphatic ketones were slowly converted to their corresponding *S,S*-acetals (Table II, entries 19–22).

The difference in reactivity of the 1,3-dibromo-5,5-dimethylhydantoin (DBH) towards aldehydes and ketones gave us impetus to study chemoselective reactions. Towards this objective, we carried out initial experiments with equimolar mixtures of an aldehyde and a ketone (Scheme 2). When an equimolar (1 mmol) mixture of *p*-methoxybenzaldehyde and acetophenone was allowed to react with 1.1 mmol of 1,2-ethanedithiol and a catalytic amount of DBH in acetonitrile at room temperature, a high yield (96%) of **I** was obtained, and unchanged acetophenone was recovered (Scheme 2).



Scheme 2

To compare DBH with previously published methods for the thioacetalization of carbonyl compounds with benzaldehyde, *p*-chlorobenzaldehyde, and *p*-methoxybenzaldehyde, we carried out the following studies, as shown in Table III. This clearly demonstrates that DBH is a good catalyst for the thioacetalization of carbonyl compounds.

In continuation of our work in organic synthesis, we decided to study the role of DBH in the deprotection of thioacetals and thioketals under various conditions (see Scheme S1, available online in the Supplemental Materials). For this purpose, acetophenone dithioacetal in methanol was stirred with DBH (0.5 mmol) at room temperature for 5 h, and the smooth formation of acetophenone was observed in 90% yield. Methanol was found to be the best solvent. In other solvents, such as carbon tetrachloride and dichloromethane, the reaction was sluggish and did not go to completion.

In recent years, there has been an increasing interest in reactions that proceed in the absence of solvents, due to the reduced pollution, low cost, and simplicity in process

Table II Thioacetalization of carbonyl compounds catalyzed by DBH in CH_3CN at ambient conditions

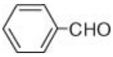
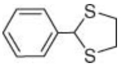
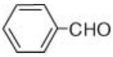
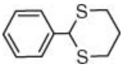
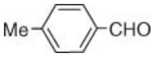
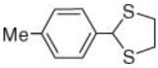
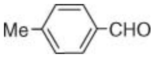
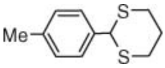
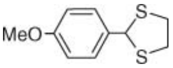
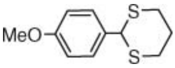
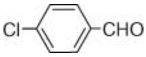
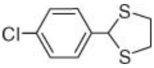
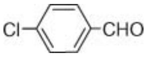
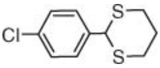
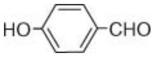
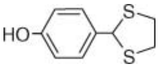
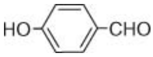
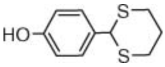
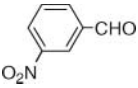
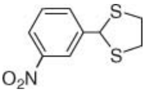
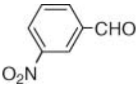
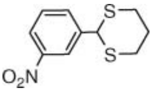
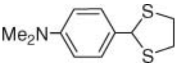
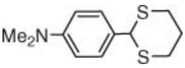
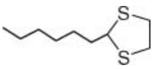
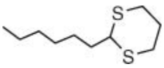
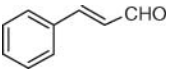
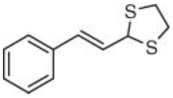
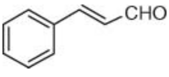
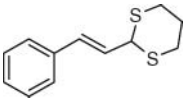
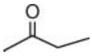
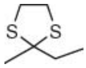
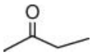
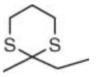
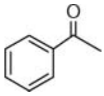
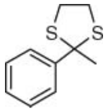
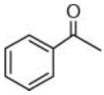
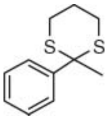
			DBH		
Entry	Substrate	Product[a]	Time (min)[h]	Yield (%)	Ref.
1			(35)	96	13
2			(35)	90	13
3			(40)	92	16
4			(45)	90	16
5			(15)	97	13
6			(20)	97	13
7			(20)	98	16
8			(25)	98	11
9			(25)	94	13
10			(30)	90	13
11			(45)	90	16
12			(55)	88	16
13			(50)	90	18
14			(55)	90	18
15			[1.6]	86	13
16			[2]	80	13
17			[1.2]	92	16
18			[1.2]	90	16

Table II Thioacetalization of carbonyl compounds catalyzed by DBH in CH_3CN at ambient conditions *(Continued)*

			DBH		
Entry	Substrate	Product[a]	Time (min)[h]	Yield (%)	Ref.
19			[4]	75	18
20			[5]	70	18
21			[4.5]	65	16
22			[5]	60	16

[a]Products were characterized from their physical properties, comparison with authentic samples, and by spectroscopic methods.

and handling of solvent-free reactions. Therefore, we decided to test this reaction under solvent-free conditions. We found that the reaction was rapid and gave excellent yields of the products when catalyzed by DBH in the presence of wet-SiO_2 (3 min, 98%, see entry 21, Table S1, Supplemental Materials).

To test the generality and versatility of this procedure in the deprotection of thioacetals and thioketals, we examined a number of 1,3-dithianes and 1,3-dithiolanes of aromatic, aliphatic, and α,β-unsaturated aldehydes and ketones using the optimized conditions

Table III Reaction times and yield for previously published methods

Ref.	Yield (%)	Reaction time	Conditions	Substrate
—	96	35 min	DBH, 1,2 propanedithiol, CH_3CN, rt	Benzaldehyde
15	80	40 min	NBS, 1,2 propanedithiol, CH_2Cl_2, rt	Benzaldehyde
13	96	165 min	$NiCl_2$, 1,2 propanedithiol, CH_2Cl_2-MeOH, rt	Benzaldehyde
46	89	300 min	$CoCl_2$, 1,2 propanedithiol, CH_3CN, rt	Benzaldehyde
14	95	60 min	Trichloroisocyanuric acid, 1,2 propanedithiol, $CHCl_3$, rt	Benzaldehyde
—	98	20 min	DBH, 1,3 propanedithiol, CH_3CN, rt	*p*-(Cl)-benzaldehyde
46	88	30 min	$CoCl_2$, 1,3 propanedithiol, CH_3CN, rt	*p*-(Cl)-benzaldehyde
15	78	30 min	NBS, 1,3 propanedithiol, CH_2Cl_2, rt	*p*-(Cl)-benzaldehyde
45	90	40 min	$Sc(OTf)_3$, 1,3 propanedithiol, CH_2Cl_2, rt	*p*-(Cl)-benzaldehyde
14	94	120 min	Trichloroisocyanuric acid, 1,2 propanedithiol, $CHCl_3$, rt	*p*-(Cl)-benzaldehyde
—	97	15 min	DBH, 1,3 propanedithiol, CH_3CN, rt	*p*-(MeO)-benzaldehyde
15	70	30 min	NBS, 1,3 propanedithiol, CH_2Cl_2, rt	*p*-(MeO)-benzaldehyde
13	89	75 min	$NiCl_2$, 1,3 propanedithiol, CH_2Cl_2-MeOH, rt	*p*-(MeO)-benzaldehyde
46	92	30 min	$CoCl_2$, 1,3 propanedithiol, CH_3CN, rt	*p*-(MeO)-benzaldehyde

(Table S1, Supplemental Materials). As shown in Table S1, various types of 1,3-dithianes and 1,3-dithiolanes (aromatic, aliphatic, and α,β-unsaturated) with electron-donating and electron-withdrawing groups were cleanly and rapidly converted to the corresponding parent carbonyl compounds in the solvent-free conditions using DBH at room temperature.

Since DBH contains bromine atoms, which are attached to the nitrogen atoms, it is very probable that they release Br^+ in situ, which would be attacked by the dithiane, making it a good leaving group with a subsequent attack by a water molecule leading to the carbonyl.[44]

CONCLUSIONS

In conclusion, in this study we have introduced a new and useful catalytic application of DBH as an efficient catalyst for the thioacetalization of aldehydes and ketones under mild reaction conditions. The method is highly chemoselective for protection of aldehydes in the presence of ketones. Moreover, the method has advantages in terms of high yields of products, short reaction times, operational simplicity, and easy workup of products. In addition, we have introduced a new and useful solvent-free application of DBH as an efficient reagent for dethioacetalization under mild reaction conditions at room temperature.

EXPERIMENTAL

General Procedure for Thioacetalization Catalyzed by 1,3-Dibromo-5,5-dimethylhydantoin (DBH) in CH_3CN

To a stirred solution of substrate (1 mmol) and DBH (0.1 mmol) in CH_3CN (3 mL), 1,2-ethanedithiol or 1,3-propanedithiol (1.1 mmol) was added at room temperature. The mixture was stirred for an appropriate time (Table II). After completion of the reaction as indicated by TLC, the organic solvent was evaporated in vacuum, and then CH_2Cl_2 (10 mL) was added, and the catalyst was removed by filtration. The filtrate was evaporated under reduced pressure to achieve crude products. The crude products were purified by recrystallization from ethanol or column chromatography using *n*-hexane/acetone (10:1) as the eluent system.

General Procedure for the Deprotection of 1,3-Dithianes and 1,3-Dithiolanes Using DBH in Solvent-Free Conditions

Substrate (1 mmol), DBH (0.5 mmol), and 0.5g wet-SiO_2 were added to a mortar, and the mixture was pulverized with a pestle. A spontaneous reaction took place (2–5 min, Table S1, monitored by TLC (9:1, hexane/acetone)]. After completion of the reaction, CH_2Cl_2 (10 mL) was added, and insoluble reagent was removed by filtration. The filtrate was evaporated under reduced pressure, and the resulting crude material was purified by chromatography column (eluent: CH_2Cl_2) to give pure carbonyl compounds.

Analytical Data for Compound 11 (Table II). IR (KBr): 3050, 2950, 2900, 1635, 1506, 1457, 1377, 1216, 1173, 1082, 742 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ_H (ppm) 3.35–3.40 (m, CH_2, 2H), 3.42–3.52 (m, CH_2, 2H), 5.64 (s, CH, 1H), 7.65–8.15 (m, CH aromatic, 4H). Anal. Calcd for $C_9H_9NO_2S_2$: C, 47.56; H, 3.99; N, 6.16. Found: C, 47.43; H, 4.05; N, 6.12. MS: $m/z = 228\ (M+H)^+$.

Analytical Data for Compound 6 (Table II). IR (KBr): 3010, 3000, 2900, 1640, 1510, 1450, 1357, 1170, 740 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ_H (ppm) 1.80–2.15 (m, CH_2, 2H), 2.80–2.91 (m, CH_2, 2H), 2.96–3.10 (m, CH_2, 2H), 3.75 (s, CH_3, 3H), 5.06 (s, CH, 1H), 6.82–7.40 (m, CH aromatic, 4H). MS: $m/z = 226$ $(M+H)^+$.

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