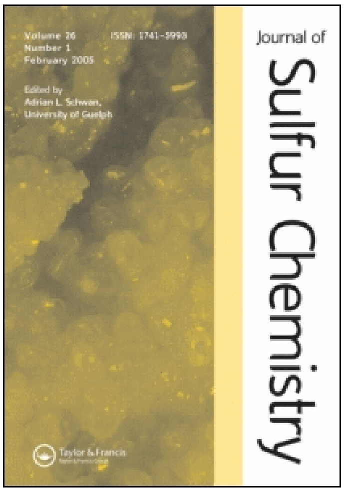

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Preparation of 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane tribromide and its application as a mild and chemoselective catalyst for thioacetalization of carbonyl compounds

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Preparation of 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane tribromide and its application as a mild and chemoselective catalyst for thioacetalization of carbonyl compounds

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1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane tribromide was prepared by oxidation of KBr by $KBrO_3$ in sulfuric acid solution. This reagent was found to be an efficient and mild reagent for the thioacetalization of aldehydes using 1,2-ethanedithiole under solvent-free conditions at room temperature. The protection of ketones was achieved under reflux conditions in ethyl acetate as solvent.

Keywords: 1-benzyl-4-aza-1-azoniabicyclo[2.2.2] octane tribromide; thioacetals; protection; solvent-free condition; carbonyl compounds

1. Introduction

Protection and deprotection of reactive functional groups are essential steps in the synthesis of natural products and polyfunctional compounds. Thioacetalization is well known as a reaction that protects carbonyl groups (*1*). Thioacetals are frequently used in the synthesis of natural products and organic compounds (*2*). Their stability under acidic and basic conditions make them versatile carbonyl-protecting groups (*3, 4*). Generally, thioacetals are prepared by condensation of carbonyl compounds with thiols or dithiols employing acid catalysts such as HCl (*5*), PTSA (*6*), $AlCl_3$ (*7*), $TiCl_4$ (*8*), $LaCl_3$ (*9*), $ZnCl_2$ (*10*), $BF_3 \cdot Et_2O$ (*11*), $ZrCl_2/SiO_2$ (*12*), titanium tetrachloride (*13*), magnesium or zinc triflate (*14*), $SOCl_2/SiO_2$ (*15*), zeolite (*16*), WCl_6 (*17*), $MoCl_5$ or MoO_2Cl_2 (*18*) and ionic liquids such as selenonium tetrafluoroborate (*19*) and 1-butyl-3-methylimidazolium tetrafluoroborate (*20*). Thus, there is further scope to explore suitable, mild and selective alternative reagents for thioacetalization of carbonyl compounds. We report here a new method for thioacetalization of aliphatic and aromatic carbonyl compounds.

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2. Results and discussion

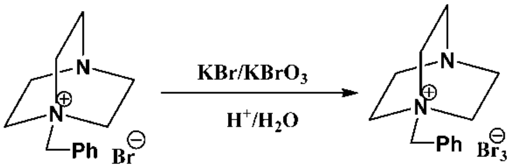
Quaternary ammonium tribromides (QATB; *21*) are extremely useful in organic synthesis, particularly for protection and deprotection of functional groups (*22*). We have recently reported the synthesis of 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane tribromide (BABOT) and its application for useful bromination of aromatic compounds (*23*). In continuation of our program to develop environmentally benign methods under solvent-free conditions (*24*), herein we report a new and environmentally benign alternative protocol for the synthesis of BABOT and its application for selective thioacetalization of compounds. The preparation of the reagent is based on the oxidation of bromide ion in sulfuric acid solution by inexpensive and commercially available $KBrO_3$ to tribromide (Br_3^-) followed by precipitation with the 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane cation (Scheme 1). The precipitate shows an intense electronic absorption at 279 nm, typical of the tribromide ion (Br_3^-; *12*). BABOT is a very stable compound and can be stored at bench for months without losing its activity.

The protection of a variety of aldehydes and ketones with 1,2-ethanedithiol in the presence of BABOT was carried out. First, we tried the protection of aldehydes by grinding the aldehyde with BABOT and 1,2-ethandithiol at room temperature under solvent-free conditions (Scheme 2).

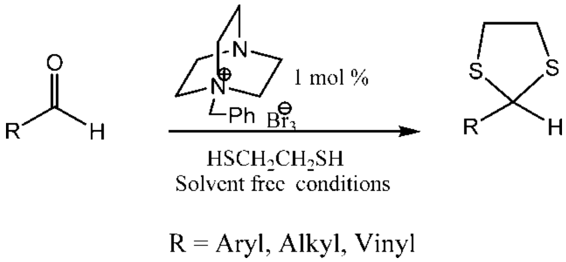
The reaction was repeated with various aldehydes containing electron-withdrawing and donating substituents (Table 1). The protection of α, β-unsaturated and heteroaromatic aldehydes was also carried out under similar reaction conditions and the results are summarized in Table 1. In each case, the reaction was completed within a short period and the products were obtained in good to excellent yield.

We found that ketones show less reactivity than aldehydes for this reaction under solvent-free conditions and the reaction times are long. Therefore, to enhance the rate of thioacetalization of ketones and increase the yields of the products, we used refluxing in ethyl acetate as solvent and 5 mol% of catalyst (Scheme 3).

The reaction of acetophenone (1 mmol) with 1,2-ethanedithiol (1.2 mmol) in reflux with ethyl acetate was carried out in the presence of 5 mol% of BABOT to afford the desired thioacetal in 98% yields. By following this reaction procedure, both aromatic as well as aliphatic ketones were converted smoothly to the corresponding cyclic dithioacetals in good to excellent yields. The results are summarized in Table 2.



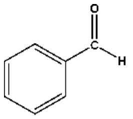
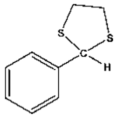
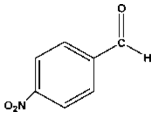
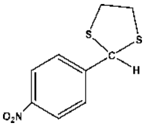
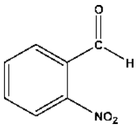
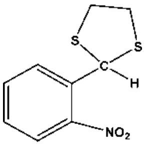
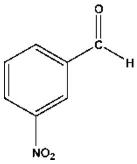
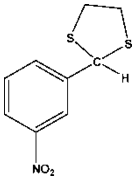
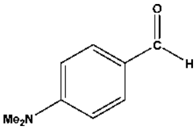
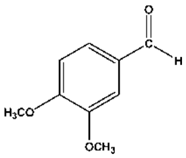
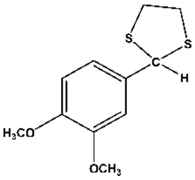
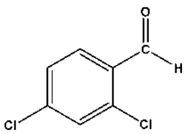
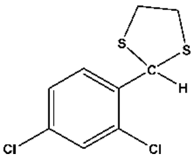
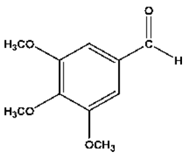
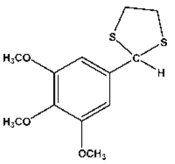
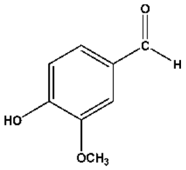
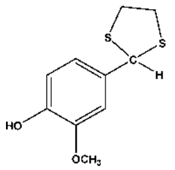
Scheme 1. Preparation of BABOT.



R = Aryl, Alkyl, Vinyl

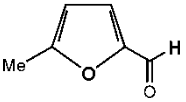
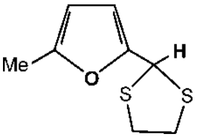
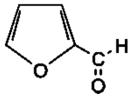
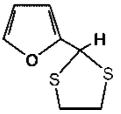
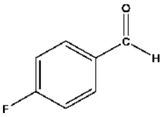
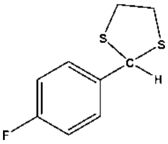
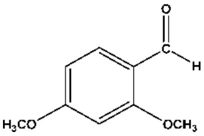
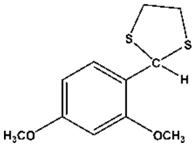
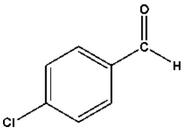
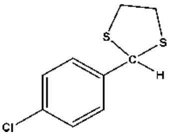
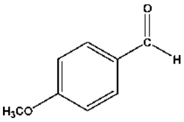
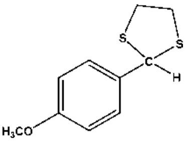
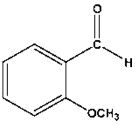
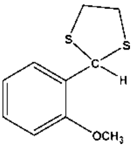
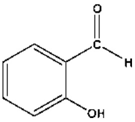
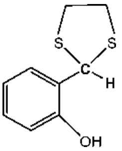
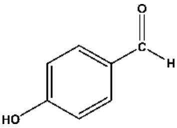
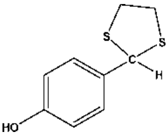
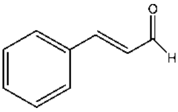
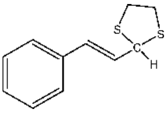
Scheme 2. Thioacetalization of aldehydes using BABOT.

Table 1. Thioacetalization of aldehydes by BABOT under solvent-free conditions at room temperature.

Entry	Substrate	Product[a]	Time	Isolated yield[b]	Ref.
1			3 min	90	(*25*)
2			8 min	85	(*25*)
3			8 min	82	(*26*)
4			6 min	85	(*24*(f))
5		No reaction	24 h	–	–
6			6 min	92	(*24*(f))
7			7 min	86	(*27*)
8			4 min	92	(*27*)
9			6 min	87	(*28*)

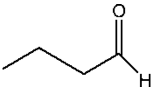
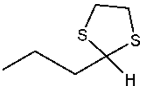
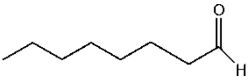
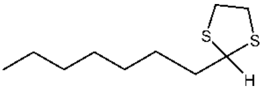
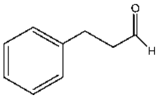
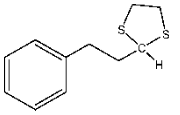
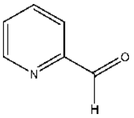
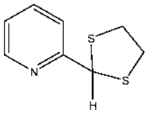
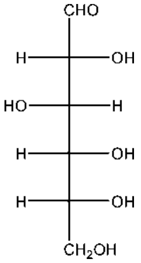
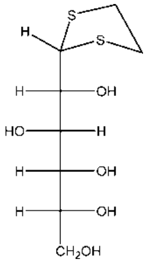
(*Continued*)

Table 1. Continued.

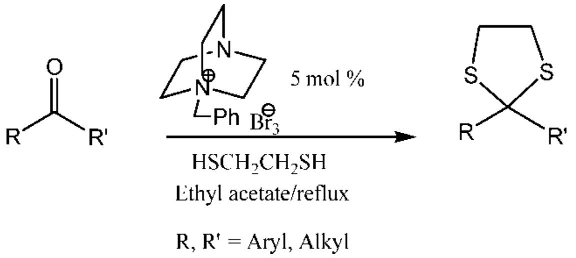
Entry	Substrate	Product^{a}	Time	Isolated yield^{b}	Ref.
10			3 min	90	(*24*(f))
11			3 min	91	(*28*)
12			5 min	89	(*29*(a))
13			5 min	90	(*24*(f))
14			7 min	82	(*25*)
15			5 min	90	(*25*)
16			5 min	92	(*25*)
17			4 min	91	(*24*(f))
18			45 min	85	(*25*)
19			7 min	87	(*28*)

(*Continued*)

Table 1. Continued.

Entry	Substrate	Product[a]	Time	Isolated yield[b]	Ref.
20			7 min	70	(*30*)
21			6 min	90	(*30*)
22			6 min	95	(*30*)
23			7 min	94	(*31*)
24			15 min	65	(*29*(b))

Notes: [a]Confirmed by comparison with authentic samples (infra red, thin-layer chromatography and ^{1}H-nuclear magnetic resonance) (*24–32*).
[b]Yield of the isolated pure product after purification.

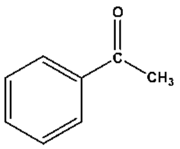
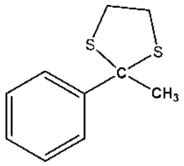
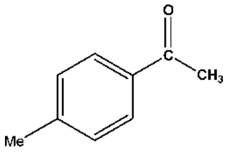
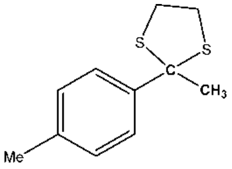
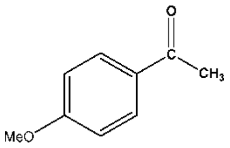
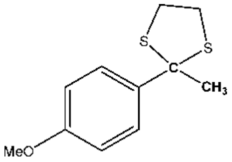
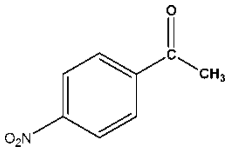
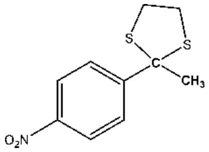
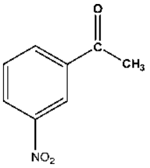
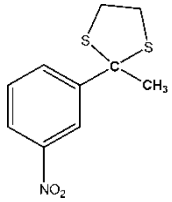
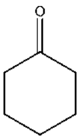
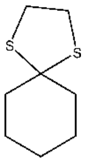
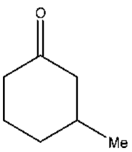
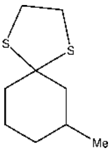
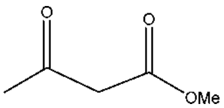
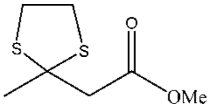
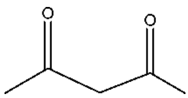
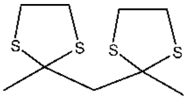


Scheme 3. Thioacetalization of ketones using BABOT.

It is interesting to note that by employing BABOT, we have been able to protect selectively the keto group in keto esters without transesterification (Table 2, entry 8; Scheme 4). On the other hand, protection of diaryl ketones like benzophenone was achieved by this method in good yield.

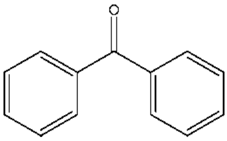
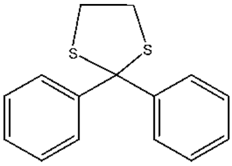
We observed that the reaction with aldehydes takes place rapidly in the presence of BABOT when compared with the rate with ketones. The difference in reactivity of the BABOT catalyst towards aldehydes and ketones gave us an impetus to study chemoselective reactions. With this objective, as a representative example, we carried out some experiments with equimolar mixtures of an aldehyde and a ketone (Scheme 5) under solvent-free conditions at room temperature. It was observed that in this mixture, the corresponding aldehyde formed the dithiolane while the ketone was almost completely recovered.

Table 2. Thioacetalization of ketones by BABOT in ethyl acetate at reflux conditions.

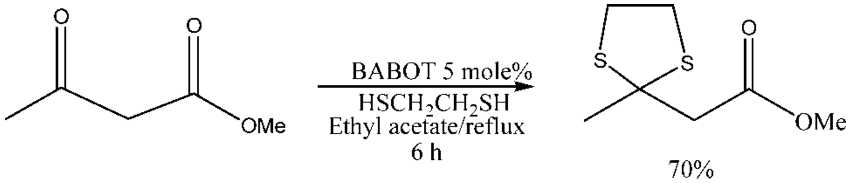
Entry	Substrate	Product[a]	Time	Isolated yield[b]	Ref.
1			45 min	98	(*29*(c))
2			1 h	98	(*25*)
3			2 h	95	(*25*)
4			7 h	85	(*29*(d))
5			10 h	70	(*29*(d))
6			5 h	90	(*29*(c))
7			6 h	95	(*31*)
8			6 h	70	(*32*)
9			4 h	90	(*32*)

(*Continued*)

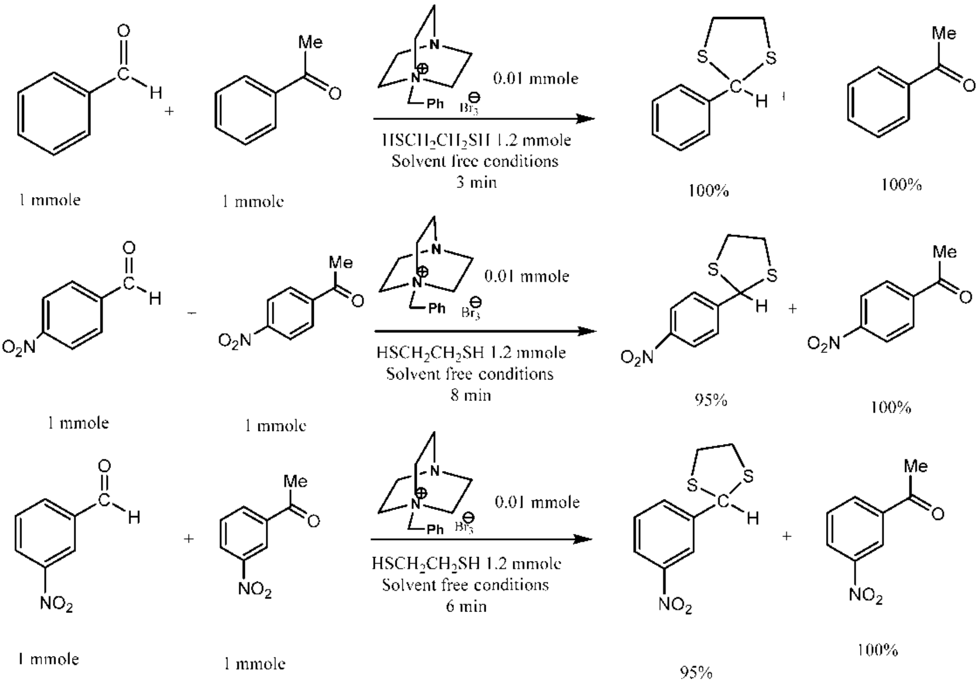
Table 2. Continued.

Entry	Substrate	Product[a]	Time	Isolated yield[b]	Ref.
10			24 h	65	(*29*(c))

Notes: [a]Confirmed by comparison with authentic samples (infra red, thin-layer chromatography and ^{1}H-nuclear magnetic resonance) (*24–32*).
[b]Yield of the isolated pure product after purification.

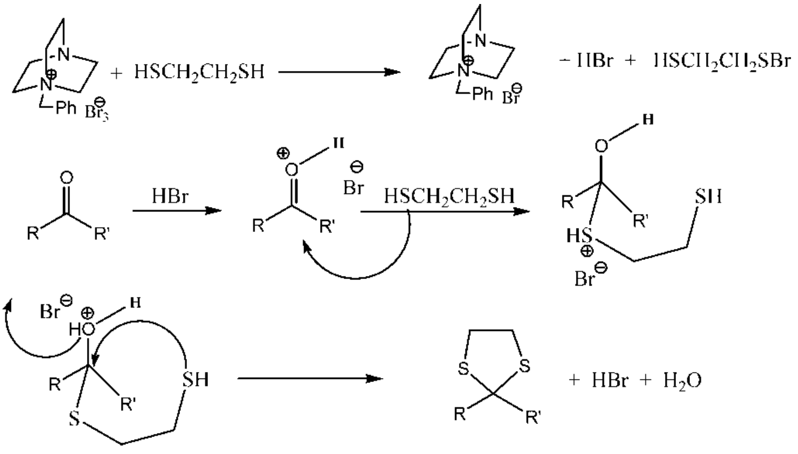


Scheme 4. Chemoselective thioacetalization of ketone group in presence of ester.



Scheme 5. Chemoselective thioacetalization of aldehydes.

The possible mechanism is shown in Scheme 6; initially BABOT reacted with 1,2-ethandithiol to generate HBr as a catalyst, and HBr activated the carbonyl group for further reaction with dithiol. The hemithioacetal-type intermediate afforded the corresponding dithioacetal derivatives by losing a H_2O molecule and HBr (Scheme 6).



Scheme 6. Mechanism of thioacetalization by BABOT.

In conclusion, we have demonstrated the preparation of BABOT by an environmentally benign and safe method and its application in thioacetalization of aromatic and aliphatic aldehydes and ketones under mild conditions. Furthermore, the relatively slow reaction rate of ketones allows for chemoselective protection of aldehydes in the presence of ketones, making this an important tool in synthetic organic chemistry. The notable advantages of this method are its chemoselectivity and the requirement for minimum amounts of catalyst.

3. Experimental

3.1. *Preparation of BABOT by oxidation of KBr with $KBrO_3$*

To a stirred solution of 1-benzyl-4-aza-1-azonia-bicyclo[2.2.2]octane bromide (9.056 g of 32 mmol), potassium bromide (6.343 g of 53.3 mmol) and potassium bromate (1.786 g of 10.7 mmol) in distilled water (30 mL) was added sulfuric acid solution (98%; 8.000 g of 80 mmol) drop by drop. A yellow-orange precipitate was formed. Stirring of the resulting mixture was continued for 1 h and then the precipitates were isolated by filtration and washed with distilled water (3 × 10 mL). The filtered cake was dried under vacuum, which resulted in yellow crystals (10.773 g; 76% yield); this physical data is consistent with that reported in the literature (*23*).

3.2. *Thioacetalization of aldehyde under solvent-free conditions*

BABOT (1 mol%) was added to a mixture of aldehyde (10 mmol) and 1,2-ethandithiole (12 mmol) in a mortar and the mixture was ground with a pestle at room temperature. After disappearance of the starting material (monitored by thin-layer chromatography or TLC), the mixture was extracted with diethyl ether (3 × 20 mL) and filtered off. The combined organic layers were dried on $MgSO_4$ and evaporated under vacuum to give almost pure corresponding dithioacetal in high yield, the physical data of which is consistent with that reported in the literature.

3.3. *Thioacetalization of ketone in ethyl acetate solution under reflux conditions*

To a solution of ketone (10 mmol) and 1,2-ethandithiole (12 mmol) in dry ethyl acetate (5 mL) was added 5 mol% of BABOT. The reaction mixture was heated under reflux condition. The progress of the reaction was followed by TLC. After completion of the reaction, the reaction mixture was filtered off and the filter cake was washed with ethyl acetate (2 × 20 mL). The combined organic layers were dried on $MgSO_4$ and evaporated under vacuum to give almost pure corresponding dithioacetal in high yield. In all these cases, crude products were sufficiently pure (TLC, Fourier transform-infra red and ^{1}H-nuclear magnetic resonance), and the products were further purified by crystallization.

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