

Poly(*N*-bromoacrylamide): an Efficient and Useful Catalyst for the Protection of Carbonyl Compounds as Dithiolanes, Dithianes and Oxathiolanes under Solvent-Free and Microwave Conditions

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Poly(*N*-bromoacrylamide) (PNBA) was prepared and used as a heterogeneous electrophilic catalyst under solvent-free and microwave conditions for the mild and efficient protection of carbonyl compounds as their dithiolane, dithiane and oxathiolane derivatives with 1,2-ethanedithiol, 1,3-propanedithiol and 2-mercaptoethanol, respectively in good to excellent yields. This method is simple, efficient and straightforward for synthesis of 1,3-oxathiolanes, 1,3-dithiolanes and 1,3-dithianes from carbonyl compounds. The catalyst is recoverable and reusable.

Keywords: Poly(*N*-bromoacrylamide), Heterogeneous catalyst, Protection, Dithioacetal, Solvent free, Microwave

INTRODUCTION

The protection of carbonyl compounds plays an important role during multistep syntheses in organic, medicinal, carbohydrate, and drug design chemistry [1]. The protection of carbonyl functionality as a dithioacetal is important in the total synthesis of complex natural and non-natural products due to the group's inherent stability under both acidic and basic conditions. Among the different carbonyl protecting groups, 1,3-dithianes, 1,3-dithiolanes, 1,3-oxathiolanes have long been used as protective groups, and as an acyl anion equivalent in carbon-carbon bond forming reactions [2]. Numerous methods that are reported for these conversions include the use of protic acids, Lewis acids, some silicon compounds, supported silica gel and ion exchange resins as catalysts or as stoichiometric reagents [3]. Recently, methods employing catalysts such as *N*-bromosuccinimide [4,5],

trichloro isocyanoric acid [6], I₂ [7], AlCl₃-SiO₂[8], NaHSO₄-SiO₂ [9], PPA-SiO₂ [10], silica chloride [11], *p*-TsOH-silica gel [12], montmorillonite K-10 [13], H₃PW₁₂O₄₀/SiO₂[14], LiBF₄[15], MoO₂(acac)₂ [16], SnCl₂·2H₂O [17], Bi(NO₃)₃ [18], ScCl₃ [19], NiCl₂[20], InCl₃ [21], ZrCl₄ [22], WCl₆ [23], LiBr [24], Y(OTf)₃ [25], VO(OTf)₂ [26], Sc(OTf)₃ [27,28] have also been reported in the literature. However, many of these procedures are associated with certain limitations such as low yields, harsh reaction conditions, difficulties in work-up, requirement for an inert atmosphere, use of stoichiometric reagents, sensitivity to moisture, long reaction times, cost, and inconvenience in handling the reagents or catalysts. Therefore, milder, simpler and more efficient alternatives for protection of carbonyl compounds are still desirable.

N-Halo compounds have been used as reagents and catalysts in organic reactions such as halogenation, oxidation and protection [29]. For protection of carbonyl compounds *N*-bromosuccinimide and trichloroisocyanoric acid have been used as catalysts [4-6].

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Application of polymer supported reagents and catalysts in organic reactions have attracted much attention mainly due to their ease of separation, regenerability, recoverability or recyclability. As far as we know, there is no report in the literature for the use of polymeric *N*-halocompounds in the protection reactions. These facts prompted us to initiate an investigation to explore the catalytic activity of poly(*N*-bromoacrylamide) (PNBA) in the protection of carbonyl compounds. George and Pillai have reported the preparation and application of PNBA as new insoluble polymeric oxidizing and brominating reagents for organic substrates. The hygroscopic nature of parent polyacrylamide has not been observed in using PNBA, presumably due to the hydrogen bonding [30,31]. Rudnicka and Nour have also reported the oxidation of acetals into esters [32]. PNBA can be stored for months without any loss in its activity and can be handled easily.

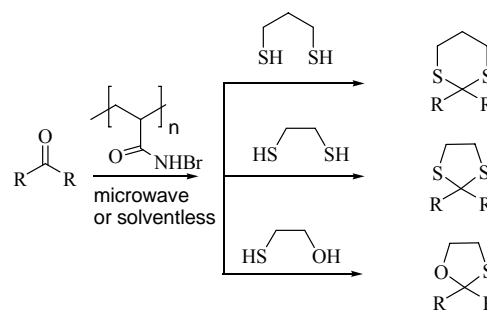
Here, we report an efficient, mild and green method for the protection of carbonyl compounds as their 1,3-dithiolanes 1,3-dithianes and 1,3-oxathiolanes using a catalytic quantity of crosslinked poly(*N*-bromoacrylamide) (PNBA) (Scheme 1).

EXPERIMENTAL

All chemicals were supplied by either Merck or Fluka chemical companies. The progress of the reactions was followed with TLC, using silica gel SILG-UV 254 plates. Silica gel 60 was used for column chromatography. Reactions were carried out using a CEM MARS 5 TM microwave oven at 220 W. The identities of products were determined by comparison of their physical and spectral data with those reported in the literature. FT-IR spectra were recorded on a Shimadzu DR-8001 spectrometer. NMR spectra were recorded on a Bruker Avance DPX 250 MHz instrument.

Procedure for Preparation of Poly(*N*-bromoacrylamide)

To a stirred suspension of polyacrylamide (5 g), NaOH (70 mmol, 2.8 g), Na₂CO₃ (105 mmol, 11.13 g) and KBr (75 mmol, 12.5 g) in H₂O (180 ml), cooled in an ice bath, was added dropwise a solution of Oxone® (75 mmol, 46.05 g) in H₂O (150 ml). A white solid precipitated during the addition of the oxidant solution, forming a dense suspension, which



Scheme 1

was stirred for 24 h. The product was isolated by filtration, washed with cold H₂O and dried in an air oven at 60 °C to afford 8.8 g of poly(*N*-bromoacrylamide) as orange granules (Yield 83%). The capacity of polymer was 5 mmol per gram determined iodimetrically.

General Procedure under Solvent Free Condition

To a stirred mixture of the carbonyl compound (1 mmol) and dithiol or mercaptoethanol (2.5 mmol) was added poly (*N*-bromoacrylamide) (0.1 g, 0.5 mmol) at 50 °C. Progress of the reaction was followed by TLC. [Under M.W condition the whole mixture was irradiated for 5 min]. On completion of the reaction, CH₂Cl₂ was added to the system and the mixture was filtered and washed successively with 10% NaOH solution (2 × 25 ml), brine (15 ml), and H₂O (15 ml). The organic layer was separated and dried (Na₂SO₄). Evaporation of the solvent under reduced pressure gave almost pure product. When the conversions were not complete, further purification was achieved by column chromatography on silica gel or recrystallization from appropriate solvent to give the desired products in good to excellent yields.

RESULTS AND DISCUSSION

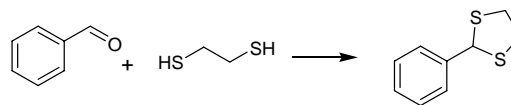
Crosslinked polyacrylamide (2% DVB) was prepared according to our previous procedure [33]. Crosslinked poly (*N*-bromoacrylamide) (PNBA) was then prepared according to Pillia's report [30,31]. We also prepared PNBA by a simple and green procedure using an aqueous solution of Oxone® excluding the organic solvents. Capacity of poly(*N*-bromoacrylamide) was determined iodometrically.

Poly (*N*-Bromoacrylamide): an Efficient and Useful Catalyst

The reactions of an aldehyde with 1,2-ethanedithiol, 1,3-propanedithiol or 2-mercaptoethanol in the presence of a catalytic amount of poly(*N*-bromoacrylamide) were attempted in solvent and under solvent-free and microwave conditions to afford the corresponding thioacetals and oxathioacetals respectively. The results showed that the reactions were completed in much less time under solvent free or MW conditions compared with the solvent systems, Table 1.

Several types of aldehydes or ketones were protected efficiently with 1,2-ethanedithiol, 1,3-propanedithiol and 2-mercaptoethanol in the presence of PNBA under solvent-free and microwave conditions to give the corresponding thioacetals and oxathioacetals, respectively, in good to excellent yields (Table 2). The obtained results clearly indicate the scope and generality of this protocol with respect to structurally diverse aldehydes and ketones. The reaction conditions were compatible with wide range of substrates bearing methyl, bromo, nitro and methoxy groups. Due to the neutrality of the reaction medium, this method is very useful for substrates with a high degree of acid sensitivity. For example, thiophene-2-carboxaldehyde (Table 2, entries 16-19) was protected in excellent yields without any difficulty. The

Table 1. Catalytic Protection of Benzaldehyde with PNBA in Various Solvents and under Solvent-Free or MW Conditions



Entry	Condition ^a	Time	%Conversion
1	CHCl ₃	2 h	70
2	Dioxane	24 h	15
3	EtOH	24 h	5
4	CH ₂ Cl ₂	140	70
5	THF	2 h	45
6	Cyclohexane	90 min	70
7	Toluene	24 h	35
8	CH ₃ CN	24 h	25
9	No solvent	15 min	100
10	Microwave	5 min	100

^a0.1 g PNBA (0.1 eq), 1 mmol benzaldehyde and 1.2 mmol 1,2-ethanedithiol at 55 °C.

Table 2. Poly(*N*-bromoacrylamide) Catalyzed Protection of Carbonyl Compounds as Oxathiolanes, Dithiolanes or Dithianes

Entry	Substrate	Thiol	Time	Product ^a (%)Conversion	Condition
1		HSCH ₂ CH ₂ SH	15 min	100	Solvent-free
			5 min	100	Mw
2		HSCH ₂ CH ₂ OH	2 h	45	Solvent-free
			5 min	60	Mw
3		HSCH ₂ CH ₂ CH ₂ SH	2 h	100	Solvent-free
			5 min	100	Mw
4		BuSH	2 h	80	Solvent-free
			5 min	100	Mw
5		HSCH ₂ CH ₂ OH	5 min	40	Mw
6		HSCH ₂ CH ₂ CH ₂ SH	5 min	60	Mw

Table 2. Continued

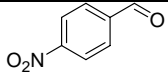
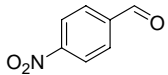
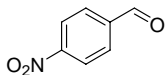
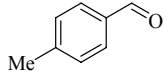
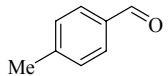
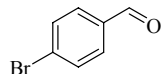
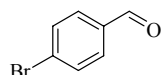
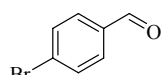
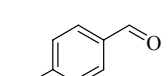
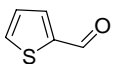
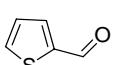
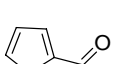
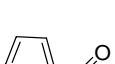
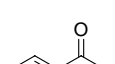
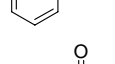
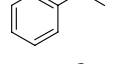
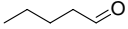
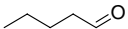
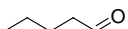
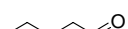
7		HSCH ₂ CH ₂ SH	5 h	70	Solvent-free
			5 min	80	Mw
8		HSCH ₂ CH ₂ OH	2 h	90	Solvent-free
			5 min	70	Mw
9		HSCH ₂ CH ₂ CH ₂ SH	5 min	100	Mw
10		HSCH ₂ CH ₂ SH	1 h	100	Solvent-free
			5 min	80	Mw
11		HSCH ₂ CH ₂ CH ₂ SH	1 h	100	Solvent-free
			5 min	85	Mw
12		HSCH ₂ CH ₂ SH	24 h	100	Solvent-free
			5 min	80	Mw
13		HSCH ₂ CH ₂ OH	2 h	80	Solvent-free
			5 min	40	Mw
14		HSCH ₂ CH ₂ CH ₂ SH	24 h	90	Solvent-free
			5 min	80	Mw
15		BuSH	24 h	100	Solvent-free
16		HSCH ₂ CH ₂ SH	4 h	95	Solvent-free
			5 min	100	Mw
17		HSCH ₂ CH ₂ OH	4 h	80	Solvent-free
			5 min	50	Mw
18		HSCH ₂ CH ₂ CH ₂ SH	4 h	90	Solvent-free
			5 min	100	Mw
19		BuSH	3 h	100	Solvent-free
			5 min	100	Mw
20		HSCH ₂ CH ₂ SH	24 h	100	Solvent-free
			5 min	60	Mw
21		HSCH ₂ CH ₂ OH	3 h	70	Solvent-free
			5 min	60	Mw
22		HSCH ₂ CH ₂ CH ₂ SH	2 h	60	Solvent-free
			5 min	60	Mw

Table 2. Continued

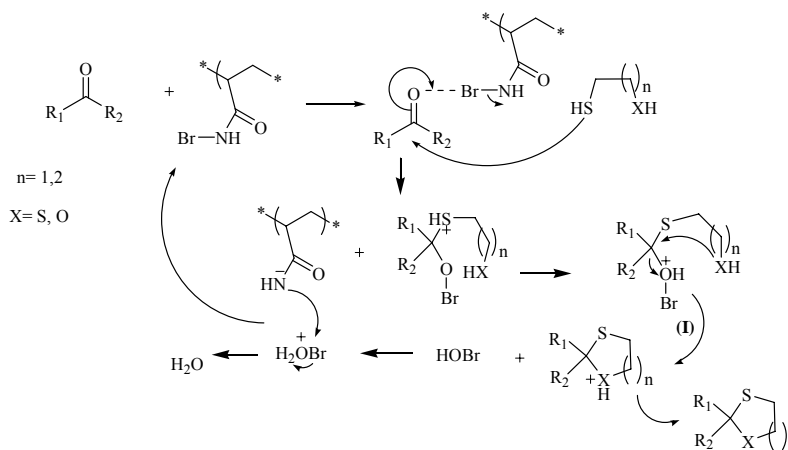
23		HSCH ₂ CH ₂ SH	5 min	90	Mw
24		HSCH ₂ CH ₂ OH	5 min	60	Mw
25		HSCH ₂ CH ₂ CH ₂ SH	5 min	80	Mw
26		BuSH	5 min	90	Mw

^aThe identity of products were determined by comparison of their physical and spectral data with those of the authentic samples.

Table 3. Efficiency of the Recovered Catalyst in the Synthesis of 2-Phenyl-[1,3]dithiolane^a

Cycle	1	2	3	4	5
Yield ^b	100	95	95	90	84

^aReaction performed at 55 °C under solvent free condition. ^bYields were analyzed by GC.



present method is highly effective to protect aliphatic aldehydes as their thioacetals and oxathioacetals. This polymeric catalyst is especially useful for the synthesis of oxathiolanes having a chiral center which can be used as a precursor for further reactions.

The method is also applicable to both open-chain thioacetals (dibutyl thiolane) and cyclic diacetals. The polymeric catalyst can be removed easily by filtration of the CH₂Cl₂ solution of the reaction products. The recovered catalyst can be used several times without appreciable change in its activity. Table 3 shows the efficiency of the recovered

catalyst in preparation of 2-phenyl [1,3] dithiolane from benzaldehyde and 1,2-ethanedithiol.

We believe that under solvent-free condition the electrophilic bromine activates the carbonyl group for the initial addition of a thiol molecule. This is followed by elimination of HOBr from intermediate hemithioacetal (I), which is attacked by a second thiol moiety. The proposed mechanism is shown in Scheme 2.

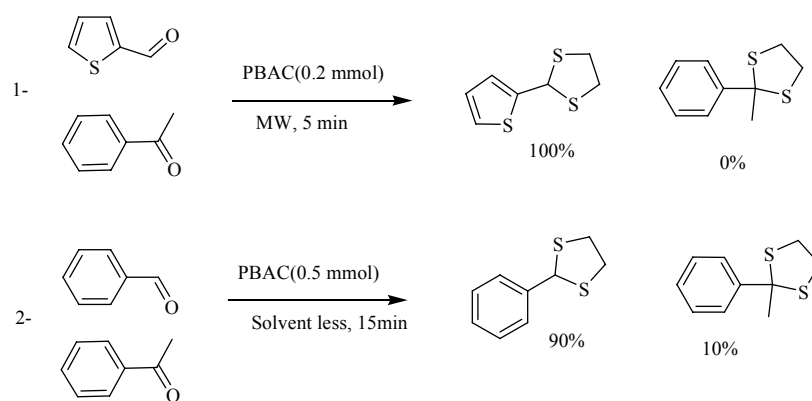
Based on our observations, we have conducted a set of competitive protection reactions between aldehydes and ketones (Scheme 3). The results show that the method

presented here is potentially applicable to chemoselective conversion of aldehydes to the corresponding 1,3-dithiolane in the presence of ketone functions.

In order to show the merit of the presented protocol, we have compared some of the results obtained by the other catalysts which have been reported recently for the reaction of benzaldehyde with 1,2-ethanedithiol, 1,3-propanedithiol or 2-mercaptoethanol in Table 4.

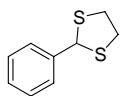
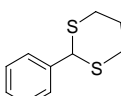
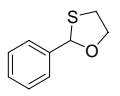
CONCLUSIONS

In conclusion, we have developed a new, mild, and efficient method for the protection of carbonyl compounds as their corresponding oxathiolane, dithiolane and dithiane derivatives in good to excellent yields with 2-mercaptoethanol, 1,2-ethanedithiol and 1,3-propanedithiol using a catalytic amount of poly(*N*-bromoacrylamide). Further, the catalyst can



Scheme 3

Table 4. Comparison of PNBA with other Reported Catalysts or Reagents for Protection of Benzaldehyde under Different Conditions

Entry	Catalyst or reagent conditions	Yield (%) 	Time (min)	Yield (%) 	Time (min)	Yield (%) 	Time (min)	Ref.
1	Poly(<i>N</i> -bromoacrylamide) (PNBA)/MW, S.F ^a	100	5	100	5	60	5	
2	NBS/CH ₂ Cl ₂	80	40	-	-	75	120	[4]
3	Amberlyst-15/CHCl ₃ or THF	83	24 h	-	-	-	-	[34]
4	NaHSO ₄ -SiO ₂ /CH ₂ Cl ₂ , H ₂ O	78	180	-	-	-	-	[9]
5	PPA-SiO ₂ /CH ₂ Cl ₂	97	30	-	-	99	30	[10]
6	TsOH-silica gel/CH ₂ Cl ₂ , Δ	93	270	-	-	-	-	[12]
7	Montmorillonite K-10/CH ₂ Cl ₂	-	-	-	-	85	30	[13]
8	MoO ₂ (acac) ₂ /CH ₃ CN	95	90	94	180	86	240	[16]
9	[bmim]BF ₄ /neat	92	150	-	-	-	-	[35]
10	SnCl ₂ .2H ₂ O/Solvent-free, MW	75	3	-	-	-	-	[17]

be readily recovered and reused, thus making the procedure more environmentally acceptable. The method affords advantages in terms of high yields of products, short reaction times, operational simplicity, and chemo selectivity. In summary, the present poly (*N*-bromoacrylamide)-catalyzed method of protection of carbonyl compounds is very general, mild, cost-effective and convenient.

ACKNOWLEDGMENTS

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