

Solvent-free methodologies for organic brominations using quaternary ammonium tribromides

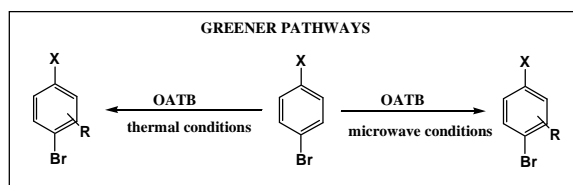
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Abstract: The efficacies of different organic ammonium tribromides were studied with different classes of organic substrates using solvent-free reaction protocols involving reactions at elevated temperature and also under microwave conditions. The reactions were regio-selective, facile and afforded good to excellent product yields in short reaction time.



Keywords: Quaternary ammonium tribromide (QATB); thermal condition; microwave; bromination; comparative study.

1. Introduction

Acknowledging the importance of bromoorganic compounds^{1,2} and the need for environmentally benign brominating reagents, some development has been made through the synthesis and use of organic ammonium tribromides as alternative sources of bromine for organic brominations.^{3-9,17} While the reaction strategies are efficient as well as benign, use of organic solvents deters these methodologies from being perfectly green. In fact, the best solvent for organic reactions is 'no solvent at all' and this can be achieved by changing the mode of reaction. Solvent-free reaction pathways, involving use of hot air oven and microwave reactors may be useful alternatives to minimize or avoid the use of solvent to carry out different types of reactions.¹⁰⁻¹⁷ Through this paper we report a series of successful bromination reactions

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under thermal and microwave condition without involvement of any solvent during reaction. The brominating reagents that have been used are tetrabutylammonium tribromide (TBATB), tetraethylammonium tribromide (TEATB), cetyltrimethylammonium tribromide (CTMATB) and tetramethylammonium tribromide (TMATB) and the substrates have been diverse, in order to prove the efficacy of the methodology.

2. Materials and Methods

All the reagents were of commercial grade and purified according to the established procedures. Organic extracts were dried over anhydrous sodium sulphate. Solvents were removed in a rotary evaporator under reduced pressure. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F₂₅₄ (0.25mm). NMR spectra were recorded in CDCl₃ or DMSO-d₆ with tetramethylsilane as the internal standard for ¹H NMR (400 MHz) and CDCl₃ or DMSO-d₆ solvents as internal standard for ¹³C NMR (100 MHz). IR spectra were recorded in KBr or neat.

QATBs were prepared by the reported methods⁴ and their purity checked by iodometric methods of analysis followed by uv/vis spectroscopy.

2.1. Typical procedure for bromination reactions under thermal conditions (in hot air oven)

A homogeneous mixture of substrate (2mmol) and reagent (2 mmol) in the ratio 1:1 was taken on petri dish. The reaction mixture was mixed thoroughly. The reaction mixture was then inserted in hot air oven in a pre-controlled temperature 60±5°C(70±5°C for reaction of anthracene). The progress of reaction was monitored by thin layer chromatography on silica gel by using ethyl acetate-hexane solvent system (volume ratio varied for different substrate). After completion of reaction the reaction mixture was diluted with 30 mL ethyl acetate and filtered through a short column of silica gel to remove the spent reagent. The crude product thus obtained was subjected to column chromatography over a pad of silica gel using ethyl acetate-hexane (volume ratio varied for different substrate) solvent system as an eluent to afford the product. The products were identified by comparison of their melting points, IR and NMR spectra with those of authentic samples.


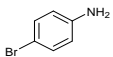

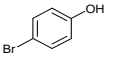

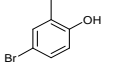
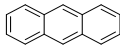
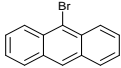

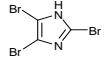
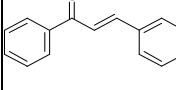
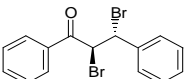

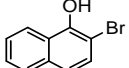
2.2. Typical procedure for bromination reactions under microwave conditions

A homogeneous mixture of substrate (2 mmol) and reagent (2 mmol) in the ratio 1:1 was taken in a 50 mL round bottomed flask. The reaction mixture was mixed thoroughly. The neck of the flask was covered with a small funnel to prevent the spreading of reaction mixture. The reaction mixture was then placed inside the microwave oven. The reactor was switched on with a controlled power P-40 with corresponding temp. 90°C. The progress of reaction was monitored by thin layer chromatography on silica gel 60 F₂₅₄ (0.25 mm) by using ethylacetate-hexane solvent system (volume ratio varied for different substrate). After completion of reaction, the reaction mixture was diluted with 30 mL ethylacetate and filtered through a short column of silica gel to remove the spent reagent. The crude product thus obtained was subjected to column chromatography over a pad of silica gel using ethylacetate-hexane solvent system (volume ratio varied for different substrate) as an eluent to afford the product. The products were identified by comparison of their melting points, IR absorption and NMR spectra with the authentic samples.

3. Results

The results obtained under thermal (hot air oven) and microwave conditions have been presented in Tables 1 and 2.


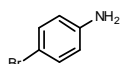

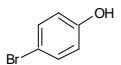

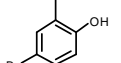
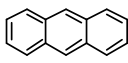
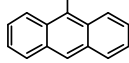

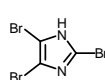
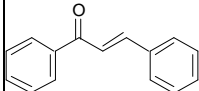
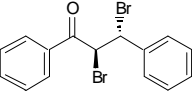

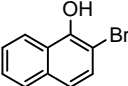
Table 1. Bromination of organic substrates with QATBs under thermal condition at temp. $60\pm 5^\circ\text{C}$.

Substrate	Product(s) ^b	TBATB		TEATB		CTMATB		TMATB	
		r.t. ^a (min)	% Y ^c	r.t. ^a (min)	% Y ^c	r.t. ^a (min)	% Y ^c	r.t. ^a (min)	% Y ^c
		10	75	25	68	8	70	15	68
		15	72	20	64	10	72	15	70
		25	65	10	60	15	60	20	68
		155	80	185	76	125	80	90	72
		10	65	10	55	10	62	25	55
		70	75	60	62	60	72	45	65
		15	78	20	70	15	74	25	69

a. Reactions were monitored by TLC. b. Products were characterized by comparison with authentic pure sample. c. Isolated yields are reported.

Different quaternary ammonium tribromide reagents were used for bromination of organic compounds and different classes of organic compounds were selected for bromination to determine the versatility of these reagents under solvent free condition. Reaction of activated benzene derivatives with these reagents resulted in the formation of para brominated products under both thermal and microwave conditions. The effect of the cationic part of the tribromide reagent on the regioselectivity of bromination of phenol, aniline and o-cresol resulted in para brominated and ortho substituted by-products in trace amount. The direct bromination of anilines and phenols with molecular bromine in solution often results in polybromination, and when brominated in the presence of oxidants, they also get oxidized rather than undergoing substitution and, in some cases, require protection of the amino ($-\text{NH}_2$) group. Anthracene did not show any significant reaction under thermal condition at 60°C so the temperature was increased to $70\pm 5^\circ\text{C}$.

Table 2. Bromination of organic substrates with QATBs under microwave conditions

Substrate	Product(s) ^b	TBATB		TEATB		CTMATB		TMATB	
		r.t. ^a (s)	%Y ^c	r.t. ^a (s)	%Y ^c	r.t. ^a (s)	%Y ^c	r.t. ^a (s)	%Y ^c
		60	83	50	80	35	85	30	79
		40	76	30	72	40	78	40	72
		45	80	40	78	35	82	45	76
		80	92	75	85	55	90	60	82
		100	72	20	65	10	78	30	71
		50	87	55	75	45	75	65	68
		25	81	20	79	45	82	30	76


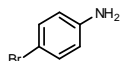

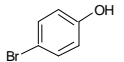

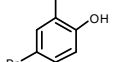
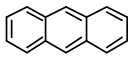
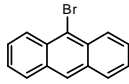

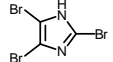
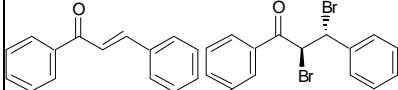
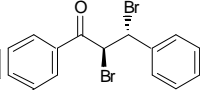
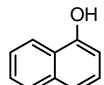
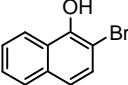
a. Reactions were monitored by TLC. b. Products were characterized by comparison with authentic pure sample. c. Isolated yields are reported.

4. Discussion

While no significant differences were found among TEATB, TBATB, CTMATB and TMATB in terms of final specific products, reaction time and yield varied from reagent to reagent as well as substrates. In general, TBATB and CTMATB were found more efficient in terms of yield. Substituted naphthols were also brominated with tribromide reagents. Transformation of α -naphthol with these tribromides resulted in quantitative and selective formation of 2-bromo product. The regioselectivity of the bromination of α & β -substituted naphthols depended on the nature of the substituent. Bromination of imidazole which is rather difficult in conventional method could be easily performed under these reaction conditions. Therefore the organic transformations afford high conversion and yields in short reaction time.

Temperature has its own relevance for speeding up the reaction. Probably the reason behind the fast reaction rate is increased intermolecular collision and friction in increased thermal condition reactions. A comparison with conventional reactions conducted under in-situ condition with acetonitrile solvent as shown in table 3, to better appreciate the advantage of this new solventless protocol in terms of reaction time and yields as well. Infact, use of solvent for organic reactions also leads to losses in product due to critical work up etc.

Table 3. Reactions by conventional methods in acetonitrile solvent at room temperature

Substrate	Product(s) ^b	TBATB		TEATB		CTMATB		TMATB	
		r.t. ^a	% Y ^c	r.t. ^a	% Y ^c	r.t. ^a	% Y ^c	r.t. ^a	% Y ^c
		3h 10min	72	3.5h	65	3.5h	69	2h 50min	62
		3h 30min	70	4.5h	60	3.5h	68	2h	70
		2h 50min	62	3h 20min	58	3h	60	4h	62
		3h 40min	70	4.5h	68	4.5h	87	4h	72
		4h 20min	68	4h	40	5h	55	3.5h	50
		5h	72	5h	55	5h	92	4.5h	65
		3h	73	4h	65	3.5h	70	3.5h	68

a. Reactions were monitored by TLC. b. Products were characterized by comparison with authentic pure sample. c. Isolated yields are reported.

5. Conclusion

In conclusion, we report a green protocol for the bromination of different classes of organic substrates. Instantaneous, facile, and regioselective bromination of industrially important anilines, phenols, o-cresol etc. in good to excellent yields and purity under ambient conditions in very short reaction time are reported.

Advantages of this protocol are:

1. Procedure is very simple
2. Reagents are solid.
3. Short reaction time.
4. High yields.
5. No involvement of solvent for conducting reaction.
6. Process is green and environment friendly, thereby preventing pollution.
7. Reactions are facile, region-selective.
8. Process is cost effective.

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