

Short communication

# A simple and improved regioselective bromination of aromatic compounds using *N*-methylpyrrolidin-2-one hydrotribromide and aqueous hydrogen peroxide under mild reaction conditions

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## Abstract

A regioselective and highly efficient method for the bromination of various aromatic compounds using *N*-methylpyrrolidin-2-one hydrotribromide (MPHT) and aqueous hydrogen peroxide has been reported. The use of MPHT alone as brominating agent gave poor yields while the addition of aqueous hydrogen peroxide enhanced the reaction rate and yielded brominated products in excellent yields in shorter reaction times.  
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**Keywords:** Bromination; Aromatic compound; MPHT; Hydrogen peroxide

## 1. Introduction

Bromination of aromatic compounds is a fundamentally important synthetic transformation as brominated arenes are extensively used as precursors in the preparation of various bioactive molecules, pharmaceuticals and play vital roles in the metal catalyzed coupling reactions [1–6]. A variety of methods using molecular bromine [7], transition metal catalysts [8] and alkali metal halides [9] have been reported in the literature. However, these methods associated with the drawbacks such as the use of toxic and hazardous bromine, which is very difficult in handling, use of expensive heavy transition metals and formation of polysubstituted and other side products.

Therefore in the recent years the main emphasis is being placed towards the use of transition metal free systems in a view to develop environmentally benign synthetic methodologies. In this context several improved methodologies using *N*-bromosuccinimide [10–15], Br<sub>2</sub>/SO<sub>2</sub>Cl<sub>2</sub> [16], *N,N,N,N*-tetrabromobenzene-1,3-disulfonyl amide [17] and hexamethylenetetraamine-Br<sub>2</sub> [18] complex have been recently reported.

Solid organic ammonium tribromides such as pyridiniumhydrobromide perbromide (PyHBr<sub>3</sub>) [19], tetramethylammonium tribromide (TMATB) [20,21], phenyltrimethylammonium tribromide (PTATB) [22], cetyltrimethylammonium tribromide (CetTMATB) [23] and tetrabutylammonium tribromide (TBATB) [24] due to their ease of handling and ability to maintain the desired stoichiometry, are finding increasing applications as the alternative substitute of toxic and hazardous molecular bromine in various organic reactions in recent years. Herein we wish to report a simple and improved protocol for the regioselective bromination of aromatic compounds using *N*-methylpyrrolidin-2-one hydrotribromide (MPHT) as a brominating agent in presence of aqueous 30% hydrogen peroxide under very mild reaction conditions (Scheme 1).

## 2. Results and discussion

The monobromination of various aromatic and heteroaromatic compounds was achieved under the reaction conditions (substrate 1 mmol, MPHT 0.5 mmol, aqueous H<sub>2</sub>O<sub>2</sub> 1 mmol at room temperature in methanol) in excellent yields, these results are presented in Table 1. Among the various substrates studied, substituted anilines, phenols and β-naphthol were found to be most reactive and converted immediately to the corresponding mono-brominated products (Table 1, entries 1–10, 14–15). Benzaldehyde and other substituted aromatic aldehydes could not be

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E-mail address: [bir\\_sain@iip.res.in](mailto:bir_sain@iip.res.in) (B. Sain).

Table 1  
Bromination of aromatic compounds using MPHT-H<sub>2</sub>O<sub>2</sub> system

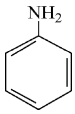
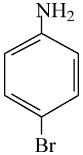
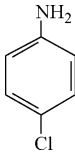
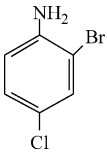
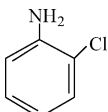
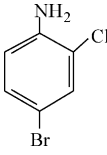
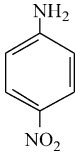
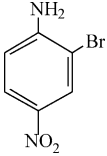
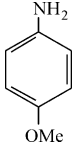
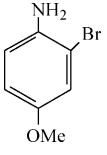
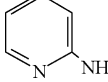
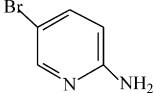
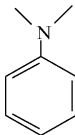
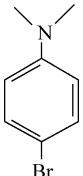
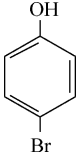
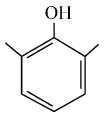
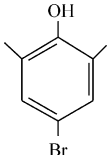
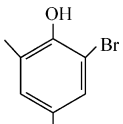
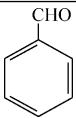
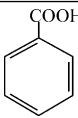
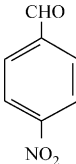
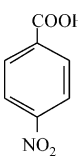
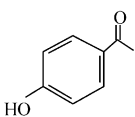
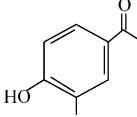
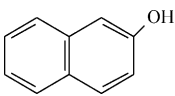
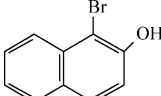
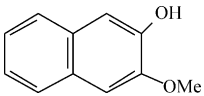
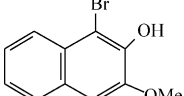
Entry	Substrate	Product	Reaction time (min)	Yield (%) <sup>a</sup>
1			10	90
2			Immediately	98
3			Immediately	97
4			30	95
5			Immediately	92
6			Immediately	94
7			Immediately	98
8			Immediately	96
9			10	85
10			20	90

Table 1 (Continued)

Entry	Substrate	Product	Reaction time (min)	Yield (%) <sup>a</sup>
11			30	97
12			45	92
13			60	80
14			Immediately	94
15			15	90

Reaction conditions: Substrate (1 mmol), MPHT (0.5 mmol), aq. H<sub>2</sub>O<sub>2</sub> (1 mmol) in methanol (3 ml) at room temperature.

<sup>a</sup> Isolated yields.

brominated under these reaction conditions and yielded corresponding carboxylic acids as the only products (Table 1, entries 11–12), indicating the higher oxidation ability of this system than bromination.

To evaluate the efficiency of this method we also carried out the bromination of phenol, 4-chloroaniline and β-naphthol with MPHT alone without using aqueous hydrogen peroxide under similar reaction conditions. These results are presented in Table 2. The reactions were found to be slow and required longer reaction times for their completion. (Table 2, entries 1–3). The effect of the various solvents was also studied for the bromination of 4-chloroaniline using MPHT/H<sub>2</sub>O<sub>2</sub> system in different organic solvents under similar reaction conditions (Table 2, entries 4–10). Among the various solvents studied such as methanol, acetonitrile, ethanol, propanol, dichloromethane, acetonitrile/methanol (1:1) mixture and with out any solvent, the methanol was found to be most promising reaction media for this transformation. The effect of the reaction temperature was also studied by carrying out the bromination of 4-chloroaniline at different reaction temperatures using MPHT/H<sub>2</sub>O<sub>2</sub> under similar reaction conditions. The selectivity of the reaction was found to highly dependent upon the reaction temperature. The bromination of 4-chloroaniline at higher temperature in refluxing methanol yielded intricate mixture of the products, while the same could be conducted more efficiently at room temperature and yielded 2-bromo-4-chloroaniline selectively.

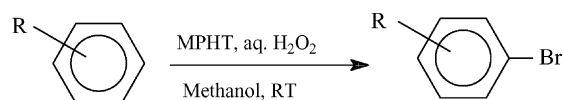
The merits of the present methodology are reflected from the fact that it provides better yields of monobrominated aromatics in shorter reaction times as compared to the recently known methods using NBS as brominating agent [26].

The exact mechanism of the reaction is not clear at this stage. The reaction probably involves the formation of hypobromous acid by the reaction of MPHT with hydrogen peroxide which on electrophilic attack of the bromonium ion on aromatic ring yielded corresponding brominated product as shown in Scheme 2. This mechanism is in analogy to mechanism proposed by Neumann and co-workers [27] for bromination of arenes with HBr and H<sub>2</sub>O<sub>2</sub>.

### 3. Experimental

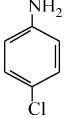
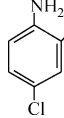
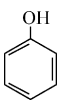
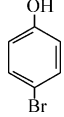
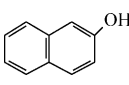
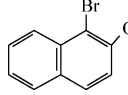
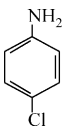
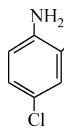
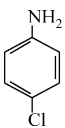
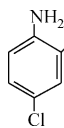
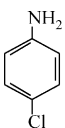
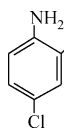
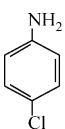
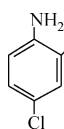
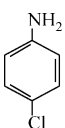
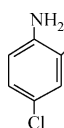
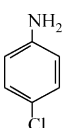
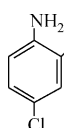
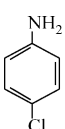
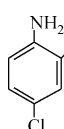
#### 3.1. General

All the substrates are commercially available. The solvents used were distilled before use. The MPHT reagent was prepared according to the literature procedure [25].



Scheme 1.

Table 2  
Bromination with MPHT under various reaction conditions

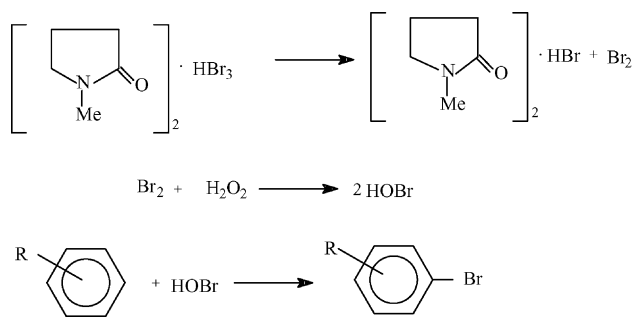
Entry	Substrate	Product	Reaction condition	Solvent	Reaction time	Yield (%) <sup>a</sup>
1			MPHT at r.t without H <sub>2</sub> O <sub>2</sub>	Methanol	3.0 h	92
2			MPHT at r.t without H <sub>2</sub> O <sub>2</sub>	Methanol	3.5 h	87
3			MPHT at r.t without H <sub>2</sub> O <sub>2</sub>	Methanol	3.5 h	90
4			MPHT + H <sub>2</sub> O <sub>2</sub> at r.t.	Methanol	Immediately	98
5			MPHT + H <sub>2</sub> O <sub>2</sub> at r.t.	Acetonitrile	30 min	80
6			MPHT + H <sub>2</sub> O <sub>2</sub> at r.t.	Ethanol	20 min	85
7			MPHT + H <sub>2</sub> O <sub>2</sub> at r.t.	Propanol	1.0 h	70
8			MPHT + H <sub>2</sub> O <sub>2</sub> at r.t.	Acetonitrile/methanol (1:1) mixture	15	90
9			MPHT + H <sub>2</sub> O <sub>2</sub> at r.t.	Dichloromethane	20 min	89
10			MPHT + H <sub>2</sub> O <sub>2</sub> at r.t.	Neat	60 min	75

<sup>a</sup> Isolated yield.

### 3.2. General experimental procedure

To a stirred mixture of substrate (1 mmol) in methanol (3 ml), was added MPHT (0.5 mmol) and aq. 30 wt.% H<sub>2</sub>O<sub>2</sub> (1 mmol) and continued the reaction at ambient temperature (25 °C).

Progress of the reaction was monitored by TLC (SiO<sub>2</sub>). At the end of reaction, the excess hydrogen peroxide was deactivated by the addition of aqueous sodium bisulfite followed by filtration through a small Büchner funnel. The solvent was evaporated under reduced pressure and the residue was taken in



to dichloromethane. The organic layer was washed with water (three times) and dried over anhydrous  $\text{MgSO}_4$ . Evaporation of the solvent under reduced pressure yielded crude product, which was purified by column chromatography on silica gel to yield pure brominated product. The reaction times and yields of the products are presented in Table 1.

#### 4. Conclusion

In conclusion the present paper describes a first example of the use of an organic ammonium tribromide in conjunction with aqueous hydrogen peroxide for the regioselective monobromination of aromatic compounds. Formation of monobrominated products in excellent yields with in very shorter reaction times and the use of substoichiometric amounts of MPHT, establish the potential synthetic merits of present protocol over known methods. Furthermore easy synthesis of reagent, mild reaction conditions and easy work-up make this an improved and facile synthetic tool for the monobromination of aromatic compounds.

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