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[Bmim]Br_3 as a New Reagent for Regioselective Mono-bromination of Activated Aromatics under Solvent-free Conditions

Zhang Gao LE[1,2,3]*, Zhen Chu CHEN[1,2], Yi HU[1,2], Qin Guo ZHENG[4]

[1] Department of Applied Chemistry, East China Institute of Technology, Fuzhou 344000
[2] Ningbo Institute of Technology Zhejiang University, Ningbo 315100
[3] Department of Chemistry, Zhejiang University Hangzhou 310028
[4]Pharmaceutical Science Reseach Institute, Aston University, Birmingham B4 7ET, UK

Abstract: Reaction of activated aromatics containing phenols, naphthol, methoxynaphthalenes, anisole *etc*. with 1-butyl-3-methylimidazolium tribromide ([Bmim]Br_3) under solvent-free conditions, selectively gave the corresponding monobromination products with excellent yields.

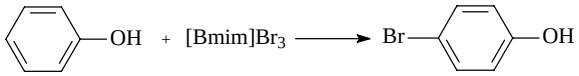
Key words: Activated aromatics, regioselective, [Bmim]Br_3.

Electrophilic aromatic bromination is an important and fundamental reaction known to organic chemists. Brominated aromatic compounds are of paramount importance as building block in organic synthesis. They are key intermediates in the preparation of organometallic reagents[1] and play vital roles in transition metal mediated coupling reaction[2]. They can be used as potant antitumor, antibacterial, antifungal, antineoplastic, antiviral, and antioxidiging agents[3]. A variety of brominating reagents (capable of bromination) are available including Br_2[4], N-bromosuccinimide (NBS) [5], tetrabutyl-ammonium tribromide[6], DBUH·Br_3[7], cetyltrimethylammonium tribromide[8], pyridinium tribromide[9], LiBr/ceric ammonium nitrate[10], HBr/DMSO[11], *etc*.. But activated aromatic compounds remain a problem due to mixtures of *ortho* and *para* products and poly-bromination[12]. There are a handful of selective bromination procedures. Therefore, the development of an efficient, selective reaction of monobromination of activated aromatics is still a major challenge in organic synthesis.

Solvent-free chemical synthesis has recently received much attention[13]. The advantage of this method over conventional reaction is that it provides greater selectivity, enhanced reaction rates, pure products, manipulative simplicity and environmentally benignity. In continuation of our ongoing program to develop environmentally benign and new synthesis methods using ionic liquids as novel promoter and selective reagents[14]. We report here a new and efficient method for the regioselective monobromination of activated aromatics using 1-butyl-3-methylimidazolium tribromide ([Bmim]Br_3), a stable liquid, which is readily prepared by reaction of equimolar amounts of 1-butyl-3-methyl-imidazolium bromide and bromine.

* E-mail: lezhang_ecit@163.com

Scheme 1



1 **2** **3**

Table 1 Monobromination of activated aromatics with $[Bmim]Br_3$

Entry	activated aromatics	Reaction condition	Product	Yield (%)
1	phenol	2 min, 0 °C	4-bromophenol	96
2	4-chlorophenol	1 h, 25 °C	2-bromo-4- chlorophenol	92
3	2-chlorophenol	1 h, 25 °C	4-bromo-2- chlorophenol	90
4	3-chlorophenol	1 h, 25 °C	4-bromo-3- chlorophenol	90
5	2-methylphenol	2 min, 5 °C	4-bromo-2 -methylphenol	97
6	4-methylphenol	2 min, -5 °C	2-bromo-4- methylphenol	95
7	2-methyoxy-phenol	2 min, 0 °C	4-bromo-2- methyoxyphenol	94
8	Anisole	10 min, 0 °C	4- bromoAnisole	95
9	1-methoxy naphthalene	1 h, 25 °C	4-bromo-1- methoxynaphthalene	92
10	2-methoxy-naphthalene	1 h, 25 °C	1-bromo-2- methoxynaphthalene	94
11	2-naphthol	1 h, 25 °C	1-bromo-2- naphthol	92

1-Butyl-3-methylimidazolium tribromide ($[Bmim]Br_3$), is an efficient and novel reagent for the regioselective monobromination of activated aromatics. We found the reaction of phenol with $[Bmim]Br_3$ (**Scheme 1**), could occurr rapidly under solvent-free conditions at 0 °C and completed within two min. The reaction leads to selective monobromination, preferentially in the *para* position (**Table 1**, Entry 1). In similar fashion, the reaction of $[Bmim]Br_3$ with a variety of phenols was investigated, we found that the reaction is general and applicable to several substituted phenols containing different groups, such as methyl, chloro, methyoxy *etc*. The results are summarized in **Table 1** (Entries 2-7). When the *para* position of substituted phenols is occupied, the reaction leads to selective monobromination in the *ortho* position. In order to explore the generality of the method developed for the synthesis of monobromination of activated aromatic substrates, we conducted the experiments with $[Bmim]Br_3$ to anisole, 1-methoxynaphthalene, 2-methoxynaphthalene, 2-naphthol, which were also effective and gave the corresponding monobromination products in excellent yields (**Table 1**, Entries 8-11).

All the products gave satisfactory mp, IR, and ^{1}HNMR data, which were consistent with the literature data.

In conclusion, we have demonstrated regioselective monobromination of phenols and activated aromatics with $[Bmim]Br_3$ can efficiently be performed under solvent-free conditions, which will be a highly useful method because of its ease, simplicity, high selectivity, excellent yield of product, and environmentally more benign.

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15. General procedure for bromination of phenols: [Bmim]Br_3 (1 mmol) was added to phenol (1 mmol) with continuous stirring (reaction conditions see **Table 1**). After the reaction was completed, the solid crude product was extracted with Et_2O, the crude product was directly purified by recrystallization with ethanol/water to give the corresponding pure product of monobromination.

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