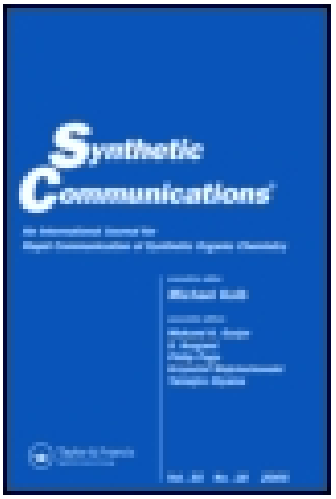

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# EFFICIENT AND REGIOSELECTIVE BROMINATION OF AROMATIC COMPOUNDS WITH ETHYLENEBIS(*N*-METHYLIMIDAZOLIUM) DITRIBROMIDE (EBMIDTB)

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***A regioselective and highly efficient method for bromination of phenol and aniline derivatives using ethylenebis(N-methylimidazolium) ditribromide (EBMIDTB) as an efficient reagent in dichloromethane at ambient temperature is reported. The reagent can be recovered and reused several times.***

***Keywords***: Anilines; bromination; ethylenebis(*N*-methylimidazolium) ditribromide; phenols

## INTRODUCTION

Brominated aromatic compounds have gained increasing attention as versatile intermediates for the synthesis of biologically active compounds such as potent antitumor, antibacterial, antifungal, antiviral, and antioxidizing agents.[1] These halides also undergo carbon–carbon bond formation via cross-coupling reactions such as Stille,[2] Suzuki,[3] Heck,[4] and Sonogashira[5] or carbon–heteroatom bond formation via aromatic functionalization protocols.[6]

Conventional bromination methods typically use elemental bromine, generating toxic and corrosive hydrogen bromide and leading to environmental pollution.[7] The reagents reported for this transformation include $Br_2$–Lewis acids,[8] N-bromosuccinimide (NBS)–$H_2SO_4$–$CF_3CO_2H$,[9] NBS–NaOH,[10] NBS–$SiO_2$,[11] $Br_2$–$Al_2O_3$,[12] NBS–Amberlyst,[13] NBS–H-form zeolite-5 (HZSM-5),[14] *tert*-BuOOH– or $H_2O_2$–HBr,[15] NBS–sulfonic-acid-functionalized silica,[16] NBS/$BF_3$–$H_2O$,[17] NBS–$NH_4OAc$,[18] NBS–tetraethyl ammonium bromide (TEAB),[19] NBS–$Pd(OAc)_2$,[20] NBS-para-toluene sulfonic acid (PTSA),[21] hexamethylenetetramine–$Br_2$,[22] $Br_2/SO_2Cl_2$/zeolite,[23] tribromoisocyanuric acid,[24] bromodichloroisocyanuric acid,[25] $NH_4VO_3$–$H_2O_2$–HBr,[26] NaBr-$PhI(OAc)_2$[27] and $CuBr_2$.[28] However, some of these methods are associated with drawbacks such as the use of

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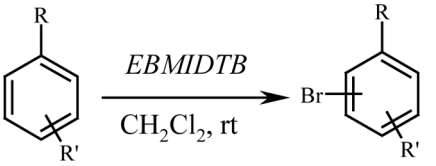



**Scheme 1.** R = OH, $NH_2$; R = electeron releasing and withdrawing groups.

nonselective hazardous mineral acids and metal halides, which can lead to separation difficulties and toxic and corrosive wastes, use of expensive heavy transition metals, and formation of polysubstituted and other side products. The replacement of such reagents with nontoxic and more selective compounds is very desirable and represents an important goal in the context of clean synthesis.

Because of their ease of handling and ability to maintain the desired stoichiometry, solid organic ammonium tribromides such as pyridiniumhydrobromide perbromide ($PyHBr_3$),[29] tetramethylammonium tribromide (TMATB),[30,31] phenyltrimethylammonium tribromide (PTATB),[32] cetyltrimethylammonium tribromide (CetTMATB),[33] tetrabutyl ammonium tribromide (TBATB),[34] 1,2-dipyridiniumditribromide-ethane,[35] alkylpyridinium tribromide,[36] and [Bmim]$Br_3$[37] are finding increasing applications as alternative substitutes for toxic and hazardous molecular bromine in various organic reactions in recent years. Some tribromide reagents have also been successfully used for efficient and more ecologically acceptable solvent-free brominations of activated aromatic compounds.[38]

In the present work, we report efficient and regioselective bromination of aromatic compounds with ethylenebis(*N*-methylimidazolium) ditribromide (EBMIDTB) (Scheme 1).

## RESULTS AND DISCUSSION

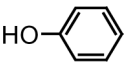
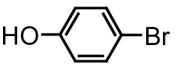
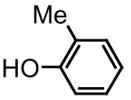
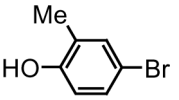
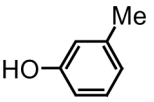
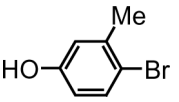
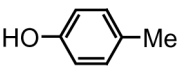
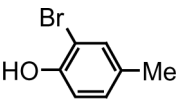
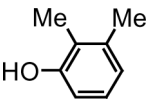
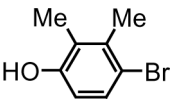
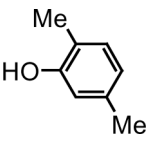
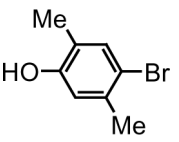
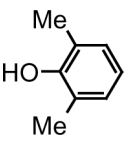
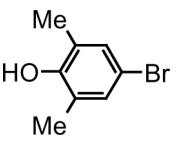
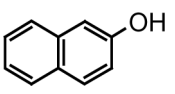
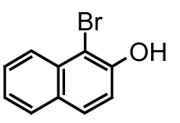
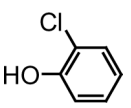
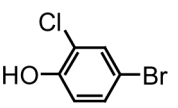
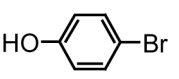
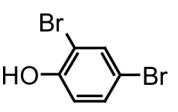
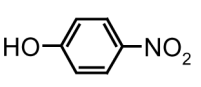
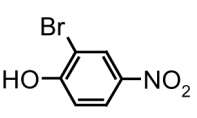
EBMIDIB is easily and cheaply prepared from *N*-methylimidazole, 1,2-dibromoethane, and bromine.[39] We prepared EBMIDTB and used it for bromination of aromatic compounds.

Initially, phenol was chosen as a model substrate to find optimal conditions. When phenol was treated with 0.5 mmol of EBMIDTB at room temperature in dichloromethane (DCM) after 30 min, *p*-bromophenol was formed in 95% yield. This reaction was carried out in different protic and aprotic solvents, and the best yield of *p*-bromophenol was achieved in $CH_2Cl_2$.

As indicated in Table 1, phenol, methyl-substituted phenols, and β-naphtol were smoothly reacted with EBMIDTB at room temperature and gave corresponding regioselective *p*-brominated product in excellent yield after 30 min (Table 1, entries 1–8). We have analyzed the products by gas chromatography (GC) and did not find any polybrominated isomers. However, when electron-withdrawing substituted phenols were applied in this reaction, only moderate yield of the corresponding monobrominated isomer was obtained (Table 1, entries 9–11).

EBMIDTB was also used to brominate aniline derivatives at ambient temperature. Various activated and deactivated anilines were brominated upon simple mixing with reagent in DCM (Table 2). The reaction with aniline itself (Table 2,

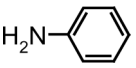
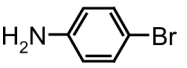
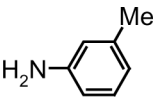
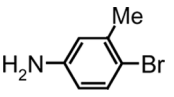
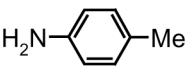
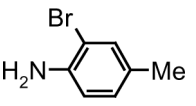
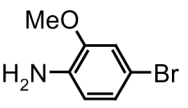
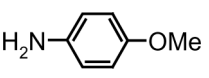
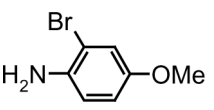
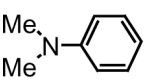
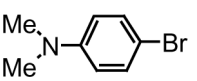
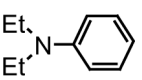
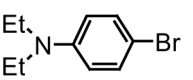
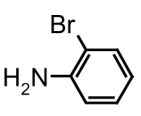
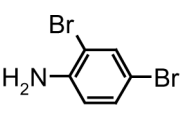
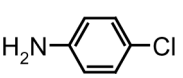
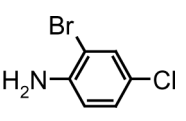
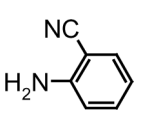
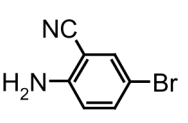
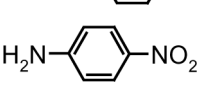
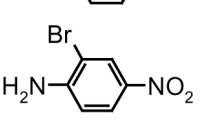
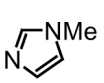
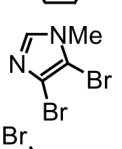
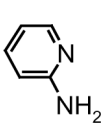
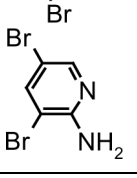
**Table 1.** Bromination of phenol derivatives using EBMIDTB

| Entry | Substrate | Product[a] | Time (min) | Yield (%)[b] | Mp (°C)[Ref.] |
|---|---|---|---|---|---|
| 1 |  |  | 30 | 97 | 64–66[40a] |
| 2 |  |  | 30 | 80 | 62–64[40a] |
| 3 |  |  | 30 | 90 | 61–63[40a] |
| 4 |  |  | 30 | 97 | 55–57[40a] |
| 5 |  |  | 30 | 90 | 82–84[40b] |
| 6 |  |  | 30 | 90 | 85–87[40a] |
| 7 |  |  | 30 | 90 | 76–79[40a] |
| 8 |  |  | 30 | 95 | 83–85[40a] |
| 9 |  |  | 240 | 60 | 47–50[40a] |
| 10 |  |  | 270 | 82 | 34–36[40a] |
| 11 |  |  | 270 | 64 | 113–116[40a] |

[a]All of the products were identified by comparing melting point and $^1$H NMR with those of authentic samples reported in the literature.

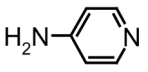
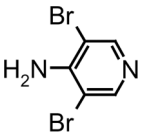
[b]Yields refer to isolated products.

**Table 2.** Bromination of aniline derivatives using EBMIDTB

| Entry | Substrate | Product[a] | Time (min) | Yield (%)[b] | Mp (°C)[Ref.] |
|---|---|---|---|---|---|
| 1 |  |  | 30 | 75 | 61–63[40a] |
| 2 |  |  | 30 | 75 | 77–79[40a] |
| 3 |  |  | 30 | 71 | 27–29[40a] |
| 4 |  |  | 30 | 75 | 59–61[40a] |
| 5 |  |  | 30 | 80 | Liquid[40c] |
| 6 |  |  | 30 | 80 | 54–56[40a] |
| 7 |  |  | 30 | 80 | 31–33[40a] |
| 8 |  |  | 60 | 75 | 78–80[40a] |
| 9 |  |  | 60 | 86 | 64–66[40a] |
| 10 |  |  | 270 | 95 | 89–92[40d] |
| 11 |  |  | 270 | 50 | 102–104[40a] |
| 12 |  |  | 20 | 60[c] | 73–75[40e] |
| 13 |  |  | 25 | 57[c] | 100–102[40a] |

(*Continued*)

**Table 2.** Continued

| Entry | Substrate | Product[a] | Time (min) | Yield (%)[b] | Mp (°C)[Ref.] |
|---|---|---|---|---|---|
| 14 |  |  | 25 | 55[c] | 167–170[40a] |

[a]All of the products were identified by comparing melting point and $^1$H NMR with those of authentic samples reported in the literature.

[b]Yields refer to isolated products.

[c]1.0 mmol of ditribromide were used.



entry 1) formed *p*-bromaniline as the main product (75%), along with 25% of 2,4-dibromo isomer (Table 2, entry 1). *N,N*-Dimethyl or *N,N*-diethyl aniline reacted with EBMIDTB to afford their *p*-bromo derivatives in good yields (Table 2, entries 6 and 7). Under reaction conditions, methyl and methoxy substituted anilines also gave the monobrominated products in good yields (Table 2, entries 2–5). *p*-Chloro aniline smoothly reacted with EBMIDTB, and a good yield of 2-bromo-4-chloroaniline was formed (Table 2, entry 9). *o*-Bromo aniline under reaction conditions gave a lesser yield of 2,4-dibromoaniline (Table 2, entry 8). *p*-Nitroaniline afforded only 50% of 2-bromo-4-nitroaniline in longer reaction time (Table 2, entry 11). *o*-Cyanoaniline required long reaction time but gave excellent yield of 4-bromo-2-cyanoaniline (Table 2, entry 10). In contrast to phenol derivatives, in the bromination of substituted anilines, a poor yield of the corresponding dibromo isomers (10–20%) was formed. Having these data in hand, we have decided to apply this method for heterocyclic compounds. *N*-Methyl imidazole and *o*- and *p*-amino pyridines were reacted with EBMIDTB under reaction conditions, and in all cases only the corresponding dibrominated products were obtained in moderate yield (Table 2, entries 12–14).

An interesting feature of this method is that the reagent can be regenerated at the end of the reaction by extraction with water[39] and can be used several times without loosing its activity.

In conclusion, we have developed an efficient and versatile method for the monobromination of active aromatic compounds using ethylenebis(*N*-methylimidazolium) ditribromide. The method is highly regioselective, offering potential in various synthetic applications. The mild reaction conditions, simple experimental procedure, rapid conversion, good yields, and reusability of the reagent are notable advantages of the method.

## EXPERIMENTAL

### General

Materials were purchased from Fluka and Merck companies. Products were characterized by comparison of their spectroscopic data ($^1$H NMR) and physical properties with those of authentic samples.

### General Procedure for Bromination of Aromatic Compounds

In a 25-mL, round-bottomed flask, EBMIDTB (0.5 mmol, 0.336 g, but 1.0 mmol for entries 12–14) was added to a solution of aromatic compound (1 mmol) in DCM (10 mL). The reaction mixture was stirred at room temperature. After disappearance of the starting material as monitored by GC, the reaction mixture was transferred into a separatory funnel and washed with water (15 mL). The organic layer was dried over anhydrous $Na_2SO_4$ and filtered, and solvent was concentrated in a rotary evaporator. The crude product was purified by passing it over a column of silica gel, using a mixture of hexane and ethyl acetate as the eluent (7:1). All of the products were identified by comparing melting point and $^1$H NMR with those of authentic samples reported in the literature.



### Selected Data

**4-Bromo-2-methylphenol (Table 1, entry 2).** $^1$H NMR (500 MHz, $CDCl_3$): δ 2.26 (s, 3H), 5.19 (s, 1H), 6.70 (d, $J = 8.47$ Hz, 1H), 7.20 (dd, $J = 8.47$, 2.30 Hz, 1H), 7.28 (d, $J = 2.30$ Hz, 1H).

**4-Bromo-3-methylphenol (Table 1, entry 3).** $^1$H NMR (500 MHz, $CDCl_3$): δ 2.31 (s, 3H), 5.28 (br s, 1H), 6.54 (dd, $J = 8.55$, 2.81 Hz, 1H), 6.72 (d, $J = 2.81$ Hz, 1H), 7.32 (d, $J = 8.55$, 1H).

**4-Bromo-3-methylaniline (Table 2, entry 2).** $^1$H NMR (500 MHz, $CDCl_3$): δ 2.27 (s, 3H), 3.90 (br s, 2H), 6.72 (d, $J = 8.14$ Hz, 1H), 6.96 (dd, $J = 8.14$, 1.30 Hz, 1H), 7.28 (d, $J = 1.30$ Hz, 1H).

**2-Bromo-4-methoxyaniline (Table 2, entry 5).** $^1$H NMR (500 MHz, $CDCl_3$): δ 3.72 (br s, 2H), 3.77 (s, 3H), 6.78 (m, 2H), 7.05 (t, $J = 1.43$ Hz, 1H).

**2,4-Dibromoaniline (Table 2, entry 8).** $^1$H NMR (500 MHz, $CDCl_3$): δ 3.70 (br s, 2H), 6.63 (d, $J = 8.52$ Hz, 1H), 7.18 (dd, $J = 8.52$, 2.04 Hz, 1H), 7.52 (d, $J = 2.04$ Hz, 1H).

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