Mild Regioselective Monobromination of Activated Aromatics and Heteroaromatics with N-Bromosuccinimide in Tetrabutylammonium Bromide

Nemai C. Ganguly,* Prithwijit De, Sanjoy Dutta
Department of Chemistry, University of Kalyani, Kalyani- 741 235, India
Fax +91(33)25828282; E-mail: nemai.g@yahoo.co.in
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Abstract: Highly regioselective nuclear bromination of activated aromatic and heteroaromatic compounds has been accomplished using N-bromosuccinimide in tetrabutylammonium bromide. Predominant para-selective monobromination of activated aromatics such as phenols and anilines, rate acceleration of bromination for moderately activated and less reactive substrates on addition of acidic montmorillonite K-10 clay, with or without microwave assistance, are the notable features of this protocol.

Key words: bromination, ionic liquid, tetrabutylammonium bromide, N-bromosuccinimide, aromatics, heteroaromatics, regioselectivity

Bromination of aromatics and heteroaromatics is an electrophilic substitution reaction of immense synthetic and industrial importance. Brominated arenes and heteroarenes are useful as pharmaceuticals, flame retardants, agrochemicals, specialty chemicals1 and synthetic intermediates capable of undergoing carbon–carbon bond formation via transmetalation reactions such as Heck, Stille, Suzuki, Sonogashira and Tamao–Kumada reactions.2 In general, ring brominated aromatics and heteroaromatics exhibit interesting biological activities.3 Halogen substituted pyrimidines and purines are particularly important for their chemotherapeutic, biochemical and biophysical properties.4 Apart from their usefulness as fluorophores and potential intermediates for photophysical probes,5a bromocoumarins are also important as synthetic precursors of furocoumarins and dihydrofurocoumarins that are widely used as photosensitizers and chemotherapeutic agents to combat skin diseases,5b–d and naturally abundant linear coumarins.5e Despite their usefulness, scanty work is documented for regiospecific monobromination of coumarins.5f,g Bromination of activated arenes and heteroarenes is often an unselective reaction resulting in a mixture of mono- and polybrominated derivatives with consequent tedious separation problems and poor atom economy. Therefore, the search for new regioselective methods of bromination has evoked great contemporary interest. Use of NBS for nuclear bromination in polar media such as DMF,6,a MeCN,5,b,c aqueous NaOH,6,d in the presence of acids,5,e,f,g silica gel,6h zeolite,6i HZSM-56j and isopropylamine7a is well-documented. These protocols offer different levels of selectivity depending primarily on the extent of activation of N–Br bond in NBS6,e,f,7a actual brominating species involved6 and control exhibited by the heterocyclic ring and oxygenated function, if present.7b,c The increasing use of room temperature ionic liquids as alternative green solvents and catalysts8 for organic transformations prompted us to evaluate the efficacy of NBS for nuclear brominations of arenes and heteroarenes in tetrabutylammonium bromide (TBAB).5a,9 Herein we reveal our results in Table 1. Activated aromatic substrates represented by phenols and anilines undergo monobromination at 100 °C with para-selectivity in a clean fast process. Gratifyingly, this method gives monobrominated products uncontaminated with di- or tribromo derivatives with these substrates, which are otherwise difficult to obtain. It is also significant that exclusive para-substitution is observed without any special para-directing additives, such as zeolites7d or cyclodextrins9 and protection-deprotection sequence. Bromination by this method was also much faster than similar bromination in DMF,6,a which took 24 hours even for activated aromatics (entries 1, 3, and 5). The free bromide ion of TBAB acts as a strong hydrogen bond base10 with phenolic hydroxy group thereby enhancing its nucleophilicity. Coupled with the activation of NBS by way of promoting nucleophilic cleavage of N–Br bond by unsolvated bromide ion (Scheme 1) this factor enhances the rate of bromination substantially.

Scheme 1

Addition of 10 mol% water to the reaction mixture dramatically slowed down the bromination in the case of 1-naphthol (entry 4, ii). This observation suggests that the presence of unsolvated bromide ion is crucial to brominating ability of this reagent system and solvation of bromide ion in the presence of water makes it a poorer nucleophile impeding its function. Exclusive para-bromination of aromatics is consistent with generation of molecular bromine at low concentration in a slow rate-determining step.
and its fast consumption by the substrate in a kinetically controlled reaction. This obviously suggests short lifetime of the ionic intermediate for bromination and similar suggestion has been made to explain the stereochemical outcome of bromine addition to alkenes and alkynes in ionic liquid. The possibility of molecular bromine forming adduct of tetrabutylammonium tribromide (TBATB) with TBAB cannot be ruled out at this stage. Significantly, \( \text{Br}_3^- \) can be ascertained from its characteristic UV absorption band in the vicinity of 267 nm (ethylene dichloride). In fact, TBATB, separately prepared, displayed \( \lambda_{\text{max}} \) at 263 nm in TBAB-CHCl\(_3\) mixture. On the other hand, a mixture of NBS in TBAB exhibited a quite different \( \lambda_{\text{max}} \) at 278 nm. The intermediacy of TBATB seems unlikely in view of this observation. It seems plausible that attainment of a reasonable concentration of TBATB in the viscous medium by a diffusion controlled process is slow or the liberated bromine is rapidly consumed by the substrate by an ionic mechanism before it engages itself in an equilibrium with TBAB. Attempted bromination of cinnamic acid with NBS in TBAB led to facile decarboxylation resulting in formation of \( \beta \)-bromostyrene (entry 19) by Hunsdiecker reaction. In contrast, TBATB is reported to yield the 2,3-dibromo-3-phenylpropionic acid thereby revealing further the different nature of the brominating species with NBS in TBAB. The formation of a mixture of \( E \)- and \( Z \)-bromoalkene is consistent with the intermediacy of benzylic \( \beta \)-bromocarbonium ion supported by the ionic nature TBAB rather than rigid cyclic bromonium ion (Scheme 2). 

No decarboxylation was observed when cinnamic acid was allowed to react with TBATB (1 mol equiv) in TBAB or NBS in dichloromethane suggesting the special catalytic role of TBAB in the Hunsdiecker reaction. Absence of side-chain bromination at the methyl groups of 4,6- and 4,7-dimethylcoumarins (entries 17, 18) despite prolonged exposure (6 h, 100 °C) is another notable feature of this protocol. For moderately activated substrates (entries 7, 8), addition of boron trifluoride etherate (1 mol equiv) (entry 6) or solid acid montmorillonite K-10 clay to the reaction mixture substantially accelerates bromination, which can be further expedited with microwave assistance. This is an obvious synthetic advantage over brominations based on TBATB, which does not work with acetanilides. Exclusive bromination at C-3 of 7-hydroxycoumarin in preference to nucleophilic sites at C-6 and C-8 ortho to hydroxy group further demonstrates the absence of directive effect of hydroxy group through its association with NBS promoting delivery of bromine at ortho-positions. This protocol is efficient for bromination of nucleoside bases uracil and cytosine in terms of reaction time and yield. However, purine bases adenine and guanine are resistant to this reagent system (36 h, r.t./8 min, MW, 300 W) due to the strong deactivating nature of purine bases.

### Table 1: Bromination of Aromatics and Heteroaromatics with NBS in TBAB

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Reaction Time</th>
<th>Yield (%)</th>
</tr>
</thead>
</table>
| 1     | \[
\begin{array}{c}
\text{CH}_2
\end{array}
\] | \[
\begin{array}{c}
\text{Br}
\end{array}
\] | 2 h | 90 |
| 2     | \[
\begin{array}{c}
\text{CH}_2
\end{array}
\] | \[
\begin{array}{c}
\text{Br}
\end{array}
\] | 2 h | 84 |
| 3     | \[
\begin{array}{c}
\text{CH}_2
\end{array}
\] | \[
\begin{array}{c}
\text{Br}
\end{array}
\] | 2.5 h | 86 |
| 4     | \[
\begin{array}{c}
\text{CH}_2
\end{array}
\] | \[
\begin{array}{c}
\text{Br}
\end{array}
\] | i. 4 h, ii. 8 h | 75, 73 |

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Reaction Time</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| 5     | \[
\begin{array}{c}
\text{NH}_2 \\
\end{array}
\] | \[
\begin{array}{c}
\text{NH}_2 \\
\text{Br}
\end{array}
\] | 4 h | 88 |
| 6     | \[
\begin{array}{c}
\text{NH}_2 \\
\text{NO}_2
\end{array}
\] | \[
\begin{array}{c}
\text{NH}_2 \\
\text{Br} \\
\text{NO}_2
\end{array}
\] | i. 10 h; ii. 6 h | 84; 87<sup>c</sup> |
| 7     | \[
\begin{array}{c}
\text{NHCOCH}_3 \\
\end{array}
\] | \[
\begin{array}{c}
\text{NHCOCH}_3 \\
\text{Br}
\end{array}
\] | i. 10 h; ii. 2 h; iii. 5 min | 80; 85<sup>d</sup>; 92<sup>e</sup> |
| 8     | \[
\begin{array}{c}
\text{NHCOPh}
\end{array}
\] | \[
\begin{array}{c}
\text{NHCOPh}
\end{array}
\] | i. 48 h; ii. 4 h; iii. 8 min | 78; 82<sup>d</sup>; 90<sup>e</sup> |
| 9     | \[
\begin{array}{c}
\text{HO} \\
\text{C} \\
\text{O} \\
\text{O}
\end{array}
\] | \[
\begin{array}{c}
\text{HO} \\
\text{C} \\
\text{O} \\
\text{Br}
\end{array}
\] | i. 3 h; ii. 6 min | 78; 82<sup>e</sup> |
| 10    | \[
\begin{array}{c}
\text{HO} \\
\text{C} \\
\text{O} \\
\text{O} \\
\text{C} \\
\text{O}
\end{array}
\] | \[
\begin{array}{c}
\text{HO} \\
\text{C} \\
\text{O} \\
\text{Br} \\
\text{C} \\
\text{O}
\end{array}
\] | 4 h | 60 |
| 11    | \[
\begin{array}{c}
\text{HO} \\
\text{Br}
\end{array}
\] | \[
\begin{array}{c}
\text{HO} \\
\text{Br}
\end{array}
\] | 3 h | 76 |
| 12    | \[
\begin{array}{c}
\text{HO} \\
\text{O} \\
\text{O}
\end{array}
\] | \[
\begin{array}{c}
\text{HO} \\
\text{O} \\
\text{Br}
\end{array}
\] | 4 h | 68 |
| 13    | \[
\begin{array}{c}
\text{H}_2\text{N} \\
\text{O} \\
\text{C} \\
\text{O}
\end{array}
\] | \[
\begin{array}{c}
\text{H}_2\text{N} \\
\text{O} \\
\text{Br} \\
\text{C} \\
\text{O}
\end{array}
\] | 4 h | 75 |
| 14    | \[
\begin{array}{c}
\text{H}_2\text{N} \\
\text{N} \\
\text{NH}_2
\end{array}
\] | \[
\begin{array}{c}
\text{H}_2\text{N} \\
\text{N} \\
\text{Br}
\end{array}
\] | i. 45 min; ii. 2.5 min | 85; 92<sup>e</sup> |
| 15    | \[
\begin{array}{c}
\text{H} \\
\text{O}
\end{array}
\] | \[
\begin{array}{c}
\text{H} \\
\text{O}
\end{array}
\] | i. 1 h; ii. 4 min | 82; 90<sup>f</sup> |
| 16    | \[
\begin{array}{c}
\text{H} \\
\text{O}
\end{array}
\] | \[
\begin{array}{c}
\text{H} \\
\text{O}
\end{array}
\] | i. 2 h; ii. 4 min | 78; 96<sup>e</sup> |
In conclusion, a mild efficient protocol for monobromination of activated aromatics and heteroaromatics has been developed employing NBS in TBAB. Para selectivity for aromatics, use of non-excess stoichiometry leading to monobromination and consequent less demanding purification procedures are the advantageous features of this method.

TBAB and NBS were procured from Spectrochem, India and E. Merck, Germany respectively. Solvents used for extraction and chromatography were distilled prior to use. A domestic microwave oven (BPL India, 2450 MHz) was used for microwave experiments.

Bromination with NBS in TBAB; 5-Bromo-6-aminocoumarin; Typical Procedure (Table 1, Entry 13)

6-Aminocoumarin (342 mg, 2.12 mmol) was added to solid TBAB (0.4 g) with stirring and when the resulting mixture became a clean melt, NBS (380 mg, 2.13 mmol) was added. This was heated to 100 °C in a closed glass vial and then kept at that temperature for 4 h (TLC monitoring). H2O (4 mL) was then added to remove succinimide followed by extraction with a minimum amount of EtOAc. The organic extract, after washing with brine, drying (Na2SO4) and careful removal of solvent, gave one product exclusively along with 5-bromo products.

Microwave-Assisted Bromination of Acetanilide with NBS-TBAB in the Presence of Montmorillonite K-10 Clay; 4-Bromoacetanilide; Typical Procedure (Table 1, Entry 7, ii)

To an intimate mixture of acetanilide (280 mg, 2.07 mmol) and TBAB (0.4 g) in an Erlenmeyer flask was added NBS (370 mg, 2.08 mmol) followed by montmorillonite K-10 clay (1 g). The mixture, after thorough stirring, was irradiated with microwave at 300 W for 2 × 2.5 min cycles with 30 s in between to allow TLC monitoring.

The reaction mixture was cooled to r.t., diluted with EtOAc (4 mL) and directly charged into a silica gel column for chromatographic purification. 4-Bromoacetanilide was obtained as a crystalline solid (400 mg, 91%) using CH2Cl2 as eluent; mp 166–167 °C. TBAB was also recovered as before from later fractions of CH2Cl2 eluates and was reused.

Bromination of Aromatics with NBS-TBAB in the Presence of Boron Trifluoride Etherate; 2-Bromo-4-nitroaniline; Typical Procedure (Table 1, Entry 6, i)

An intimate mixture of 4-nitroaniline (148 mg, 1.08 mmol) and TBAB (0.22 g) was heated at 100 °C. The mixture was cooled to r.t., and to it was added NBS (195 mg, 1.09 mmol) and finally BF3·OEt2 (155 mg, 1.07 mmol) in a glass vial. The closed glass vial was kept at r.t. for 6 h and it was then quenched with sat. aq NaHCO3 (3 mL). This was followed by extraction with EtOAc (2 × 4 mL) and chromatographic filtration over silica gel to afford 2-bromo-4-nitroaniline (200 mg, 87%); mp 103–104 °C (Lit.15 mp 104.5 °C) and TBAB.

Characterization Data of Some Selected Products
3-Bromo-7-hydroxycoumarin
Mp 214–216 °C.
FTIR (KBr): 3257, 3048, 1695, 1621, 1591, 1362, 1260, 1045, 838, 751 cm–1.
1H NMR (300 MHz, DMSO-d6): δ = 6.94 (1 H, d, J = 2.1 Hz, H-8), 6.82 (1 H, dd, J = 2.1, 8.7 Hz, H-6), 7.53 (1 H, d, J = 8.7 Hz, H-5), 8.48 (1 H, s, H-4), 10.76 (1 H, s, 7-OH).
EIMS (70 eV): m/z (%): 242, 240 (89.0, 84.3, M+), 214, 212 (19.3, 24.2), 186, 184 (7.5, 8.0), 161 (23.2).
Anal. Calcd for C9H5O3Br: C, 44.83; H, 2.07. Found: C, 44.89; H, 2.01.

Note: This compound has been reported16 as an oil with 1H NMR spectrum (90 MHz, DMSO-d6) exhibiting H-4 at δ = 7.8 and 7-OH at δ = 5.5; both values seem unusual in view of the fact that 3-Br will certainly cause substantial low-field shift of H-4 which usually appears at δ = 7.8. Hydroxy proton of 7-hydroxycoumarins usually appears in the region δ = 10–11 in DMSO-d6. However, no supportive mass spectral and elemental analysis data were reported for the oil.
3-Bromo-4-methyl-7-methoxycoumarin

Mp 130–133 °C.

IR (KBr): 3180, 3120, 1660, 1600, 1540, 1530, 1455, 1430, 1380, 1290, 1270, 1240, 1170, 1160, 1140, 1120, 1090, 1070, 1050, 1030, 1020, 990, 980, 940, 890 cm–1.

1H NMR (300 MHz, DMSO-d6): δ = 3.97 (2 H, br s, 6-NH2), 6.46 (1 H, d, J = 9.6 Hz, H-3), 6.97 (1 H, d, J = 8.7 Hz, H-7), 7.14 (1 H, d, J = 8.7 Hz, H-8), 8.03 (1 H, d, J = 9.6 Hz, H-4).

Anal. Calcd for C9H6BrO2: C, 43.38; H, 1.96; N, 5.93. Found: C, 43.43; H, 2.01; N, 5.86.

5-Bromo-6-hydroxycoumarin

Mp 210–211 °C.

IR (KBr): 3320, 3230, 2920, 1660, 1610, 1580, 1530, 1500, 1455, 1430, 1380, 1290, 1270, 1240, 1170, 1160, 1140, 1120, 1090, 1070, 1050, 1030, 1020, 990, 980, 940, 890 cm–1.

1H NMR (300 MHz, CDCl3): δ = 4.07 (2 H, br s, 6-NH2), 6.83 (1 H, d, J = 9.6 Hz, H-3), 7.12 (1 H, d, J = 9.6 Hz, H-7), 7.22 (1 H, d, J = 9.6 Hz, H-8), 8.39 (1 H, d, J = 9.6 Hz, H-4).

Anal. Calcd for C9H6BrO2: C, 43.38; H, 1.96; N, 5.93. Found: C, 43.43; H, 2.01; N, 5.86.

5-Bromo-6-aminocoumarin

Mp 168–169 °C.

FTIR (KBr): 3320, 3230, 2920, 1660, 1610, 1580, 1530, 1500, 1455, 1430, 1380, 1290, 1270, 1240, 1170, 1160, 1140, 1120, 1090, 1070, 1050, 1030, 1020, 990, 980, 940, 890 cm–1.

Anal. Calcd for C9H11BrO2: C, 44.88; H, 4.45; N, 5.49. Found: C, 44.88; H, 4.45; N, 5.49.

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References

(d) Buckles, R. E.; Popov, A. I.; Zelezny, W. F.; Smith, R. J. *J. Am. Chem. Soc.* 1951, 73, 4525.

