CHAPTER V

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5.1. INTRODUCTION

Bromination of organic substrate, particularly aromatics, has garnered a significant amount of attention in recent years.\textsuperscript{1-8} Bromo-compounds have considerable commercial importance as potent antitumor, antineoplastics, antiviral and antioxidising agent.\textsuperscript{9} These compounds can be used as industrial intermediates for the manufacture of specialty chemicals, pharmaceuticals and agrochemicals. Electrophilic aromatic bromination is one of the older reactions known to organic chemists. Aryl halides are important synthetic intermediates for a variety of transformations that ranges from formation of functionalized aromatic compound.
5.2. REVIEW OF THE LITERATURE

There are a handful of selective bromination procedures. Smith\textsuperscript{10} has reported a method (Scheme 5.1) for the regioselective one-pot bromination of aromatic amine.

\begin{center}
\begin{tikzpicture}
\node[draw, circle, align=center] (a) {NH\textsubscript{2}};
\node[draw, circle, align=center] (b) at (1,0) {Br};;
\node[draw, circle, align=center] (c) at (1,-0.5) {NH\textsubscript{2}};\node[draw, circle, align=center] (d) at (-1,-0.5) {NH\textsubscript{2}};\node[draw, circle, align=center] (e) at (0,-1) {Br};
\draw[->] (a) -- (b);
\draw[->] (c) -- (d);
\draw[->] (d) -- (e);
\end{tikzpicture}
\end{center}

\textbf{Scheme 5.1}

In this method aniline treated with n-butyllithium and then trimethyltin chloride to give the tin amide in situ. Without isolation of the tin amide, reaction with bromine and workup with aqueous fluoride ion give p-bromoaniline 76\% yield with no dibromoaniline or o-bromoaniline. Literature search revealed several methods for selective bromination of aniline. Tetrabutylammonium tinamide,\textsuperscript{11,12} DBUH . Br\textsubscript{3},\textsuperscript{13} cetyltrimethylammonium tribromide,\textsuperscript{14} and pyridinium bromide perbromide\textsuperscript{15} have been reported as mild brominating agents. Aniline reacted with Tetrabutylammonium tinamide, to give 82\% of monobrominated product
along with some dibrominated product. However, acetanilide and pyridine did not react with this reagent.\(^\text{16}\) This contrasts with pyridinium bromide perbromide, which brominated pyridine, aniline and its derivatives, although reaction with aniline gave a 19:68 ratio of o- to p- bromoaniline.\(^\text{17}\) A recent study used LiBr / ceric ammonium nitrate as a brominating agent, converting N, N-dimethylaniline to a 2:3 mixture of o- and p-bromo derivatives in 70% yield.\(^\text{18}\) Majetich and co-workers, who has showed that aniline reacted with HBr / DMSO to give a 76% yield after 6h, in a remarkably selective reaction, reported one of the most useful methods.\(^\text{19}\) Velusamy and his coworker has reported a method for the bromination of aniline and N-substituted aniline encapsulated in β-cyclodextrin.\(^\text{20}\) Handliova et al has discussed a method for the non-catalyzed oscillation reaction in the aniline-KBrO\(_3\)-H\(_2\)SO\(_4\) system.\(^\text{21}\) Kitagawa and his coworker has developed an efficient method for the preparation of aromatic bromides.\(^\text{22}\) Mohan Krishna has achieved a method for the novel bromination of aniline and anisoles using ammonium bromide and H\(_2\)O\(_2\) in acetic acid.\(^\text{23}\) Hallas \textit{et al} developed a method for p-bromination of aromatic amine using molecular bromine as brominating agent (Scheme 5.2).\(^\text{24}\)

![Scheme 5.2](image-url)
Park et al. reported a method for bromination of aromatic compound using tetrabutylammonium peroxydisulfate.\textsuperscript{25} Newman has discussed coordination of aniline to a metal, in which aniline was converted to the $N$-magnesium compound (PhNHMgBr), and upon reaction with oxygen, $p$-bromoaniline was obtained.\textsuperscript{26} Mousseron-Canet has developed a method for bromination of aminonaphthalenes.\textsuperscript{27} Smith has achieved a method for the bromination of carbazole with NBS.\textsuperscript{28}
5.3. PRESENT WORK

Bromination of organic substrates is an important reaction in organic chemistry. After successful attempt for the synthesis of alkoxy bromide, we presumed that the intermediate bromonium ion (Scheme 2.10) can be opened with any nucleophile to get the desired bromo-product. Interestingly, when we have carried out the bromohydrin formation reaction in presence of aniline we got bromoaniline as one of the product. So this observation made us to think for an alternative procedure for bromination of anilines.
5.4. OBJECTIVE OF THE PRESENT WORK

When we have carried out the bromohydrin formation reaction in anhydrous acetonitrile in presence of aniline as nucleophile the reaction did not go in the direction that we expected. Analysis of the reaction mixture revealed that bromoaniline is one of the major product. Then we sought to investigate the bromination of anilines using $N,N$-dibromo-$p$-toluene sulfonamide (TsNBr$_2$) (Scheme 5.3).

![Scheme 5.3](image-url)
5.5. RESULT AND DISCUSSION

Initially we have carried out an investigation to study the effect of the reagent \( N, N \)-dibromo-\( p \)-toluene sulfonamide (TsNBr\(_2\)) on aniline. The reaction was carried out by adding TsNBr\(_2\) (0.5, 1.0, 1.5 equiv.) to a solution of organic substrate (1.1 equiv.) in acetonitrile (2ml) at room temperature (Table 5.1).

**Table 5.1:** Variation of time and yield in different equiv. brominating agent.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Brominating agent (equiv.)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCN (2 ml)</td>
<td>TsNBr(_2) (0.5)</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>MeCN (2 ml)</td>
<td>TsNBr(_2) (1.0)</td>
<td>55</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>MeCN (2 ml)</td>
<td>TsNBr(_2) (1.5)</td>
<td>40</td>
<td>95</td>
</tr>
</tbody>
</table>

After optimizing the reaction condition, it is found that as the amount of TsNBr\(_2\) increases the rate and yield of the reaction increases. Then, we have extended the process to a variety of aniline, which are summarized in Table 5.2. The reaction took relatively shorter time when we used 1.5 equiv. of TsNBr\(_2\).

In this reaction, we observed that, after addition, the yellow color of solution changes to wine red color. Change of yellow color is indication of the completion of reaction, which was further confirmed by monitoring the reaction by TLC. The products formed in the reaction are confirmed by IR, NMR, and
The yield of the product formed is high. The formation of bromocompounds take 25 – 40 mins.

Table 5.1: Synthesis of bromoaniline of various aniline using TsNBr₂

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time(min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NH₂</td>
<td>Br₂NH₂Br</td>
<td>40</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>NH₂CH₃</td>
<td>Br₂NH₂Br</td>
<td>30</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>NH₂</td>
<td>Br₂NH₂Br</td>
<td>25</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>NH₂NO₂</td>
<td>Br₂NH₂NO₂</td>
<td>35</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>NH₂NO₂</td>
<td>Br₂NH₂NO₂</td>
<td>30</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>NH₂CH₃NO₂</td>
<td>Br₂NH₂NO₂</td>
<td>30</td>
<td>94</td>
</tr>
</tbody>
</table>

From Table 5.2, it is confirmed that in case of 4-bromo aniline the yield of the reaction is high and takes less time to complete the reaction relative to the other substrate.

The IR spectrum of the 2, 4, 6 Tribromoaniline showed peaks at 3401, 3450, 1615, 1376, 704 cm⁻¹ for N-H symmetric stretching, N-H asymmetric
The GC-Mass spectra of the 2, 4, 6, Tribromoaniline is given in (Figure 5.1). The mass spectra appeared prominent peaks at m/z value 329, 250, 170, 65 for the ion fragment (M⁺), [ArBr₂NH₂]⁺, [ArBrNH₂]⁺, and [C₅H₅]⁺ respectively. The ¹H NMR spectrum of the representative tribromoaniline is given below (Figure 5.2). The spectra showed singlet signal at δ = 4.54 ppm for the 2H of NH₂ group. Another singlet signal also observed at δ = 7.5 ppm for the 2H of aromatic ring.

Figure 5.1: GC-Mass spectra of the 2, 4, 6 Tribromoaniline
Figure 5.2: $^1$H NMR spectra of the 2, 4, 6 Tribromoaniline

2, 6 Dibromo, 4 methylaniline appeared signals at 3421, 3470, 1618, 1285, 705 cm$^{-1}$ for the N-H symmetric stretching, N-H asymmetric stretching, N-H deformation, C-N stretching, C-Br stretching band respectively in IR spectroscopy. The (GC-MS) spectra showed signals at m/z value 184, 105, 89, 65 for the [M]$^+$, [ArCH$_3$NH$_2$]$^+$, [ArCH$_3$]$^+$, and [C$_5$H$_5$]$^+$ respectively. The $^1$H NMR spectra (Figure 5.3) gives three singlet peak at $\delta$= 2.2, 4.3, 7.20 ppm for the 3H of CH$_3$, 2H of NH$_2$ groups and for the 2H of aromatic ring respectively.
Figure 5.3: $^1$H NMR spectra of the 2,6 dibromo-4-methylaniline

4, 6 Dibromo-2-nitroaniline showed bands at 3478, 3389, 2924, 2356, 1575, 1456, 1256, 668 cm$^{-1}$ for N-H symmetric stretching, N-H asymmetric stretching, N-H deformation, aromatic C-H stretching, N-O stretching, C-N stretching, and C-Br stretching respectively. The mass spectra appeared predominant peaks at m/z value 294, 136, 121, 89, 73 for the [M]$^+$, [Ar NH$_2$NO$_2$]$^+$, [ArNO$_2$]$^+$, [ArN]$^+$, [Ar]$^+$ respectively in GC-MS spectra.

2, 6-Dibromo- 4-nitro aniline showed bands at 3477, 3385, 2928, 2350, 1577, 1453, 1260, 664 cm$^{-1}$ for N-H symmetric stretching, N-H asymmetric stretching, N-H deformation, aromatic C-H stretching, N-O stretching, C-N stretching, and C-Br stretching respectively. The mass spectra appeared
predominant peaks at m/z value 294, 136, 121, 89, 73 for the [M]+, [ArNH2NO2]+, [ArNO2]+, [ArN]+, [Ar]⁺ respectively in GC-MS spectra.

In IR spectra 6-Bromo 4-nitro-o-toluidine observed bands at 3480, 3381, 1627, 1345, 734, 2979 cm⁻¹ for N-H symmetric stretching, N-H asymmetric stretching, N-H deformation, N-O stretching, C-Br stretching, aromatic C-H stretching, and C-N stretching band. The GC-MS spectra showed signals at m/z value 231, 150, 104, 91, 74 for the ion [M]+, [ArNH2CH₃NO₂]+, [ArNH₂CH₃]+, [ArNH₂]+, and [Ar]⁺ respectively.

5.6 EXPERIMENTAL SECTION

GENERAL PROCEDURE FOR THE BROMINATION OF ANILINE

To a solution of aniline (1.1 mmol) in acetonitrile (2 ml) was added TsNBr₂ (0.5 mmol). The color of TsNBr₂ as well as the aniline changes slowly from light yellow to wine red. After the reaction was complete sodium thiosulfate (200 mg approximately) was added to the reaction mixture with 1 or 2 ml of water and was stirred for 20 min. The reaction mixture was taken up in ethyl acetate, washed with brine, dried (Na₂SO₄) and concentrated. Purification of the crude product by flash chromatography on silica gel (230-400 mesh) with petroleum ether-EtOAc (5 %) as eluent gave the pure product.
**EXPERIMENTAL DATA**

(1) **2,4,6-Tribromoaniline**
Yield: 95 %
IR (KBr, cm$^{-1}$) 3401, 3450, 1615, 1376, 704
Mass (M/Z, %) 329 (100), 250 (35), 170 (40), 65 (8)
$^1$H NMR (MHz) 4.56 (s, 2H), 7.50 (s, 2H)

(2) **2,6-Dibromo, 4 methylaniline**
Yield: 93 %
IR (KBr, cm$^{-1}$) 3421, 3470, 1618, 1285, 705
Mass (M/Z, %) 184 (90), 105 (45), 89 (5), 65 (12)
$^1$H NMR (MHz) 2.2 (s, 3H), 4.3 (s, 2H), 7.20 (s, 2H)

(3) **2,4,6-Tribromoaniline**
Yield: 96 %
IR (KBr, cm$^{-1}$) 3401, 3450, 1615, 1376, 704
Mass (M/Z, %) 329 (100), 250 (35), 170 (40), 65 (8)

(4) **4,6-Dibromo 2-nitroaniline**
Yield: 90 %
IR (KBr, cm$^{-1}$) 3478, 3389, 2924, 2356, 1575, 1456, 1256, 668.
Mass (M/Z, %) 294 (5), 136 (3), 89 (45), 73 (48)
2,6-Dibromo 4-nitroaniline

Yield: 92%

IR (KBr, cm⁻¹) 3477, 3385, 2928, 2350, 1577, 1453, 1260, 664

Mass (M/Z, %) 294 (5), 136 (3), 89 (45), 73 (48)

6-Bromo 4-nitro-o-toluidine

Yield: 94%

IR (KBr, cm⁻¹) 3480, 3381, 1627, 1345, 734, 2979, 1287

Mass (M/Z, %) 231 (5), 150 (70), 104 (79), 91 (8), 74 (15)

5.7. CONCLUSION

\[ N, N\text{-dibromo-}p\text{-toluenesulfonamide} \text{ is found to be a good brominating agent for the bromination of anilines. The procedure is rapid, easy to perform at room temperature, and applicable to different kinds of aromatic amines to give corresponding bromoaniline in excellent yield. 4-Bromo aniline gives more yield and takes less time in comparison with other substrate for completion of the reaction.} \]
5.8. REFERENCE


28) Smith, K.; James, D. M.; Mistry, A. G.; Bye, M. R.; Faulkner, D. J.

*Terahedron* 1992, 36, 7479.