PART B

Formation of C-N bond using $NN$- dibromo-$p$-toluene sulfonamide ($TsNBr_2$)
CHAPTER 6

General Introduction
W-dihalosulfbnamides are important reagents for various organic transformations. The simplicity, efficiency and unique chemical behavior of these reagents\(^1\) increase their synthetic utility for organic chemist. Apparently they exhibit properties to behave as a halogen donor as well as nitrogen donors. Very limited number of such reagents has been reported in literature. Some important reagents of that category include \(N,N\)-dichloro-2-nitrobenzenesulfonamide,\(^2\) \(N,N\)-dichloro-\(p\)-tolunesulfonamide,\(^3,1d,1f,1h\) \(N,N\)-dichlorobenzenesulfonamide,\(^4\) \(N,N\)-dibromobenzene-sulfonamide,\(^5\) etc.

\(N,N\)-dibromo-\(p\)-toluenesulfonamide (TsNBr\(_2\)) is one of such reagents. However the utility of this source is not studied to a reasonable extent. This reagent is very simple and easy to prepare. This reagent acts as an efficient source of bromonium ion (Br\(^+\)) and provides nuclophilic sulfonamide counterpart to form C-N bond. These properties led to the synthesis of aminobromination using the reagent. Apart from this, they can also act as a strong oxidizing agent as well as good source of nitrene. Here in the following survey we are showing different synthetic utility of TsNBr\(_2\) exhibiting all of these properties.

Kharasch and Priestley introduced \(N,N\)-dibromo-\(p\)-toluenesulfonamide as reagent for the synthesis of haloamines.\(^6\) They applied the reagent to activate styrene, anethole and sosafole. With styrene, they successfully synthesized 2-phenyl-2-(\(p\)-toluenesulfonamido)-1-bromoethane (Scheme 6.1)

![Scheme 6.1](image_url)
The same reagent was also used by Paul et al.\(^7\) for the synthesis of 3,5-dihydroxy-1-substituted piperidines from 1,4-pentadiene. They achieved the synthesis via an intermediate methoxy bromide, which was synthesized by the treating the reagent with olefin in methanol. However, the yield of the methoxy bromide was found to be very low.

However in this initial stage of work, the reagent was not studied expeditiously. During 1970, Terauchi and coworkers carried out reaction of TsNBr\(_2\) with 2-methyl-3,4-dihydronaphthalene in a solution dichloromethane at 0 °C to produce aminobromine. However the reaction yield was found to be low (Scheme 6.2).\(^8\)

During that period, Hermann and Klaus\(^9\) had synthesized some cyclic compounds with the adamantane structure by ring closure reactions with \(N,N\)-dibromo-\(p\)-toluenesulfonamide (Scheme 6.3). Similar strategy was applied by Hegedus for the synthesis of some other nitrogen heterocycles.\(^10\)

Later, this reagent was mainly used in the field of analytical chemistry. Nair and Indrasenan\(^11\) had introduced TsNBr\(_2\) as an ideal oxidimetric titrant in acetic acid during
a process for developing new redox titrants in nonaqueous media. Later on its analytical applicability gradually becomes wider.\textsuperscript{12} However the utility of the TsNBr\textsubscript{2} as a reagent for organic transformation was not developed during the early stages. Khazaei \textit{et al.} had shown TsNBr\textsubscript{2} as a catalyst for acylation reaction. They observed that \textit{N}, \textit{N}-dibromo-\textit{p}-toluenesulphonamide efficiently catalyzes acylation of structurally diversified alcohols by the action of acetic anhydride in dichloromethane at room temperature.\textsuperscript{13} They investigated this reaction with different types of alcohols including primary (acyclic, and benzylic), secondary (acyclic, cyclic and benzylic), and sterically hindered tertiary alcohols (Scheme 6.4).

\[
\begin{align*}
R_1 R_2 \text{CHOH}^+ & \overset{\text{TsNBr}_2 (0.05-0.3 \text{ mmol})}{\text{Ac}_2\text{O}} \rightarrow \text{CH}_3\text{COOCHR}_1 R_2 \\
R_1, R_2 & = \text{alkyl, aryl, cyclic}
\end{align*}
\]

Scheme 6.4

Huang \textit{et al.} had used TsNBr\textsubscript{2} as an electrophilic reagent. They presented a reaction pathway of 2,3-allenoates with \textit{N},\textit{N}-dibromo-\textit{p}-tolune sulfonamide (TsNBr\textsubscript{2}) as electrophile in the presence of \(K_2\text{CO}_3\) to produce (1\textit{E},2\textit{E})- 3-bromo-4-oxo-\textit{N}'-tosyl-2-alkenoxylimidic acid ethyl esters. The reaction proceeds in a highly stereoselective fashion (Scheme 6.5).\textsuperscript{14} The reaction was found to be effective at -65 °C in \textit{CH}_2\textit{Cl}_2 as solvent. Mechanistically, the attack of the allenoate with a bromonium ion released from TsNBr\textsubscript{2} to form a cyclic cation which is attacked further by a nucleophile [TsNBr\textsuperscript{-}].

\[
\begin{align*}
R^1 & \text{H} \overset{\text{TsNBr}_2}{+} \text{2.0 eq. } K_2\text{CO}_3 \\
& \text{-65°C, 15min} \rightarrow \text{then rt, 30 min}
\end{align*}
\]

\[
R^1= \text{alkyl, Ph} \\
R^2= \text{H, Bn, Me, n-Bu via}
\]

Scheme 6.5
However the reaction of TsNBr$_2$ of ethyl 2-methyl-4-(naphthalen-1-yl)buta-2,3-dienoate following the same procedure, an interesting and potentially very useful product, 4-bromo-5-ethoxy-3-methyl-5-(naphthalen-1-yl)-1-tosyl-1H-pyrrol-2(5H)-one was obtained in 48% isolated yield (Scheme 6.6) instead of the predicted product.

![Scheme 6.6]

Huang et al. again carried out another electrophilic addition reaction of (Z)-alk-2-en-4-ynoates with TsNBr$_2$ as electrophile (Scheme 6.7). The procedure reported a facile and highly regio and stereoselective synthesis of densely functionalized aziridine derivatives.

![Scheme 6.7]

The optimization of the reaction condition reveals that lower amount of TsNBr$_2$ (below 3 equiv) results lower yield. They also observed functional group tolerability under the reaction condition. They found that the reaction of TsNBr$_2$ and (Z)-allyl 5-phenylpent-2-en-4-ynoate (Scheme 6.8) afford the corresponding aziridine in 53% yield without effecting the allyl group.

![Scheme 6.8]
The mechanistic study shows formation of Br\(^+\) which attack the substrate to form acyclic cation which further react with nucleophilic [TsNBr\(^-\)]. These studies on the TsNBr\(_2\) reagent established that it is a very good source for Br\(^+\) ion and behave as an excellent electrophilic reagent.

Han and coworkers used this reagent for the synthesis of bromoalkylbranched imidazolines by using CuI-PPh\(_3\) as the catalyst and \(N,N\)-dibromo-\(p\)-toluenesulfonamide\(^{16}\) as the nitrogen and halogen sources (Scheme 6.9). A good scope of alkene substrates, including \(\alpha,\beta\)-unsaturated ketones, \(\alpha,\beta\)-unsaturated esters and simple olefins, was achieved for this reaction.

![Scheme 6.9](image)

Sanjun Zhi \textit{et al.} used TsNBr\(_2\) for formation of aminobromine and found to be more efficient if the reaction is carried out in presence of Mn(OAc)\(_2\) with addition of \(p\)-toluene sulphonamide (Scheme 6.10).\(^{17}\) The combination of TsNBr\(_2\) and TsNH\(_2\) was found to be an efficient bromine and nitrogen source for the aminobromination of \(\beta\)-methyl-\(\beta\)-nitrostyrenes with manganese (II) acetate as the catalyst in the presence of 4 Å molecular sieves. The reaction results in vicinal bromoamino nitroalkanes with the opposite regioselectivity comparing with those reported for \(\beta\)-nitro styrene.\(^{18}\) The products were obtained with good yield (40-79\%). For the substrate with para-MeO, a strong electron-donating group, on the aromatic ring, the highest yield was observed (79\%). Nitro substitution on the aromatic ring lowers the yield substantially. All the reactions showed good to excellent stereoselectivities with ratios ranging from 10:1 to 20:1 and all the reactions provide only one regioisomer.

![Scheme 6.10](image)
The mechanistic study of the reaction reveals that the catalyst Mn(OAc)$_2$ activates the N–Br bond of TsNBr$_2$ to generate an intermediate which delivered ‘Br⁺’ to the C–C double bond of β-methyl-β-nitrostyrene to form bromonium intermediate. The positively charged bromonium intermediate is opened by p-toluenesulfonylamine on its α-position which is more positively charged than its β-position, giving the final vicinal bromoamine product.

Our group recently has a couple of reports on TsNBr$_2$ in various organic transformations. During 2006, Phukan et al.\textsuperscript{19} had shown the utility of the reagent for synthesis of bromohydrins and alkoxybromides. They developed a very rapid and efficient method for the synthesis of vicinal bromohydrins and alkoxybromides directly from an olefin without any catalyst. The reaction was performed in CH$_3$CN: water (4:1) or alcohol using $N,N$-dibromo-p-toluenesulfonylamine (TsNBr$_2$) as the brominating agent (Scheme 6.11). Various olefins such as styrenes, cinnamates, acrylates and cyclohexene etc work very well to produce corresponding bromohydrins instantaneously. Excellent yields and regio- and stereoselectivities have been obtained. All products were found to be anti-selective. The same reagent was used to synthesize alkoxy bromides by treating the olefin with anhydrous alcohol. Formation of alkoxybromides takes 30-60 min at room temperature. Interestingly, when the reaction was performed in a mixture of tert-butanol and water, a mixture of tert-butoxy bromide and bromohydrine was obtained in 1:3 ratio.

\[
\begin{align*}
R' & \begin{array}{c}
\rightleftharpoons \\
\text{MeCN : H$_2$O (4:1)} \\
\text{or ROH, rt}
\end{array} \\
& \xrightarrow{\text{TsNBr$_2$}} \\
R'' & \begin{array}{c}
\rightleftharpoons \\
\text{Br}
\end{array}
\end{align*}
\]

\(R' = H, \text{Ar} \quad R'' = H, \text{COOEt, COOMe} \quad X = \text{OH or OR}\)

\(R', R'' = -(\text{CH$_2$})_n\)

\textbf{Scheme 6.11}

As an efficient Br⁺ ion donor, the utility of the TsNBr$_2$ is facing tremendous attention for organic transformation. The high reactivity as well as catalyst free generation for Br⁺ increases its potentiality. The idea with competitive reaction between
nucleophilic counterparts of TsNBr₂ which is a sulfonamide anion with some other external nucleophile in reaction medium provides wider organic transformations. In continuation of the work with TsNBr₂, our laboratory has used the reagent for the synthesis of vicinal bromoazides. In this procedure, vicinal bromoazides were directly prepared from olefin using TsNBr₂ without any catalyst in acetonitrile at room temperature (Scheme 6.12).²⁰ It was found that, the reaction is very fast producing the corresponding bromoazides instantaneously in high yield. This procedure was applicable to various olefins such as cinnamates, chalcone, styrenes, and acrylate to provide the corresponding 1,2-bromoazide in an excellent yield. However the method is not effective for aliphatic substances.

\[
\begin{align*}
R' & \quad \text{TsNBr₂} \\
\text{MeCN, rt} & \\
\rightarrow & \\
R & = \text{H, Aryl} \\
R' & = \text{Aryl, alkyl, COR, COOR}
\end{align*}
\]

Scheme 6.12

Phukan et al. had also carried out another cohalogenation reaction (bromoformyloxlation and bromoacetoxylation) of alkene.²¹ The reaction was carried out by adding TsNBr₂ to a solution of olefin in DMF under nitrogen atmosphere at room temperature (Scheme 6.13). The one step reaction goes very smoothly and instantaneously without any catalyst. The aqueous work up leads to the formation of the bromoformyloxy product. All kinds of olefins such as styrene, cinnamate, acrylate, chalcone, aliphatic olefins produce corresponding product in excellent yield with high regio and stereoselectivity. The idea was then extended for preparing bromoacetoxy product by using CH₃COOH as solvent. Satisfactory results come out with a number of olefins similarly to that for bromoformyloxlation. The reaction is very efficient and completed around 10 min. The high stereoselectivity and regioselectivity increases the utility of the procedure.
TsNBr$_2$ also act as a mild oxidizing agent. In a seminal report of Phukan and his group they had shown the use of $N,N$-dibromo-$p$-toluenesulfonamide (TsNBr$_2$) as a efficient reagent for oxidation of alcohols.$^{22}$ The use of 1 equivalent of TsNBr$_2$ is enough to promote complete oxidation without any catalyst in acetonitrile as the reaction medium. This procedure works well at room temperature and applicable to different kinds of primary and secondary alcohols, such as aromatic, aliphatic, cyclic and benzylic alcohols to give corresponding carbonyl compounds in excellent yield (Scheme 6.14). The remarkable feature of this reagent is that it oxidizes primary alcohols very efficiently in excellent yields besides other secondary and benzylic alcohols, which undergo oxidation within a short time. Primary benzyl alcohol is converted to both aldehyde and acid simultaneously whereas aliphatic primary alcohol gets converted to aldehyde only.

$$\begin{align*} 
\text{OH} & \quad \text{TsNBr}_2 (1 \text{ equiv}) \\
\text{R}_1 \text{R}_2 & \quad \text{MeCN, rt} \\
\rightarrow & \quad \text{R}_1' \text{R}_2'
\end{align*}$$

$R = \text{aryl, alkyl, cycloalkyl}$

$R' = \text{H, alkyl, cycloalkyl}$

**Scheme 6.14**

The same group also developed another oxidative method for the synthesis of epoxide from cinnamic esters without any catalyst.$^{23}$ The reaction was performed in a mixture of acetonitrile and water in 4:1 ratio using TsNBr$_2$ at room temperature followed by the addition of potassium carbonate (Scheme 6.15). The reaction proceeds via the formation of bromohydrin and addition of base generates the epoxide. This one pot procedure can be utilized for stereoselective synthesis of epoxides from cinnamic esters.
in excellent yield in a shorter reaction time with exclusive formation of the trans-isomer. The method was also extended successfully to styrenes.

\[
\begin{align*}
\text{TsNB} &= \text{MeCN : H}_2\text{O (4:1)} \\
&\text{K}_2\text{CO}_3, \text{rt}
\end{align*}
\]

\textbf{Scheme 6.15}

Another oxidative transformation with TsNBBr was obtained for deprotection of oximes to corresponding carbonyl compounds. Deprotection of different oximes to their parent aldehydes and ketones in high yields has been carried out by using \(N,N\)-dibromo-p-toluene sulfonamide.

A major breakthrough comes out during 2011, when Phukan et al. for the first time reported TsNBBr as a potential source of nitrene for aziridination of alkene. They performed aziridination reaction of alkenes by using \(N, N\)-dibromo-p-toluene sulfonamide in presence of a base without any catalyst. The reaction was carried out by treating the olefin with 1.2 equivalent of olefin in presence of 2.5 equivalent of potassium carbonate (Scheme 6.16). The reaction proceeds well at room temperature to afford the corresponding \(N\)-sulfonylated aziridine in a short time. However, cinnamates reacted slowly as compared to styrenes. They established that the reaction proceed via the formation of a nitrene from \(N,N\)-dibromo-p-toluene sulfonamide by debromination in the presence of a base. They extended the procedure to various kinds of olefins such as indene, \(\beta\)-methyl styrene, cyclohexene, 1-octene, ethyl acrylate, cyclohexenone, ethyl cinnamate, etc., which produced the corresponding aziridine in high yields.

\[
\begin{align*}
\text{TsNBBr (1.2 equiv)} &\xrightarrow{\text{K}_2\text{CO}_3 (2.5 equiv)} \\
&\text{EtOAc, rt, 10-240 min}
\end{align*}
\]

\textbf{Scheme 6.16}

From well known carbene generation by \(\alpha\)-dehalogenation of gem-dihalo compounds, it was presumed that, analogous to carbene formation, it should be possible to generate
nitrene from $N,N$-dibromo-$p$-toluenesulfonamide by debromination in the presence of a base.

The versatile nature of the TsNBr$_2$ has opened a new window for organic chemist to carry out various organic transformations. This part of the thesis encloses the efficiency of TsNBr$_2$ towards different organic transformations leading to the formation of carbon-nitrogen bond. In chapter 7 and 8 we have shown C-H bond activation through noncatalytic nitrene transfer process using TsNBr$_2$ as a new source of nitrene. Chapter 7 composed of benzylic C-H bond activation of alkyl aromatics while chapter 8 includes acyl C-H bond activation of aldehydes. In Chapter 9, we have again explored an efficient procedure for the synthesis of methyl carbamates via Hofmann rearrangement in the presence of TsNBr$_2$. 

165
6.2. References


18. (a) Li, G.; Wei, H. X.; Kim, S. H. Org. Lett. 2000, 2, 2249; (b) Raghavan, S.;
Reddy, S. R.; Tony, K. A.; Kumar, C. N.; Nanda, S. Synlett 2001, 851; (c) Qi, X.;


22. Saikia, I.; Chakraborty, P.; Phukan, P. ARKIVOC 2009 (xiii) 281.


Minkin, V. I.; Simkin, Ya. B.; Glukhovtsev, M. N. Pure Appl. Chem. 1992, 64,
265.