CHAPTER – III

Development of novel synthetic methodologies
SECTION-A

Overview on amino phosphonates
Introduction on amino phosphonates

Phosphonates are important and valuable, degradable organophosphorus compounds, containing C-PO(OH)$_2$ or C-PO(OR)$_2$ groups (where R=alkyl, aryl). Primarily these type of compounds are used in pest control instead of chlorinated hydrocarbons which persist in the environment. First time bisphosphonates were synthesized by Von Baeyer and Hofmann in 1897.\(^1\)

The naturally occurring phosphonate 2-aminoethylphosphonic acid\(^2\) (Fig. 1) was first time identified by Horiguchi and Kandatsu in 1959 from plants and many animals. These phosphonates are quite common in many organisms, which are prokaryotes to eubacteria and fungi, insects, mollusks. Phosphorous containing compounds plays essential key role in various living organism such as genetic information carriers, signalling, regulatory and energy transfer.\(^3\) Phosphonates are also used in medicine for treatment of disorders with bone formation and calcium metabolism.

\[
\begin{align*}
\text{O} \quad \text{NH}_2 \\
\text{HO} \quad \text{OH}
\end{align*}
\]

\text{2-aminoethyl phosphonic acid (1)}

Fig. 1

Due to this pivotal role, pharmacologically important phosphorous compound have become therapeutic targets in various modern medicinal techniques, such as antisense\(^4\) and antigene\(^5\) approaches to modulation gene expression, or a gene silencing technique using short interfering RNA (siRNA).\(^6\) Additionally these phosphonates are used as
a chelating agents. An important industrial application of phosphonates is as cooling waters, desalination. In paper and textile industries they serve as peroxide bleach stabilizer by chelating metals that could inactivate the peroxide.

α-Amino phosphonates and its derivatives possess outstanding biological activities such as antifungal, antibacterial, herbicidal activities and also useful as fire retardants for cotton. They are also employed enzyme inhibitors, peptide mimics and utilized as insecticides. (R)-α-Biphenylsulfonylamino 2-methylpropyl phosphonates attained highly potential against several MMPs and are the most effective inhibitors based on phosphonate as zinc binding group.

Phosphonates can be synthesized by using Michaelis-Arbuzov reaction, and α-amino phosphonates were synthesized by condensation of aldehyde, aniline and trialkyl phosphate in presence of catalytic amount Lewis acid. In organic synthesis phosphonates were used in Horner-wadsworth-Emmons reaction.

**Previous reported protocols for synthesis of amino phosphonates:**

1. **Synthesis of α-amino phosphonates from α-amino acids**

   Alicia Boto and co-workers reported synthesis of optically active α-amino phosphonates starting from optically active α-amino acids. The products formed mixture of diastereoisomers with (4:1) ratio in 79% yield (Scheme 1).
Scheme 1

2. O-Silyl triflate-promoted synthesis of α-amino phosphonates starting from chiral aldonitrones\(^{11}\)

Carmela de Rasi and co-workers synthesized α-amino phosphonates starting from chiral aldonitrones through addition of diethyl phosphite to N-benzyl nitrones which was derived from chiral α-alkoxy and N-protected α-amino aldehydes (Scheme 2).

Scheme 2

3. Synthesis of enantiomerically enriched α-amino phosphonic acid derivatives\(^{12}\)

Jacobson et al. reported the enantioselective synthesis of α-amino phosphonic acid derivatives by treatment of N-benzyl imines with alkyl phosphites in the presence of chiral thiourea as a catalyst, the product were formed with highly enantioselective manner (81-99% ee) (Scheme 3).
Scheme 3

4. Asymmetric synthesis of α-amino phosphonates using La-K-Binol Complexes

Sasai and co-workers reported asymmetric synthesis of α-amino phosphonates by the Michael addition of phosphite to imines in the presence of chiral lanthanoid-potassium Binol heterobimetallic complex (Scheme 4). By using above procedure a series of α-amino phosphonates were synthesized from different N-protected aldimes with high enantioselectively.

Scheme 4

5. Synthesis of triazolinyl and aziridinyl phosphonates

Romuald Bartnik and co-workers reported the synthesis of triazolinyl and aziridinyl phosphonates (Scheme 5) from diethyl diazomethyl phosphonates. Initially the reaction of diethyl diazomethyl phosphate with imine in MeOH for 3 days gave triazolinyl phosphonate, cycloaddition of diethyl diazomethyl phosphonates and 1,3,5-triaryl-hexahydro-1,3,5-triazine gives aziridinyl phosphonates.
6. Synthesis of \(\beta\)-amino phosphonates using cyclic sulfamidates\(^{15}\)

B. Das et al. first time reported the synthesis of \(\beta\)-amino phosphonates utilizing cyclic sulfamidates which were prepared from alpha amino acids and beta amino alcohols (Scheme 6).

7. Synthesis of \(\alpha\)-aminophosphonates catalyzed by magnesium perchlorate\(^{16}\)

Chakraborty et al. reported magnesium perchlorate as extremely efficient catalyst for the synthesis of \(\alpha\)-aminophosphonates. A three component protocol of aldehyde or ketone, aniline and dialkyl phosphite or trialkyl phosphite under neat condition at short reaction time gave high yield (Scheme 7).
8. Nano CeO₂ catalyzed synthesis of α-aminophosphonates under ultrasonication

Agawane and co-workers reported one pot multicomponent synthesis of α-aminophosphonates. The condensation of aldehyde, aniline and triethyl phosphite in the presence of nano ceriumoxide as a catalyst under ultra sound irradiation and solvent free condition gave desired product in high yield (Scheme 8).

![Scheme 8](image)

9. Synthesis of α-aminophosphonates using TaCl₅–SiO₂ as a heterogeneous condition

Chandrasekhar et al reported silica supported TiCl₄ as an efficient catalyst for the multicomponent reaction of aldehyde or ketone and aniline, alkyl phosphite to furnish α-aminophosphonates (Scheme 9).

![Scheme 9](image)
10. Synthesis of β-hydroxyphosphonates by iron-catalyzed oxidative addition of phosphonyl radicals to alkenes\textsuperscript{19}

Taniguchi and co-workers reported synthesis of beta hydroxyphosphonates by treatment of α-methylstyrenes and diethyl phosphorohydrazidate in the presence of catalytic amount of Fe(pc) catalyst and air oxygen in THF at reflux condition to give β-hydroxyphosphonates (Scheme 10).

\begin{equation}
\text{R}_1\text{R}_1\text{P}(\text{O})(\text{OEt})_2\text{NHNH}_2 + \text{Fe(Phc)(catalytic)} \rightarrow \text{Scheme 10}
\end{equation}

\text{Fe(Pc)- iron phthalocyanine}

11. Aminobromination of Unsaturated Phosphonates\textsuperscript{20}

Qi et al. reported aminobromination of unsaturated phosphonates gives unexpected syn β-amino-α-bromo phosphonates instead of aminohydroxylation product (Scheme 11).

\begin{equation}
\text{Scheme 11}
\end{equation}

12. \text{InCl}_3 catalyzed one-pot synthesis of new (2-amino-3-cyano-4\textit{H}-chromen-4-yl) phosphonic acid diethyl ester\textsuperscript{21}
Jayashri and co-workers reported first time multicomponent protocol for synthesis of (2-Amino-3-cyano-4H-chromen-4-yl) Phosphonic Acid Diethyl Ester from salicylaldehyde, malononitrile and triethyl phosphite in the presence of catalytic amount Lewis acid (InCl₃) in EtOH at room temperature (Scheme 12).

![Scheme 12](image)

13. One-Pot Synthesis of 2-Amino-4H-chromen-4-yl Phosphonate derivatives using β-CD as a reusable catalyst

Murthy et al reported three component reaction of salicylaldehyde, malononitrile or ethyl cyanoacetate, dialkyl phosphite or trialkyl phosphite in water using β-CD as a reusable catalyst at 60 °C to give 2-amino-4H-chromen-4-yl phosphonate derivatives (Scheme 13).

![Scheme 13](image)

14. Highly effective and enantioselective Phospho-Aldol condensation of diphenylphosphite with N-alkylated isatins catalyzed by quinine
Peng and co-workers first time successfully reported enantioselective phosphor-aldol reaction of diphenyl phosphite to a variety of N-alkylated isatin derivatives using quinine as a catalyst in CH₂Cl₂ at 0 °C furnished optically active 3-hydroxy-phospho substituted oxindoles (Scheme 14).

Scheme 14

15. Asymmetric hydrophosphonylation of protected benzaldimine derivatives

Saito et al reported asymmetric hydrophosphonylation of various benzaldimine derivatives using chiral aluminium salalen complex, the products were formed high enantioselectivity, respectively (Scheme 15).

Scheme 15
Present Work

1. Iodine catalyzed efficient hydrophosphonylation of N-tosyl aldimes

Sulfonamido phosphonates (α-aminophosphonates) and their derivatives possess various biological activities including antifungal, antibacterial\textsuperscript{25} and herbicidal\textsuperscript{7} properties. Additionally, these compounds exhibits fire retardants for cotton.\textsuperscript{7} A few methods have
been reported for synthesis of these compounds at high temperature or by using some catalysts.\textsuperscript{7,26}

Here we report that α–aminophosphonates can efficiently be synthesized by using \(N\)-tosyl aldimines and trimethylsilyl phosphites in the presence of iodine at 0 °C to room temperature (Scheme 16).

\[
\begin{align*}
\text{Ts} \quad \text{H} \quad + \quad \text{R}_1 \text{O} \quad \text{P} \quad \text{OR}_1 & \quad \xrightarrow{\text{I}_2 (20 \text{ mol} \%)} \quad \text{Ts} \quad \text{NH} \quad \text{OR}_1 \\
2 & \quad \xrightarrow{\text{CH}_2\text{Cl}_2, 0 \degree \text{C to rt}} \quad 1.5 - 2.5 \text{ h} & \quad \xrightarrow{86-94\%} \quad 3 \\
\end{align*}
\]

\textbf{Scheme 16}

Initially the reaction of \(N\)-tosyl benzaldimine with various phosphites in the presence of different Lewis acids was thoroughly studied. Alkyl phosphites (e. g. \(\text{P(OMe)}_3\), \(\text{P(OEt)}_3\), \(\text{HP(O)(OEt)}_2\), \(\text{HP(O)(OMe)}_2\)) did not give desired product in the presence of different Lewis acids, only dialkyl trimethylsilyl phosphites furnish the corresponding sulphonamide phosphonates in the presence of iodine at 0 °C in 93% yield (Table 3A. 1). Beside Iodine various other Lewis acids (e. g. \(\text{FeCl}_3\), \(\text{ZnCl}_2\)) were also utilized to carry out the reaction. However, considering reaction time and yield iodine was found to be effective. Using above conditions a series of sulfonamido phosphonates were prepared from different \(N\)-tosyl aldimines (Table 3A. 2). The aromatic aldehydes containing both electron-withdrawing as well as electron-donating groups underwent the conversion smoothly. The aliphatic aldimine derivatives also furnished the α-amino phosphonates conveniently. The reaction was carried out 0 °C.
Conversion was completed within 1.5 h and sulfonamide phosphonates were formed in excellent yields (86 – 94%).

These N-tosyl aldimine intermediates were prepared from benzaldehydes, paratoluene sulfonamide and triethyl amine in the presence of TiCl₄ at 0°C.²⁷ᵃ Using this procedure aromatic aldimines were successfully prepared. Aliphatic N-tosyl aldimines were prepared through α-amido sulfones which were prepared by condensation of aldehyde, para toluene sulfonamide and sodium p-toluenesulfonate.²⁷ᵇ

**Table 3A. 1 Reaction of N-tosyl benzaldimine with various phosphites and phosphates in the presence of different catalysts†**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phosphite</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield (%)ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me₃SiOP(OMe)₂</td>
<td>I₂</td>
<td>1.5</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FeCl₃</td>
<td>2.5</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZrCl₄</td>
<td>3.0</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>Me₃SiOP(OEt)₂</td>
<td>I₂</td>
<td>1.5</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FeCl₃</td>
<td>2.5</td>
<td>85</td>
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<td></td>
<td></td>
<td>ZrCl₄</td>
<td>3.0</td>
<td>80</td>
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<tr>
<td>3</td>
<td>HP(O)(OMe)₂</td>
<td>I₂</td>
<td>2.0</td>
<td>NRᵇ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FeCl₃</td>
<td>3.0</td>
<td>NRᵇ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZrCl₄</td>
<td>3.5</td>
<td>NRᵇ</td>
</tr>
<tr>
<td>4</td>
<td>HP(O)(OEt)₂</td>
<td>I₂</td>
<td>2.0</td>
<td>NRᵇ</td>
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<tr>
<td></td>
<td></td>
<td>FeCl₃</td>
<td>2.5</td>
<td>NRᵇ</td>
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<td></td>
<td></td>
<td>ZrCl₄</td>
<td>3.0</td>
<td>NRᵇ</td>
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<td>I₂</td>
<td>1.5</td>
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<td></td>
<td>FeCl₃</td>
<td>2.5</td>
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<td></td>
<td></td>
<td>ZrCl₄</td>
<td>3.5</td>
<td>NRᵇ</td>
</tr>
<tr>
<td>6</td>
<td>P(OEt)₃</td>
<td>I₂</td>
<td>2.0</td>
<td>NRᵇ</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FeCl₃</td>
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<tr>
<td></td>
<td></td>
<td>ZrCl₄</td>
<td>3.0</td>
<td>NRᵇ</td>
</tr>
</tbody>
</table>

†Reaction conditions: N-tosyl aldimine (1.0 mmol), phosphite/phosphate (1.3 mmol), catalyst (20 mol %), DCM (2 ml), 0°C, N₂ atmosphere.

ᵇIsolated yield. ℃No Reaction.
The N-tosyl group of the products can easily deprotected using different conditions to afford the corresponding α-amino phosphonates which can be used for different pharmacological activities.

The structure of the products 4 (Table 3A. 2) were settled from their spectral [IR, 1H NMR, 13C NMR and ESIMS] data. For example, in the IR spectrum of 4a (Table 3A. 2, Fig. 3A. 1), presence of strong absorption band at 3134 cm⁻¹ indicated -NHTs functional group. In 1H NMR spectrum (Fig. 3A. 2) of product characteristic –CH proton resonated at δ 4.84 (1H, dd, J = 24.0, 10.0 Hz) indicating –CH proton coupling with phosphorous nuclei. In 13C NMR spectrum (Fig. 3A. 3) of 4a, the chemical shift value at δ 55.2 (d, J = 156.2 Hz), 54.4 (d, J = 6.5 Hz), 54.1 (d, J = 6.0 Hz) indicated phosphorous attached carbon and oxygenated carbons. The HRMS spectrum of compound 4a showed m/z value at 370.0874 [M+H]⁺ (Fig. 3A. 4). All these spectral data conformed the structure of product.

In the in IR spectrum (Table 3A. 2, Fig. 3A. 13) of 4e, presence of strong absorption band at 3133 cm⁻¹ indicated amine functional group. 1H NMR spectrum (Fig. 3A. 14) of product 4e showed signal at δ 5.10 (1H, dd, J = 24.0, 10.0 Hz) due to –CH functional group. In 13C NMR spectrum (Fig. 3A. 15) of 4e, the carbon resonated at δ 54.2 (d, J = 7.2 Hz), 53.3 (d, J = 6.2 Hz), 52.4 (d, J = 150.0 Hz) indicating phosphorous attached carbon and oxygenated carbons. In HRMS spectrum (Fig. 3A. 16) of 4e, showed m/z value at 415.0729 [M+H]⁺ supporting the structure.
Similarly, the $^1$H NMR spectrum of product 4n (Table 3A. 2, Fig. 3A. 24) showed the characteristic signal at $\delta 6.09$ (1H, dd, $J = 10.0$, 3.0 Hz) indicating the presence of –CH proton attached to phosphorous. Its IR spectrum (Fig. 3A. 23) showed broad band at 3110 cm$^{-1}$ indicating the presence of –NHTs functional group. It was also supported by the HRMS which showed signal at $m/z$ 358.0854 [M+Na]$^+$ (Fig. 3A. 26).

Table 3A. 2 Synthesis of α-aminophosphonate by the reaction of various N-tosyl aldimines and dialkyl trimethyl phosphites in the presence of iodine

<table>
<thead>
<tr>
<th>entry</th>
<th>Substrate (2)</th>
<th>Phosphite (3)</th>
<th>Product (4)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>( \text{Ts}^-\text{N}^-\text{H} )</td>
<td>MeO(\text{P}^-\text{O}^-\text{Me} )</td>
<td>MeO(\text{P}^-\text{O}^-\text{Me} )</td>
<td>1.5</td>
<td>93</td>
</tr>
<tr>
<td>b</td>
<td>( \text{Ts}^-\text{N}^-\text{H} )</td>
<td>[Cl(\text{P}^-\text{O}^-\text{Me} )</td>
<td>[Cl(\text{P}^-\text{O}^-\text{Me} )</td>
<td>1.5</td>
<td>90</td>
</tr>
<tr>
<td>c</td>
<td>( \text{Ts}^-\text{N}^-\text{H} )</td>
<td>[Cl(\text{P}^-\text{O}^-\text{Me} )</td>
<td>[Cl(\text{P}^-\text{O}^-\text{Me} )</td>
<td>1.5</td>
<td>92</td>
</tr>
<tr>
<td>d</td>
<td>( \text{Ts}^-\text{N}^-\text{H} )</td>
<td>[Cl(\text{P}^-\text{O}^-\text{Me} )</td>
<td>[Cl(\text{P}^-\text{O}^-\text{Me} )</td>
<td>1.75</td>
<td>89</td>
</tr>
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<td></td>
<td>Structure 1</td>
<td>Structure 2</td>
<td>Value 1</td>
<td>Value 2</td>
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<td>e</td>
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<td>91</td>
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<td>90</td>
<td></td>
</tr>
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</table>
In conclusion, we have developed a facile method for the synthesis of α-amino phosphonates from N-tosyl aldimines and dialkyl trimethyl silyl phosphites in the presence of iodine as a catalyst. The simple experimental procedure, mild reaction conditions, application of an easily available, inexpensive catalyst, impressive yields and short reaction times are the notable advantages of the method.
2. Simple, efficient and catalyst-free synthesis of 2-amino-4H-chromen-4-yl phosphonates in polyethylene glycol

2-Aminochromenyl phosphonates are outstanding pharmacologic as well as pesticidal agents including enzyme inhibitors and peptide mimetics. A few reports have been developed for synthesis of these compounds by multicomponent protocol using InCl$_3$ and β-CD as a catalyst. However, both of these two methods involved with the synthesis of phosphonic acid diethyl esters and one of the methods reported only the synthesis of 2-amino-3-cyano-4H-chromen-4-yl phosphonates.

Here we have observed that the multicomponent reaction of salicylaldehydes, malononitrile or ethyl cyanoacetate and trialkyl phosphites in polyethylene glycol (PEG) under catalyst free condition at 80 °C gives the corresponding 2-amino-4H-chromen-4-yl phosphonate derivatives (Scheme 16).
Initially the reaction of salicylaldehyde, malononitrile and various phosphites in the presence of polyethylene glycol was thoroughly studied (Table 3A. 3). Considering the reaction times and the yields of the prepared 2-amino-4\(H\)-chromen-4-yl phosphonates \(8a\), \((R = H, R^1 = \text{CN}, R^2 = \text{Me or Et})\), it was realized that the activity of phosphites was comparable, when the reaction was carried out at 80 °C (Table 3A. 3). On the other hand, when the reaction was carried out at room temperature no product at all could be obtained. Finally, both the phosphites\(\text{P(OMe)}_3\) and \(\text{P(OEt)}_3\) were used in polyethylene glycol at 80 °C to prepare a series of 2-amino-4\(H\)-chromen-4-yl phosphonate derivatives (Table 3A. 4).

Table 3A. 3. Reaction of Salicylaldehyde and Malononitrile with Various Phosphites by Using PEG at 80 °C

<table>
<thead>
<tr>
<th>entry</th>
<th>salicylaldehyde</th>
<th>malononitrile</th>
<th>product((8))</th>
<th>alkyl phosphite</th>
<th>time</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
<td></td>
<td>((5))</td>
<td>((6))</td>
<td>((7))</td>
<td>((7))</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 1     | \[
\begin{array}{c}
\text{H} \\
\text{O} \\
\text{CN} \\
\text{CN}
\end{array}
\] | \[
\begin{array}{c}
\text{CN} \\
\text{CN} \\
\text{CN} \\
\text{CN}
\end{array}
\] | \[
\begin{array}{c}
\text{R=Me or Et}
\end{array}
\] | \[
\begin{array}{c}
\text{P(OMe)}_3 \\
\text{P(OEt)}_3 \\
\text{Me}_2\text{SiOP(OMe)}_2 \\
\text{HP(O)(OMe)}_2 \\
\text{HP(O)(OEt)}_2 \\
\text{P(OMe)}_3^c
\end{array}
\] | 7 | 92     |
|       |                 |               |                | \(\text{P(OMe)}_3\) | 7    | 91     |
|       |                 |               |                | \(\text{P(OEt)}_3\) | 7    | 91     |
|       |                 |               |                | \(\text{Me}_2\text{SiOP(OMe)}_2\) | 7 | 86     |
|       |                 |               |                | \(\text{HP(O)(OMe)}_2\) | 8 | 84     |
|       |                 |               |                | \(\text{HP(O)(OEt)}_2\) | 8 | NR<sup>d</sup> |
|       |                 |               |                | \(\text{P(OMe)}_3^c\) | 24   | NR<sup>d</sup> |

<sup>a</sup> Reaction conditions: salicylaldehyde \((5)\) (1.0 mmol), malononitrile \((6)\) (1.1 mmol), alkyl phosphite \((7)\) (1.1 mmol), PEG-400 (2 g).
<sup>b</sup> Yield of isolated phosphonates.
<sup>c</sup> Reaction carried out at room temperature.
<sup>d</sup> No reaction.
The phosphonates 8 were efficiently synthesized from various salicylaldehydes. 3-Hydroxy-3-naphthaldehyde also underwent the conversion smoothly (Table 3A. 4, entry 8j). Both malononitrile and ethyl cyanoacetate were applied to prepare the products. The conversion was complete within 7 - 9 h and the products were formed in high yields (81-92 %). No additional solvent or catalyst was required.

The structures of the products were established from their spectral (IR, ¹H NMR, ¹³C NMR and MS) spectra and analytical data. The ¹H NMR spectrum (Table 3A. 4, Fig 3A. 27) of 8a, the chemical shift value at δ 5.41(2H, s, br.) indicated –NH₂ group and 3.89 (1H, d, J = 18.0 Hz) indicated -CH proton couple with phosphorous nuclei. In ¹³C NMR spectrum of 8a, phosphorous attached carbon signal resonated at δ 34.6 (d, J = 145.0 Hz). The mass spectrum showed the signal at m/z 309 [M+H]⁺.

Similarly, the ¹H NMR spectrum (Table 3A. 4, Fig 3A. 33) of product 8j, showed the resonated signal at δ 4.47-3.98 (2H, s, brs) indicating –NH₂ group and 4.58 (1H, d, J = 18.0 Hz) indicating phosphorous attached –CH proton. It was also supported by the ESIMS spectrum which give signal at m/z 331 [M+H]⁺ (Fig 3A. 34).

Polyethylene glycol (PEG-400) is an eco-friendly, biologically acceptable, and inexpensive water soluble compound. It is thermally stable, recyclable and non-toxic polymer, its applications as a reaction medium has not yet been fully explored. In the present conversion it has successfully been utilized for the preparation of 2-amino-4H-
chromen-4-yl phosphonate derivatives. The role of PEG is possibly to activate the carbonyl group of salicylaldehydes by H-bonding and thus facilitating the nucleophilic attack by the malononitrile or ethyl cyanoacetate to form the products. The PEG was recovered from the reaction mixture and was recycled three times without loss of activity.

**Table 3A. 4. Synthesis of 2-Amino-4H-chromen-4-yl Phosphonates in Polyethylene glycol at 80 °C**

<table>
<thead>
<tr>
<th>entry</th>
<th>salicylaldehyde (5)</th>
<th>malononitrile (or)ethyl cyanoacetate (6)</th>
<th>alkyl phosphite (7)</th>
<th>product (8)</th>
<th>time (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>O</td>
<td>C</td>
<td>P(OEt)₃</td>
<td>OEtOPOEtCN</td>
<td>7</td>
<td>91</td>
</tr>
<tr>
<td>b</td>
<td>O</td>
<td>C</td>
<td>P(OEt)₃</td>
<td>OEtOPOEtCN</td>
<td>8</td>
<td>89</td>
</tr>
<tr>
<td>c</td>
<td>O</td>
<td>C</td>
<td>P(OEt)₃</td>
<td>OEtOPOEtCN</td>
<td>8</td>
<td>90</td>
</tr>
<tr>
<td>d</td>
<td>O</td>
<td>C</td>
<td>P(OEt)₃</td>
<td>OEtOPOEtCN</td>
<td>8</td>
<td>87</td>
</tr>
<tr>
<td>e</td>
<td>O</td>
<td>C</td>
<td>P(OEt)₃</td>
<td>OEtOPOEtCN</td>
<td>8</td>
<td>89</td>
</tr>
</tbody>
</table>
a) Reaction conditions: salicylaldehyde (1) (1.0 mmol), malononitrile (or) ethyl cyanoacetate (2) (1.1 mmol), triethyl phosphite (or) trimethyl phosphite (3) (1.1 mmol), PEG-400 (2 g). b) isolated Yield.
In conclusion, we have developed a convenient and facile method for the preparation of 2-amino-4H-chromen-4-yl phosphonates from salicylaldehydes, malononitrile or ethyl cyanoacetate and alkyl phosphites in polyethylene glycol (PEG). The application of environment-benign reaction medium, catalyst-free condition, recyclization of the medium, high yield and operation simplicity are the notable advantages of the method. To our knowledge, this is the first protocol of the one-pot synthesis of 2-amino-4H-chromen-4-yl phosphonic acid dimethyl esters.
**EXPERIMENTAL**

**General experimental procedure for synthesis of N-tosyl α-aminophosphonates:**

To a stirred solution of tosylimine (1mmol) in CH₂Cl₂ (2mL) under nitrogen I₂ (20 mol %) was added. The mixture was kept at 0 °C, Dialkyl trimethyl silyl phosphite (1.3 mmol) was added and the mixture was stirred for 1.5 h. The reaction was monitored by TLC. After completion the reaction was quenched with hypo solution (10 mL) and the mixture was extracted with CH₂Cl₂ (25 mL). The extract was washed with water, dried over Na₂SO₄ and concentrated under reduced pressure. The residue was subjected to column chromatography (silica gel, hexane-EtOAc) to furnish pure sulfonamido phosphonate.

The spectral (IR, ¹H and ¹³C NMR, and HRMS) data of the representative products are given below.

**Entry-4a (Table 3A. 2)**

![Structure of Entry-4a](image)

**White solid, mp 167-169°C**

**Molecular formula** : \( \text{C}_{16}\text{H}_{20}\text{NO}_{5}\text{PS} \)

**IR Spectrum** : \( \nu_{\text{max}} \) 3134, 1598, 1456, 1332, 1241, 1165 cm⁻¹  

(Fig. 3A. 1).
\textbf{\textsuperscript{1}H-NMR spectrum} : (300 MHz, CDCl$_3$):

\[ \delta 7.46 \text{ (2H, d, } J = 8.0 \text{ Hz)}, 7.29-7.20 \text{ (3H, m),} \]
\[ 7.16-7.05 \text{ (3H, m), 6.97 \text{ (2H, d, } J = 8.0 \text{ Hz),} \]
\[ 4.84 \text{ (1H, dd, } J = 24.0, 10.0 \text{ Hz), 3.89 \text{ (3H, d, } J = 10.0 \text{ Hz),} \]
\[ 3.41 \text{ (3H, d, } J = 10.0 \text{ Hz), 2.24 \text{ (3H, s) (Fig. 3A. 2).} \]

\textbf{\textsuperscript{13}C-NMR spectrum} : (75 MHz, CDCl$_3$)

\[ \delta 142.8, 138.0, 133.4, 129.0, 128.3, 128.0, \]
\[ 127.1, 55.2 \text{ (d, } J=156.2 \text{ Hz), 54.4 \text{ (d, } J=6.5 \text{ Hz),} \]
\[ 54.1 \text{ (d, } J=6.0 \text{ Hz), 21.2 (Fig. 3A. 3).} \]

\textbf{HRMS-spectrum} : 370.0874 (Calcd for C$_{16}$H$_{19}$ClNO$_5$PS: m/z 370.0873)

(Fig. 3A. 4).

\textbf{Entry-4b (Table 3A. 2)}

\begin{center}
\includegraphics[width=0.2\textwidth]{figure}
\end{center}

White solid, mp 145-147°C

\textbf{Molecular formula} : C$_{16}$H$_{19}$ClNO$_5$PS

\textbf{IR Spectrum} : \( \nu_{\text{max}} \) 3125, 1458, 1336, 1238, 1162 cm$^{-1}$ (Fig. 3A. 5).
**1H-NMR spectrum**: (300 MHz, CDCl₃):

δ 7.49 (2H, d, J = 8.0 Hz), 7.18-7.06 (4H, m), 7.02 (2H, d, J = 8.0 Hz), 6.90 (1H, dd, J = 10.0, 4.0 Hz), 4.80 (1H, dd, J = 24.0, 10.0 Hz), 3.92 (3H, d, J = 10.0 Hz), 3.49 (3H, d, J = 10.0 Hz), 2.31 (3H, s) (Fig. 3A. 6).

**13C-NMR spectrum**: (75 MHz, CDCl₃)

δ 143.2, 137.8, 135.1, 134.2, 129.6, 129.2, 128.0, 127.1, 126.5, 55.1 (d, J = 6.7 Hz), 54.5 (d, J = 150.2 Hz), 54.2 (d, J = 6.7 Hz), 21.2 (Fig. 3A. 7).

**HRMS-spectrum**: 426.0325 (Calcd for C₁₆H₁₉ClNO₅PSNa: m/z 426.0307) (Fig. 3A. 8).

**Entry-4d (Table 3A. 2)**

![Chemical structure](image)

White solid, mp 164-166°C

**Molecular formula**: C₁₆H₁₈ClFNO₅PS

**IR Spectrum**: νₘₐₓ 3126, 1600, 1502, 1338, 1238, 1165 cm⁻¹ (Fig. 3A. 9).
**1H-NMR spectrum** : (300 MHz, CDCl₃):

δ 7.89 (1H, br dd, J = 8.0, 2.0 Hz), 7.48 (2H, br d, J = 8.0 Hz), 7.27 (1H, d, J = 8.0 Hz), 7.11 (1H, m), 7.01 (2H, d, J = 8.0Hz), 6.87 (1H,dd, J = 10.0, 8.0 Hz), 4.81 (1H, dd, J = 24.0, 10.0 Hz), 4.01 (3H, d, J = 10.0 Hz), 3.52 (3H, d, J = 10.0 Hz), 2.29 (3H, s) (Fig. 3A. 10).

**13C-NMR spectrum** : (75 MHz, CDCl₃)

δ 155.9, 143.2, 138.0, 130.9, 130.2 (d, J = 8.0 Hz), 129.0, 128.1 (d, J = 8.0 Hz), 126.9, 121.1 (d, J = 15.0 Hz), 116.2 (d, J = 15.0 Hz), 55.3 (d, J = 6.0 Hz), 54.2 (d, J = 150.0 Hz), 54.1 (d, J = 6.0 Hz), 21.2 (Fig. 3A. 11).

**HRMS-spectrum** : 422.0398 (Calcd for C₁₆H₁₉ClFNO₅PS: m/z 422.0389) (Fig. 3A. 12).

**Entry-4e (Table 3A. 2)**

![Molecular structure](image)

White solid, mp 226-228 °C

**Molecular formula** : C₁₆H₁₈ClFNO₅PS

**IR Spectrum** : ν max 3141, 2860, 1511, 1455, 1334, 1240 cm⁻¹ (Fig. 3A. 13).
**H-NMR spectrum** : (300 MHz, CDCl$_3$):

\[ \delta 9.01 (1H, dd, J = 10.0, 3.0 \text{ Hz}), 7.95 (2H, d, J = 8.0 \text{ Hz}), 7.51 (2H, d, J = 8.0 \text{ Hz}), 7.46 (2H, d, J = 8.0 \text{ Hz}), 7.08 (2H, d, J = 8.0 \text{ Hz}), 5.10 (1H, dd, J = 24.0, 10.0 \text{ Hz}), 3.70 (3H, d, J = 10.0 \text{ Hz}), 3.49 (3H, d, J = 10.0 \text{ Hz}), 2.19 (3H, s) \]

(Fig. 3A. 14).

**C-NMR spectrum** : (75 MHz, CDCl$_3$)

\[ \delta 146.6, 142.7, 142.2, 138.0, 129.6, 129.0, 126.8, 122.9, 54.2 \text{ (d, } J=7.2 \text{ Hz)}, 53.3 \text{ (d, } J=6.2 \text{ Hz}), 52.4 \text{ (d, } J=150.0 \text{ Hz}), 20.4 \]

(Fig. 3A. 15).

**HRMS-spectrum** : 415.0729 \((\text{Calcd for } C_{16}H_{20}N_2O_7PS: m/z 415.0723)\) (Fig. 3A. 16).

**Entry-4j (Table 3A. 2)**

![Chemical structure](image)

White solid, mp 150-152°C

**Molecular formula** : C$_{14}$H$_{18}$NO$_5$PS$_2$

**IR Spectrum** : \(\nu_{\text{max}}\) 3131, 1465, 1330, 1241, 1161 cm$^{-1}$.

**H-NMR spectrum** : (300 MHz, CDCl$_3$):

\[ \delta 7.58 (2H, d, J = 8.0 \text{ Hz}), 7.20-6.96 (5H, m), 6.75 (1H, m), 5.10 (1H, dd, J = 24.0, 10.0 \text{ Hz}), \]
3.89 (3H, d, J = 10.0 Hz), 3.51 (3H, d, J = 10.0 Hz), 2.32 (3H, s) (Fig. 3A. 17).

\[ ^{13}\text{C-NMR spectrum} : \quad (75 \text{ MHz, CDCl}_3) \]
\[ \delta \quad 143.1, \quad 138.4, \quad 135.5, \quad 129.2, \quad 127.7, \quad 126.9, \]
\[ 126.7, \quad 126.1, \quad 54.8 \quad (d, \quad J = 6.2 \text{ Hz}), \quad 54.1 \quad (d, \quad J = \]
\[ 6.0 \text{ Hz}), \quad 50.2 \quad (d, \quad J = 156.2 \text{ Hz}), \quad 21.2 \quad \text{(Fig. 3A. 18)}. \]

\[ ^{13}\text{C-NMR spectrum} : \quad (75 \text{ MHz, CDCl}_3) \]
\[ \delta \quad 143.1, \quad 138.4, \quad 135.5, \quad 129.2, \quad 127.7, \quad 126.9, \]
\[ 126.7, \quad 126.1, \quad 54.8 \quad (d, \quad J = 6.2 \text{ Hz}), \quad 54.1 \quad (d, \quad J = \]
\[ 6.0 \text{ Hz}), \quad 50.2 \quad (d, \quad J = 156.2 \text{ Hz}), \quad 21.2 \quad \text{(Fig. 3A. 18)}. \]

\[ \text{HRMS-spectrum} : \quad 398.0267 \quad (\text{Calcd for } \text{C}_{14}\text{H}_{18}\text{NO}_5\text{PS}_2\text{Na}: \quad m/z \]
\[ 398.0256). \]

Entry-4k (Table 3A. 2)

White solid, mp 124-126°C

Molecular formula : C_{18}H_{24}NO_{5}PS

IR Spectrum : \( \nu_{\text{max}} \) 3109, 1460, 1336, 1239, 1165 cm\(^{-1}\) (Fig. 3A. 19).

\[ ^{1}\text{H-NMR spectrum} : \quad (300 \text{ MHz, CDCl}_3): \]
\[ \delta \quad 7.99 \quad (1H, \quad m), \quad 7.43 \quad (2H, \quad d, \quad J = 8.0 \text{ Hz}), \quad 7.28-
\[ 7.17 \quad (2H, \quad m), \quad 7.12-6.93 \quad (3H, \quad m), \quad 6.85 \quad (2H, \quad d, \quad J \]
\[ = \quad 8.0 \text{ Hz}), \quad 4.79 \quad (1H, \quad dd, \quad J = \quad 24.0, \quad 10.0 \text{ Hz}), \]
\[ 4.42-4.28 \quad (2H, \quad m), \quad 3.88 \quad (1H, \quad m), \quad 3.60 \quad (1H, \quad m), \]
\[ 2.21 \quad (3H, \quad s), \quad 1.42 \quad (3H, \quad t, \quad J = \quad 7.0 \text{ Hz}), \quad 1.02 \quad (3H,
$^{13}$C-NMR spectrum : (75 MHz, CDCl$_3$)

$\delta$ 143.2, 138.4, 134.5, 129.1, 128.7, 128.0, 126.8, 64.6 (d, $J = 6.0$ Hz), 64.4 (d, $J = 6.2$ Hz), 54.9 (d, $J = 151.2$ Hz), 20.4, 15.3 (d, $J = 6.0$ Hz), 15.1 (d, $J = 6.2$ Hz) (Fig. 3A. 21).

HRMS-spectrum : 420.1022 (Calcd for C$_{18}$H$_{24}$NO$_5$PSNa: $m/z$ 420.1010) (Fig. 3A. 22).

Entry-4n (Table 3A. 2)

![Structure](image)

White solid, mp 116-118°C

Molecular formula : C$_{13}$H$_{22}$NO$_5$PS

IR Spectrum : $\nu_{max}$ 3110, 1599, 1471, 1330, 1128 cm$^{-1}$ (Fig. 3A. 23).

$^1$H-NMR spectrum : (300 MHz, CDCl$_3$):

$\delta$ 7.79 (2H, d, $J = 8.0$ Hz), 7.30 (2H, d, $J = 8.0$ Hz), 6.09 (1H, dd, $J = 10.0$, 3.0 Hz), 3.72 (1H, m), 3.68 (6H, d, $J = 10.0$ Hz), 2.42 (3H, s), 1.67 (1H, m), 1.52 (1H, m), 1.42-1.28 (2H, m), 0.79 (3H, t, $J = 7.0$ Hz) (Fig. 3A. 24).
**13C-NMR spectrum**: (75 MHz, CDCl₃)

δ 143.1, 138.6, 129.2, 127.1, 53.9 (d, J = 6.2 Hz), 53.0 (d, J = 6.2 Hz), 49.9 (d, J = 155.5 Hz), 32.2, 21.1, 18.2 (d, J = 6.5 Hz), 13.4 (Fig. 3A. 25).

**HRMS-spectrum**: 358.0854 (Calcd for C_{13}H_{22}NO_{5}PSNa: m/z 358.0854) (Fig. 3A. 26).

**General experimental procedure for the synthesis of 2-amino-4H-chromen-4-yl phosphonate derivatives**:

To a mixture of salicylaldehyde (1.0 mmol), malononitrile or ethyl cyanoacetate (1.1 mmol), alkyl phosphite (1.1 mmol) and PEG-400 (2 g) was added. The mixture was heated on oil bath at 80°C and the reaction was monitored by TLC. After completion, the reaction mixture was poured onto water (10 mL) and was extracted with AcOEt (30 mL). The extract was concentrated under reduced pressure. The crude mass was subjected to column chromatography (silica, hexane-AcOEt) to obtain the pure phosphonates. The aqueous portion was filtered and the filtrate was lyophilized to recover the PEG which was subsequently reused three times for the same reaction without affecting the yields of the products.

The spectral \(^1\text{H}\) and \(^{13}\text{C}\) NMR, and Ms and analytical data of the representative products are given below.

**Entry-8a (Table 2A. 4)**
Molecular formula : \( \text{C}_{14}\text{H}_{17}\text{N}_{2}\text{O}_{4}\text{P} \)

IR Spectrum : \( \nu_{\text{max}} \) 3319, 3170, 2190, 1647, 1406, 1232, 1023 cm\(^{-1}\).

\(^1\text{H}-\text{NMR spectrum} \) : (300 MHz, CDCl\(_3\)):

\( \delta \) 7.32–7.21 (m, 2H), 7.11 (1H, t, \( J = 8.0 \) Hz), 6.94 (1H, d, \( J = 8.1 \) Hz), 5.41 (2H, brs), 4.15–3.15 (4H, m), 3.89 (1H, d, \( J = 17.9 \) Hz), 1.34 (3H, t, \( J = 7.0 \) Hz), 1.22 (3H, t, \( J = 7.0 \) Hz) (Fig. 3A. 27).

\(^{13}\text{C}-\text{NMR spectrum} \) : (75 MHz, CDCl\(_3\))

\( \delta \) 162.1, 149.8, 129.3, 122.8, 124.7, 119.5, 116.4, 116.3, 63.1, 62.8, 50.5, 36.2, 34.3, 16.3, 16.2.

ESIMS-spectrum : \( m/z \) 309 \([\text{M+H}]^+\).

Entry-8b (Table 2A. 4)
Molecular formula : $\text{C}_{14}\text{H}_{15}\text{Cl}_{2}\text{N}_{2}\text{O}_{4}\text{P}$

IR Spectrum : $\nu_{\text{max}}$ 3357, 3162, 2195, 1661, 1413, 1238, 1045 cm$^{-1}$.

$^1\text{H}-\text{NMR}$ spectrum : (300 MHz, CDCl$_3$):

δ 7.32 (1H, t, $J = 2.2$ Hz), 7.20 (1H, t, $J = 2.2$ Hz), 5.35 (2H, br s), 4.19–4.03 (4H, m), 3.83 (1H, d, $J = 18.8$ Hz), 1.39–1.25 (6H, m) (Fig. 3A. 28).

$^{13}\text{C}-\text{NMR}$ spectrum : (75 MHz, CDCl$_3$)


ESIMS-spectrum : $m/z$ 378 [M+H]$^+$. 

Entry-8c (Table 2A. 4)

Molecular formula : $\text{C}_{16}\text{H}_{20}\text{Cl}_{2}\text{N}_{2}\text{O}_{6}\text{P}$

IR Spectrum : $\nu_{\text{max}}$ 3217, 2987, 1740, 1464, 1233, 1035 cm$^{-1}$. 
**$^1$H-NMR spectrum**: (300 MHz, CDCl$_3$):

$\delta$ 7.29–7.25 (1H, m), 7.18 (1H, t, $J = 2.2$ Hz), 5.46 (2H, br s), 4.23–4.01 (6H, m), 3.87 (1H, d, $J = 19.0$ Hz), 1.38–1.15 (9H, m).

**$^{13}$C-NMR spectrum**: (75 MHz, CDCl$_3$)

$\delta$ 165.4, 160.2, 149.5, 128.7, 126.4, 126.0, 124.6, 122.9, 63.7, 63.5, 57.8, 37.7, 36.1, 16.1, 16.0.

**ESIMS-spectrum**: $m/z$ 425 [M+H]$^+$.

**Entry-8g (Table 2A. 4)**

![Molecular Structure](image)

**Molecular formula**: $C_{15}H_{19}Cl_2N_2O_5P$

**IR Spectrum**: $\nu_{\text{max}}$ 3300, 3171, 2189, 1640, 1404, 1215, 1018 cm$^{-1}$.

**$^1$H-NMR spectrum**: (300 MHz, CDCl$_3$):

$\delta$ 7.05 (1H, t, $J = 7.8$ Hz), 6.88 (2H, d, $J = 6.8$ Hz), 6.50 (2H, br s), 4.07 (2H, t, $J = 6.8$ Hz), 4.05–3.95 (2H, m), 3.89 (1H, d, $J = 19.5$ Hz), 3.84 (3H, s), 1.32–1.15 (6H, m) (**Fig. 3A. 29**).

**$^{13}$C-NMR spectrum**: (75 MHz, CDCl$_3$)
δ 161.4, 146.0, 138.1, 122.7, 119.3, 118.8, 116.7, 110.0, 61.2, 61.0, 54.3, 46.7, 35.0, 33.1, 14.9, 14.8.

ESIMS-spectrum : \( m/z \ 339 \ [M+H]^+ \).

Entry-8i (Table 2A. 4)

Molecular formula : \( C_{12}H_{13}N_2O_4P \)

IR Spectrum : \( \nu_{\text{max}} \) 3308, 3181, 2146, 1633, 1459, 1197 cm\(^{-1} \).

\(^1\)H-NMR spectrum : (300 MHz, CDCl\(_3\)):

δ 7.38–7.22 (2H, m), 7.16(1H, d, \( J = 8.0 \) Hz), 6.99 (1H, d, \( J = 8.0 \) Hz), 5.31 (2H, br s), 3.93(1H, d, \( J = 18.0 \) Hz), 3.76 (3H, d, \( J = 10.0 \) Hz), 3.66 (3H, d, \( J = 10.0 \) Hz) \( \text{Fig. 3A. 30} \).

\(^{13}\)C-NMR spectrum : (75 MHz, CDCl\(_3\))

δ 162.1, 149.8, 129.4, 129.1, 124.9, 119.5, 116.5, 53.7 (d, \( J = 6.5 \) Hz), 53.4 (d, \( J = 6.5 \) Hz), 49.4, 35.9 (d, \( J = 144.0 \) Hz) \( \text{Fig. 3A. 31} \).

ESIMS-spectrum : \( m/z \ 281 \ [M+H]^+ \) \( \text{Fig. 3A. 32} \).

Entry-8j (Table 2A. 4)
**Molecular formula**: $C_{16}H_{15}N_2O_4P$

**IR Spectrum**: $\nu_{\text{max}}$ 3279, 3166, 2137, 1631, 1424, 1219 cm$^{-1}$.

**$^1$H-NMR spectrum**: (300 MHz, CDCl$_3$):

\[
\begin{align*}
\delta & \quad 8.05 \ (1H, d, J = 8.0 \text{ Hz}), \\
& \quad 7.82 \ (1H, t, J = 8.0 \text{ Hz}), \\
& \quad 7.79 \ (1H, d, J = 8.0 \text{ Hz}), \\
& \quad 7.61 (1H, t, J = 8.0 \text{ Hz}), \\
& \quad 7.50 \ (1H, t, J = 8.0 \text{ Hz}), \\
& \quad 7.21 \ (1H, d, J = 8.0 \text{ Hz}), \\
& \quad 4.58 \ (1H, d, J = 18.0 \text{ Hz}), \\
& \quad 4.47-3.98 \ (2H, \text{ brs}), \\
& \quad 3.71 \ (3H, d, J = 10.0 \text{ Hz}), \\
& \quad 3.55 \ (3H, d, J = 10.0 \text{ Hz}) \quad \text{(Fig. 3A.33)}.
\end{align*}
\]

**$^{13}$C-NMR spectrum**: (75 MHz, CDCl$_3$)

\[
\begin{align*}
\delta & \quad 162.9, \\
& \quad 133.0, \\
& \quad 130.6, \\
& \quad 129.2, \\
& \quad 128.4, \\
& \quad 126.4, \\
& \quad 124.0, \\
& \quad 118.9, \\
& \quad 117.8, \\
& \quad 54.0 \ (d, J = 6.5 \text{ Hz}), \\
& \quad 53.8 \ (d, J = 6.5 \text{ Hz}), \\
& \quad 48.9, \\
& \quad 32.8 \ (d, J = 145.0 \text{ Hz}).
\end{align*}
\]

**ESIMS-spectrum**: $m/z$ 331 [M+H]$^+$ (Fig. 3A.34).

**Entry-8k (Table 2A.4)**
Molecular formula : C₁₆H₂₂N₃O₄P

IR Spectrum : $\nu_{\text{max}}$ 3367, 3159, 1762, 1437, 1227 cm$^{-1}$.

$^1$H-NMR spectrum : (300 MHz, CDCl$_3$):

$\delta$ 7.01 (1H, $d$, $J = 8.0$ Hz), 6.39 (1H, $dd$, $J = 8.0$, 1.5 Hz), 6.30 (1H, $d$, $J = 1.5$ Hz), 5.87 (2H, brs), 4.51 (1H, $d$, $J = 20.0$ Hz), 3.59 (6H, $d$, $J = 10.0$ Hz), 3.41-3.28 (4H, m), 1.13 (6H, $t$, $J = 7.0$ Hz) (Fig. 3A. 35).

$^{13}$C-NMR spectrum : (75 MHz, CDCl$_3$)

$\delta$ 160.9, 152.3, 148.8, 130.3, 116.2, 108.5, 99.8, 54.4 ($d$, $J = 6.0$ Hz), 53.3 ($d$, $J = 6.0$ Hz), 49.8, 44.9, 34.6 ($d$, $J = 144.0$ Hz) 12.9 (Fig. 3A. 36).

ESIMS-spectrum : $m/z$ 352 [M+H]$^+$.

Entry-8l (Table 2A. 4)

Molecular formula : C₁₅H₂₀N₂O₇P
**IR Spectrum** : \( \nu_{\text{max}} 3291, 3142, 1723, 1416, 1249 \) cm\(^{-1}\).

**\(^1\text{H-NMR spectrum}\)** : (300 MHz, CDCl\(_3\)):

\[\delta\] 7.08 (1H, t, \(J = 8.0\) Hz), 6.95 (1H, dd, \(J = 8.0, 1.5\) Hz), 6.83 (1H, dd, \(J = 8.0, 1.5\) Hz), 4.41(1H, d, \(J = 18.0\) Hz), 4.22 (2H, q, \(J = 7.0\) Hz), 3.90 (3H, s), 3.71 (3H, d, \(J = 10.0\) Hz), 3.53 (3H, d, \(J = 10.0\) Hz), 1.31 (3H, t, \(J = 7.0\) Hz) \(\text{(Fig. 3A. 37).}\)

**\(^{13}\text{C-NMR spectrum}\)** : (75 MHz, CDCl\(_3\))

\[\delta\] 168.7, 162.0, 154.3, 147.9, 124.6, 121.9, 121.1, 111.0, 77.3, 60.0, 56.1, 53.3, (d, \(J = 6.5\) Hz), 35.0 (d, \(J = 144.0\) Hz), 14.8.

**ESIMS-spectrum** : \(m/z 358 \text{ [M+H]}^+\) \(\text{(Fig. 3A. 38).}\)

**REFERENCES**


SECTION-B

Overview on \(N\)-tosyl imines

- Simple and efficient access to \(N\)-tosyl \(\beta\)-amino ketones and their conversion into 2,4-disubstituted azetidines
- Synthesis of \(\alpha\)-aminonitriles through Strecker reaction of \(N\)-tosyl aldimines using molecular iodine
**Introduction on imines**

An imine is the functional group having carbon-nitrogen double bond with nitrogen attached to hydrogen atom or organic functional group (e.g. Ts, Cbz, Boc and Bn) and the carbon having two additional double bonds (1).

\[ \text{Imine (1)} \]

The imines are classified into two types – if one of the \( R_1 \) or \( R_2 \) replaced by hydrogen (H), these imines is called aldimine and both \( R_1 \) and \( R_2 \) have carbon groups called ketimines.

Imines are prepared by condensation of aldehyde and amines or amides and less commonly ketones. The reaction proceed via the nucleophilic addition of aniline to aldehyde to furnish hemiaminal intermediate, followed by elimination of water molecule to yield imine (Scheme 1). The equilibrium in this reaction usually favours the carbonyl compound and amine, to reduce this backward reaction using dehydrating agents such as molecular sieves is required to forward reaction in favour of imine formation.

![Scheme 1](image-url)
*N*-Sulfonylimines and their derivatives are useful precursor for synthesis of oxaziridines, aziridines\(^1\) and also a key intermediate for the synthesis of nitrogen containing heterocycles, especially in the area of alkaloids.\(^2\) *N*-Sulfonylimines can be synthesized by direct condensation of *para* toluene sulfonamides and benzaldehydes or ketones in the presence of strong Lewis acids such as TiCl\(_4\), AlCl\(_3\) using dehydrating agents (4A\(^\circ\) molecular sieves, MgSO\(_4\)).\(^1\)\(^a\) Later number of method developed for synthesis of *N*-sulfonylimines among this condensation of simple as well as hindered ketones with para toluene sulfonamides in the presence of TiCl\(_4\) and Et\(_3\)N in CH\(_2\)Cl\(_2\) at 0°C.\(^3\) Aliphatic *N*-sulfonylimines also successfully prepared by using \(\alpha\)-amidosulfones.\(^4\)

**Previous reports on *N*-Sulfonylimines and related imines:**

1. **Synthesis of meso-tetraphenyl porphyrins via condensation of dipyrrromethanes with *N*-tosyl imines\(^5\)**

Temeli et al reported synthesis of tetraphenyl porphyrins using 5-substituted dipyrrromethanes with *N*-tosyl imines in the presence of Cu(OTf)\(_2\) followed by oxidation with DDQ to furnish meso-substituted tetraphenyl porphyrins (**Scheme 2**).
Scheme 2

2. The reaction of N-tosyl imines with heteroaromatic compounds: a new access to triheteroarylmethanes

Temeli et al reported preparation of useful triheteroaryl methanes from N-tosyl imines, pyrrole in the presence of Cu(OTf)$_2$ and montmorillonite K-10 caly as a catalyst (Scheme 3).

```
\begin{align*}
\text{Ts-} & \quad \text{Cu(OTf)$_2$} \\
\text{HN} & \quad 60^\circ\text{C, 1h} \\
\text{HN} & \quad 40-85\%
\end{align*}
```

Scheme 3

3. An efficient synthesis of α-aryl β-(N-tosyl) amino phosphonate derivatives from α-diazophosphonate

Zhao and co-workers synthesized β-aryl β-(N-tosyl) amino α-diazophosphonic acid derivatives by using α-diazophosphonates and aryl N-tosyl imines in presence of DBU in MeCN at room temperature (Scheme 4).

```
\begin{align*}
\text{Ts-} & \quad \text{10\% DBU} \\
\text{Ar} & \quad \text{MeCN, rt} \\
\text{N$_2$} & \quad 9\text{ h} \\
\text{Ph} & \quad 54-89\%
\end{align*}
```

Scheme 4

4. Rhodium-catalyzed and sonication-accelerated addition of aryltin and aryllead reagents to imines in air and water
Ding et al investigated, the reaction of $N$-tosyl imine with phenyl trimethylnitn or phenyl trimethyllead in the presence of $\text{Rh}_2(\text{COD})_2\text{Cl}_2$ as a catalyst in water at 60 °C to give the addition product $N$-tosyldiphenylmethyamine (Scheme 5).

Scheme 5

5. Imino-ene reaction of $N$-tosyl arylaldimines with $\alpha$-methylstyrene: application in the synthesis of important amines\(^9\)

Singh and co-workers investigated $\text{Cu(OTf)}_2$ in combination with $\text{TMSCl}$ for effectively activation of C-H bond for the imine-ene reaction of $N$-tosylarylaldimines with $\alpha$-methyl styrene to give the imine-ene adduct which was converted into $\beta$-aminoketones (Scheme 6).

Scheme 6

6. Palladium-catalyzed asymmetric umpolung allylation of imines with allylic alcohols\(^10\)

Qiao et al reported palladium catalysed asymmetric umpolung allylation reaction of imine with allylic alcohol using chiral ligand, the
allylation accomplished with high yield and good enantioselectivities (Scheme 7).

**Scheme 7**

7. **Phosphine-catalyzed enantioselective [3+2] annulations of 2,3-butadienoates with imines**

Marinetti et al reported the first systematic screening of chiral phosphines in [3+2] cyclo addition reactions between 2, 3 butadienoates and N-tosyl imines to furnish 3-pyrroline derivatives (Scheme 8).

**Scheme 8**

8. **The effect of coordination on the reaction of N-tosyl imines with diethylzinc**

Geo et al investigation, the effect of coordination in between N-tosyl imines and diethyl zinc. Due to this strong coordination, N-tosyl imines could be reduced directly through beta hydrogen transfer mechanism by diethylzinc in non-polar solvents to gives the
corresponding secondary amines in high yield and mild reaction condition (Scheme 9).

![Scheme 9](image)

9. Highly enantioselective titanium-catalyzed cyanation of imines at room temperature

Seayad and co-workers reported the asymmetric hydrocyanation of imines using PHTA-precatalyst with readily available N-salicyl-β-amino alcohol ligand at room temperature. Followed by hydrolysis afford chiral α-amino acids (Scheme 10).

![Scheme 10](image)

10. Dual-activation of asymmetric Strecker reaction of aldimines and ketimines catalyzed by a tethered bis (8-quinolinolato) aluminum complex

Abell et al reported the asymmetric catalytic synthesis of α-amino acids through hydrocyanation of imines in the presence of chiral aluminium catalyst furnished α-amino-protected hydronitrile product (Scheme 11).
11. Synthesis of \( \alpha \)-amino nitriles through Strecker reaction of aldimines and ketoimines by using nanocrystalline magnesium oxide\(^{15} \)

Kantam and co-workers reported Strecker reaction of various aldimines and ketoimines with trimethylsilyl cyanide in the presence of nanocrystalline magnesium oxide as a catalyst to give \( \alpha \)-amino nitriles and \( \alpha,\alpha \)-disubstituted \( \alpha \)-amino nitriles in high yield (Scheme 12).

**Scheme 11**

**Scheme 12**
Present Work

1. Simple and efficient access to N-tosyl β-amino ketones and their conversion into 2,4-disubstituted azetidines

β-Amino carbonyl compounds possess various important biological as well as pharmacological properties including hypoglycemic, antiketogenic and antifungal activities.\(^{16}\) They are also useful synthetic intermediates for construction of various valuable pharmaceuticals and bioactive natural products.\(^{17}\) Taxol, a highly potent anticancer agent, contains β-amino carbonyl skeleton in its side chain.\(^{18}\) β-amino carbonyl compounds can easily converted into γ-amino alcohols which are structural units in various natural nucleoside antibiotics.\(^{19}\) The Mannich-type reactions involving aldehydes, amines (or directly imines) and enolizable ketones are widely applied for synthesis of β-amino carbonyl compounds and various methods have been developed on the basis of these reactions for preparation of these β-amino carbonyl compounds.\(^{20}\)

Here we report that β-amino carbonyl compounds can efficiently be synthesized by using N-tosyl aldimines 2 and acetophenone 3 in the presence of BF\(_3\).OEt\(_2\), to afford the corresponding N-tosyl β-Amino ketones 4 at room temperature (Scheme 13).
Initially the reaction of $N$-tosyl benzaldimine (4a, $R=\text{Ph}$) with acetophenone was carried out using various Lewis acid catalysts (Table 3B. 1). Considering reaction time and yield, BF$_3$OEt$_2$ was the most effective catalyst. Using above conditions a series of $N$-tosyl $\beta$-Amino ketones were prepared from different $N$-tosyl aldimines (Table 3B. 2). The aromatic aldehyde having electron-withdrawing as well as electron-donating groups underwent conversion smoothly. The aliphatic aldimine derivatives also furnished the $N$-tosyl $\beta$-Amino ketones conveniently. The reaction was carried out room temperature, conversion was completed within 6-9 h and $N$-tosyl $\beta$-amino ketones were formed in excellent yields $\left(77 - 86\%\right)$. 

Scheme 13

$$\begin{align*}
\text{Ts} & \quad \text{H} \\
2 & \quad \text{Ph} \\
\text{R} & \\
\text{H} \\
\text{O} \\
\text{4} \\
\text{Ph} \\
\end{align*}$$

$$\text{BF}_3\text{OEt}_2 \quad \text{DCM, rt} \quad 6-9 \text{ h} \quad \text{Ts} \quad \text{NH} \quad \text{O} \quad \text{Ph}$$

$$77-86\%$$
Table 3B. 1. Evaluation of the catalytic activity of different catalysts for the preparation of \(N\)-tosyl \(\beta\)-amino ketones\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Tosyl imine (2)</th>
<th>B-amino ketone (4)</th>
<th>catalyst</th>
<th>Time (h)</th>
<th>Yield (%)(^b)</th>
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<tr>
<td>1</td>
<td><img src="image" alt="Tosyl imine" /></td>
<td><img src="image" alt="B-amino ketone" /></td>
<td>BF(_3):OEt(_2)</td>
<td>6</td>
<td>86</td>
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<tr>
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<td></td>
<td>Cu(OTf)(_2)</td>
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<td>Bi(OTf)(_3)</td>
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<td>24</td>
<td>15</td>
</tr>
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<td><img src="image" alt="Tosyl imine" /></td>
<td><img src="image" alt="B-amino ketone" /></td>
<td>BF(_3):OEt(_2)</td>
<td>9</td>
<td>77</td>
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<td></td>
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<td>17</td>
<td>51</td>
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<td></td>
<td>Bi(OTf)(_3)</td>
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<td></td>
<td>SnCl(_2)</td>
<td>24</td>
<td>NR(^c)</td>
</tr>
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</table>

\(^a\)Reaction conditions: \(N\)-tosyl aldmine (1.0 mmol), acetophenone (1.2 mmol), catalyst (25 mol %), CH\(_2\)Cl\(_2\) (3 mL), rt, N\(_2\) atmosphere.\(^b\)Isolated yield.\(^c\)No reaction.
The structures of the products 4 (Table 3B. 2) were settled from their spectral [IR, \(^1\)H NMR, \(^{13}\)C NMR and ESIMS] data. For example, in the IR spectrum of 4a (Table 3A. 2, Fig. 3B. 1), the presence of strong absorption band at 3336 cm\(^{-1}\) indicated amine functional group. In \(^1\)H NMR spectrum (Fig. 3B. 2) of product characteristic –CH and –COCH\(_2\) protons resonated at \(\delta\) 4.89 (1H, m), 3.59(1H, dd, \(J = 17.0, 5.0\) Hz) and 3.42 (1H, dd, \(J = 17.0, 6.0\) Hz) indicated methyne and methylene protons attached to electron withdrawing groups. In \(^{13}\)C NMR spectrum (Fig. 3B. 3) of 4a, the chemical shift value at \(\delta\) 54.8, 50.9, 20.6 conformed the structure. The structure was supported by the mass spectrum which gave signal in HRMS at m/z 402.1139 [M+Na]\(^+\) (Fig. 3B. 4).

Similarly, in the \(^1\)H NMR spectrum of product 4b (Table 3B. 2, Fig. 3B. 6), the characteristic –CH and –COCH\(_2\) protons resonated at \(\delta\) 4.83(1H, m), 3.52 (1H, dd, \(J = 17.0, 5.0\) Hz) and 3.41 (1H, dd, \(J = 17.0, 6.0\) Hz). It was also supported by mass spectrum which gave signal for HRMS: m/z 414.0925 (Fig. 3B. 8).

**TABLE 3B. 2. Synthesis of N-tosyl β-amino ketones by the reaction of various N-tosyl aldimines and acetophenone in the presence of BF\(_3\).OEt\(_2\)\(^a\)**
<table>
<thead>
<tr>
<th>Entry</th>
<th>Tosyl imine (2)</th>
<th>β-amino ketones</th>
<th>Time (h)</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td></td>
<td></td>
<td>6</td>
<td>86</td>
</tr>
<tr>
<td>4b</td>
<td></td>
<td></td>
<td>7</td>
<td>85</td>
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<tr>
<td>4c</td>
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<td>4g</td>
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<td>77</td>
</tr>
<tr>
<td>4h</td>
<td></td>
<td></td>
<td>9</td>
<td>78</td>
</tr>
</tbody>
</table>
**Reaction conditions:** $N$-tosyl aldimine (1.0 mmol), acetophenone (1.2 mmol), BF$_3$.OEt$_2$ (0.25 mmol), CH$_2$Cl$_2$ (3 mL), rt, N$_2$ atmosphere.

<p>| | | | |</p>
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<thead>
<tr>
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<tr>
<td>4i</td>
<td><img src="image1.png" alt="image" /></td>
<td><img src="image2.png" alt="image" /></td>
<td>8</td>
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<tr>
<td>4j</td>
<td><img src="image3.png" alt="image" /></td>
<td><img src="image4.png" alt="image" /></td>
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<td>4k</td>
<td><img src="image5.png" alt="image" /></td>
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<td>4l</td>
<td><img src="image7.png" alt="image" /></td>
<td><img src="image8.png" alt="image" /></td>
<td>9</td>
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</tbody>
</table>

$^a$Reaction conditions: $N$-tosyl aldimine (1.0 mmol), acetophenone (1.2 mmol), BF$_3$.OEt$_2$ (0.25 mmol), CH$_2$Cl$_2$ (3 mL), rt, N$_2$ atmosphere. $^b$Isolated yield.

$N$-Tosyl $\beta$-amino ketones have been successfully converted into $N$-tosyl azetidines by reduction followed by cyclisation. Azetidines are four membered nitrogen-containing heterocyclic compounds and they possess outstanding biological properties.$^{21}$ including anti-influenza virus A activity and anti-HIV and anti-HSV-1 and HSV-2 properties.$^{22}$ Azetidine moiety has also been found in some natural bioactive molecules.$^{23}$ In addition, ring-opening reactions of azetidines have been utilized to construct various nitrogen-containing bioactive compounds.$^{24}$ However, the methods for the preparation of 2,4-disubstituted $N$-tosyl azetidines are limited.$^{25}$ We have investigated, that the prepared $N$-tosyl $\beta$-amino ketones can conveniently be converted into 2,4-disubstituted azetidines (Scheme 14).
**Scheme 14.** Synthesis of a 2,4-disubstituted N-tosyl azetidine from an N-tosyl aldimine

\[
\text{Ts}^+ - \text{N}^+ - \text{H}^+ + \text{Ph} - \text{CO} \xrightarrow{\text{BF}_3\text{OEt}_2, \text{DCM}, \text{rt}, 6 \text{~h}} \text{Ts}^+ - \text{NH} - \text{O} - \text{Ph} \\
\text{Ph} - \text{N}^+ - \text{Ts} \xrightarrow{\text{TsCl}/\text{KOH, THF, reflux for 45 min}} \text{Ts}^+ - \text{NH} - \text{OH} + \text{Ts}^+ - \text{NH} - \text{OH} \quad \text{(diastereomeric ratio 76:24)}
\]

*N*-Tosyl β-amino ketones 4a was reduced with NaBH₄ in MeOH at room temperature to obtain *N*-tosyl γ-amino alcohols 5a and 5b in high yields with diastereomeric ratio of 76:24 and the diastereomers were separated by column chromatography. The major amino alcohol 5a was treated with TsCl/KOH in dry THF at reflux condition to furnish 2,4-disubstituted *N*-tosyl azetidine 6a in three steps (overall yield 64%) (Table 3B. 3). Following a similar method (Scheme 14), β-amino ketones 4g and 4i were converted into corresponding *N*-tosylazetidines 6b (overall yield 57%) and 6c (overall yield 61%).

The structures of the 2,4-disubstituted *N*-tosyl azetidine 6 were settled from their spectral [IR, ¹H and ¹³C, ESIMS and HRMS(ESI)] data. In ¹H NMR spectrum (Table 3A. 3, Fig. 3B. 18) of product 6a, characteristic ring –CH and –CH₂ protons resonated at δ 4.92 (2H, t, J
= 8.0 Hz), 2.81 (1H, m), 2.41 (3H, s) and 2.13 (1H, m) indicating methyne and methylene protons in azetidine ring. In $^{13}$C NMR spectrum (Fig. 3B. 19) of 6a, the chemical shift value at δ 62.1, 35.7, 21.1 conformed the structure. The structure was supported by the mass spectrum which gave signal in HRMS at m/z 386.1200 [M+Na]$^+$ (Fig. 3B. 20).

Table 3B. 3. Synthesis of 2,4-disubstituted N-tosyl azetidines from N-tosyl aldimines

<table>
<thead>
<tr>
<th>entry</th>
<th>Tosyl imine (2)</th>
<th>2,4-disub.N-tosylazetidines (6)</th>
<th>Overall yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td><img src="image" alt="Ts-N" /></td>
<td><img src="image" alt="R1=CsH5" /></td>
<td>64</td>
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<tr>
<td>6b</td>
<td><img src="image" alt="MeO" /></td>
<td><img src="image" alt="R1=3,4,5(MeO)CsH2" /></td>
<td>57</td>
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<tr>
<td>6c</td>
<td><img src="image" alt="Ts-N" /></td>
<td><img src="image" alt="R1=2-C10H7" /></td>
<td>61</td>
</tr>
</tbody>
</table>

$^a$Overall yield starting from N-tosyl aldimines, after column chromatographic purification

In conclusion, we have developed a simple, mild and efficient protocol for synthesis of N-tosyl β-amino ketones and also converted these compounds into the corresponding 2,4-disubstituted N-tosyl
azetidines. These amino ketones and azetidines can be utilised for bioevaluation as well as for construction of various nitrogen-containing molecules of biological importance.

2. Synthesis of α-aminonitriles through Strecker reaction of N-tosyl aldimines using molecular iodine
α-Aminonitriles are useful intermediates for the preparation of α-aminoacids\textsuperscript{26} and various nitrogen containing heterocycles such as imidazoles and thiadiazoles.\textsuperscript{27} α-Aminoacids are great importance in chemistry and biology as valuable building blocks.\textsuperscript{28} The Strecker reaction involving nucleophilic addition of a cyanide ion to imine, is of great importance to modern organic chemistry as it offers one of the most direct feasible method for the preparation of α-aminonitriles. Many methods have been developed for synthesis of this compound using various Lewis acids.\textsuperscript{29}

Here we report our work on the synthesis of α-aminonitriles which can efficiently be synthesized by treatment of N-sulfonyl aldimines with trimethyl silyl cyanide in the presence of iodine as a catalyst at room temperature (Scheme 15).

\begin{equation}
\begin{array}{c}
\text{Ts}^+ \\
R_7H \\
\text{T}
\end{array}
\xrightarrow{\text{TMSCH}_2} \\
8 \\
\text{DCM, rt, 6 h} \\
\text{Ts}^+ \\
R_9CN \\
86-94\%
\end{equation}

Scheme 15

Initially we carried out the reaction of N-tosyl benzaldimine and its two derivatives with trimethyl silyl cyanide in the presence of different Lewis acid catalysts. However, considering the reaction time and yield iodine was found to be effective (Table 3B. 4). Finally a series of N-tosyl-α-aminonitriles were prepared (Table 3B. 5) from different N-tosyl aldimines derived from various aromatic, heteroaromatic and aliphatic aldehydes using trimethyl silyl cyanide in the presence of iodine at room temperature. The aromatic aldehydes contained both
electron-donating as well as electron-withdrawing groups and the aliphatic aldimine derivatives also underwent conversion into \(N\)-tosyl-\(\alpha\)-aminonitriles. The reaction was conducted at room temperature. The conversion was completed within 1-1.5 h and the protected \(\alpha\)-aminonitriles were formed in high yields (86 – 94%).

**Table 3B. 4. Evaluation of the catalytic activity of different catalysts for the preparation of \(\alpha\)-aminonitrile**

<table>
<thead>
<tr>
<th>entr</th>
<th>Tosylimine (7)</th>
<th>(\alpha)-Aminonitrile (9)</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield(^b) (%)</th>
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</thead>
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Reaction conditions: N-tosyl aldimine (1.0 mmol), trimethylsilylcyanide (1.3 mmol), catalyst (15 mol %), CH₂Cl₂ (2 mL), room temperature.

Isolated yield

The structures of the N-tosyl-α-aminonitriles 9 were settled from their spectral [IR,¹H and ¹³C, ESIMS and HRMS (ESI)] data. In ¹H NMR spectrum (Table 3A. 5, Fig. 3B. 25) of product 9a, presence of signal resonated at δ 5.60 (1H, d, J = 10.0 Hz) indicated –CH proton attached strong electron withdrawing group. In ¹³C NMR spectrum (Fig. 3B. 26) of 9a, chemical shift values at δ 116.5 and 48.3 indicated nitrile and methylene functionality. The structure was supported by the mass spectrum which gave signal in ESIMS at m/z 309 [M+Na]+ (Fig. 3B. 27).

Similarly, in the ¹H NMR spectrum of product 9b (Table 3B. 5, Fig. 3B. 28) the characteristic methyledene –CH pron resonated at δ 5.59 (1H, d, J = 10.0 Hz) indicating the methyledene proton. It was also supported by the mass spectrum which gave signal for ESIMS: m/z 343, 345 [M+Na]+ (Fig. 3B. 30).

Table 3B. 5. Iodine catalysed synthesis of α-aminonitriles by the reaction of N-tosyl benzaldimines and trimethylsilylcyanide

<table>
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<tr>
<th>Entry</th>
<th>Tosylimine (7)</th>
<th>α-aminonitrile (9)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
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a
b
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</table>
In conclusion, we have developed alternative facile straightforward method for the synthesis of α-aminonitriles from N-tosyl aldimines and trimethylsilyl cyanide using iodine as a catalyst. The operational simplicity, mild reaction conditions, less expensive and application of an easily available catalyst, short reaction times and high yields are the notable advantages of the method.
EXPERIMENTAL

General experimental procedure for synthesis of \(N\)-tosyl \(\beta\)-amino ketones:

To a solution of \(N\)-tosyl aldimine 2 (1.0 mmol), acetophenone 3 (1.1 mmol) in CH\(_2\)Cl\(_2\) (3 mL) was added BF\(_3\).OEt\(_2\) (0.25 mmol) to this mixture under N\(_2\) atmosphere. The mixture was stirred at room temperature and the reaction was monitored by TLC. After completion, the reaction mixture was washed with ice cold water (20 mL) and
subsequently extracted with CH$_2$Cl$_2$ (20 mL). The extract was dried and concentrated under reduced pressure. The residue was subjected to column chromatography (silica gel, hexane-EtOAc) to furnish pure N-tosyl β-amino ketone 4.

**Entry 4a-(Table 3B. 2)**

![Molecular structure](image)

**Molecular formula** : C$_{22}$H$_{21}$NO$_3$S

**IR Spectrum** : $\nu_{\text{max}}$ 3336, 1677, 1593, 1444, 1328 cm$^{-1}$

(Fig. 3B. 1).

**$^1$H-NMR spectrum** : (300 MHz, CDCl$_3$):

$\delta$ 7.81 (2H, d, $J = 8.0$ Hz), 7.62 (2H, d, $J = 8.0$ Hz), 7.55 (1H, t, $J = 8.0$ Hz), 7.40 (2H, t, $J = 8.0$ Hz), 7.24 – 7.10 (7H, m), 5.86 (1H, brs), 4.89 (1H, m), 3.59 (1H, dd, $J = 17.0$, 5.0 Hz), 3.42 (1H, dd, $J = 17.0$, 6.0 Hz), 2.36 (3H, s)

(Fig. 3B. 2).

**$^{13}$C-NMR spectrum** : (75 MHz, CDCl$_3$)

$\delta$ 198.0, 143.7, 140.0, 137.2, 136.4, 133.7, 129.9, 129.2, 128.6, 127.5, 127.3, 126.4, 126.2, 54.8, 40.9, 20.6 (Fig. 3B. 3).

**HRMS-spectrum** : 402.1127 ($m/z$ calcd for C$_{22}$H$_{21}$NO$_3$SNa
Entry 4b-(Table 3B. 2)

\[
\text{Molecular formula} : \quad \text{C}_{22}\text{H}_{20}\text{ClNO}_3\text{S}
\]

**IR Spectrum** : \(\nu_{\text{max}} 3258, 1691, 1598, 1452, 1312 \text{ cm}^{-1}\)

*(Fig. 3B. 5).*

**\(^1\text{H-NMR spectrum}** : (300 MHz, CDCl\(_3\)):

\[
\begin{align*}
\delta & \quad 7.80 \ (2\text{H}, \text{d}, \ J = 8.0 \ \text{Hz}), \ 7.60 \ (2\text{H}, \text{d}, \ J = 8.0 \ \text{Hz}), \ 7.58 \ (1\text{H}, \text{t}, \ J = 8.0 \ \text{Hz}), \ 7.41 \ (2\text{H}, \text{t}, \ J = 8.0 \ \text{Hz}), \ 7.19 - 7.07 \ (6\text{H}, \text{m}), \ 5.96 \ (1\text{H}, \text{brs}), \ 4.83 \\
& \quad (1\text{H}, \text{m}), \ 3.52 \ (1\text{H}, \text{dd}, \ J = 17.0, 5.0 \ \text{Hz}), \ 3.41 \\
& \quad (1\text{H}, \text{dd}, \ J = 17.0, 6.0 \ \text{Hz}), \ 2.34 \ (3\text{H}, \text{s}) \ (\text{Fig. 3B. 6}).
\end{align*}
\]

**\(^{13}\text{C-NMR spectrum}** : (75 MHz, CDCl\(_3\))

\[
\begin{align*}
\delta & \quad 198.2, \ 142.8, \ 139.4, \ 137.5, \ 137.0, \ 134.8, \\
& \quad 134.6, \ 130.0, \ 129.8, \ 128.9, \ 128.0, \ 127.9, \\
& \quad 126.7, \ 126.1, \ 52.8, \ 44.9, \ 22.2 \ (\text{Fig. 3B. 7}).
\end{align*}
\]

**HRMS-spectrum** : 414.0925 (m/z calcd for C\(_{22}\)H\(_{21}\)ClNO\(_3\)S (M+H)^+ 414.0925) *(Fig. 3B. 8).*

Entry 4e-(Table 3B. 2)
Molecular formula : $C_{23}H_{23}NO_3S$

IR Spectrum : $\nu_{\text{max}}$ 3276, 1680, 1598, 1448, 1325 cm$^{-1}$.

$^1$H-NMR spectrum : (300 MHz, CDCl$_3$):

$\delta$ 7.81 (2H, d, $J = 8.0$ Hz), 7.63 (2H, d, $J = 8.0$ Hz), 7.53 (1H, t, $J = 8.0$ Hz), 7.40 (2H, t, $J = 8.0$ Hz), 7.18 (2H, d, $J = 8.0$ Hz), 7.09 – 6.96 (4H, m), 5.72 (1H, d, $J = 8.0$ Hz), 4.81 (1H, m), 3.59 (1H, dd, $J = 17.0$, 5.0 Hz), 3.42 (1H, dd, $J = 17.0$, 6.0 Hz), 2.38 (3H, s), 2.25 (3H, s) (Fig. 3B. 9).

$^{13}$C-NMR spectrum : (75 MHz, CDCl$_3$)

$\delta$ 198.0, 142.7, 137.1, 137.0, 136.8, 135.7, 134.0, 129.5, 129.2, 129.0, 128.6, 127.3, 126.9, 54.1, 44.9, 20.4, 20.2 (Fig. 3B. 10).

HRMS-spectrum : 394.1474 ($m/z$ calcd for $C_{23}H_{24}NO_3S$ (M+H)$^+$ 394.1471) (Fig. 3B. 11).

Entry 4g-(Table 3B. 2)
Molecular formula : C_{25}H_{27}NO_{6}S

IR Spectrum : \nu_{\text{max}} 3277, 1681, 1595, 1460, 1332 \text{ cm}^{-1}.

^{1}H-NMR spectrum : (300 MHz, CDCl_{3}):
\delta 7.82 (2H, d, J = 8.0 \text{ Hz}), 7.61 - 7.50 (3H, m), 7.42 (2H, t, J = 8.0 \text{ Hz}), 7.13 (2H, d, J = 8.0 \text{ Hz}), 6.31 (2H, s), 5.39 (1H, brs), 4.82 (1H, m), 3.72 (3H, s), 3.69 (6H, s), 3.60 (1H, dd, J = 17.0, 5.0 \text{ Hz}), 3.48 (1H, dd, J = 17.0, 6.0 \text{ Hz}), 2.32 (3H, s) (Fig. 3B. 12).

^{13}C-NMR spectrum : (75 MHz, CDCl_{3})
\delta 198.2, 152.8, 143.3, 137.0, 136.5, 136.0, 134.4, 129.5, 129.0, 128.4, 126.6, 104.1, 60.4, 56.0, 55.0, 44.9, 21.2 (Fig. 3B. 13).

HRMS-spectrum : 492.1445 (m/z calcd for C_{25}H_{27}NO_{6}SNa (M+Na)^{+} 492.1456) (Fig. 3B. 14).

Entry 4i-(Table 3B. 2)

Molecular formula : C_{26}H_{23}NO_{3}S

IR Spectrum : \nu_{\text{max}} 3261, 1681, 1597, 1452, 1305 \text{ cm}^{-1}.

^{1}H-NMR spectrum : (300 MHz, CDCl_{3}):
\delta 7.82 (2H, d, J = 8.0 \text{ Hz}), 7.76 - 7.64 (3H, m),
7.60 – 7.50 (4H, m), 7.49 – 7.38 (4H, m), 7.29 (1H, d, J = 8.0 Hz), 7.02 (2H, d, J = 8.0 Hz), 5.91 (1H, brs), 5.05 (1H, m), 3.66 (1H, dd, J = 17.0, 5.0 Hz), 3.52 (1H, dd, J = 17.0, 6.0 Hz), 2.22 (3H, s) (Fig. 3B. 15).

**13C-NMR spectrum**: (75 MHz, CDCl₃)

δ 198.4, 147.1, 138.3, 138.1, 136.7, 133.0, 132.5, 132.3, 130.0, 129.7, 128.4, 128.3, 128.0, 127.8, 127.2, 127.0, 126.3, 124.8, 55.0, 45.0, 22.2 (Fig. 3B. 16).

**HRMS-spectrum**: 452.1278 (m/z calcd for C₂₆H₂₃NO₃SNa (M+Na)⁺ 452.1296) (Fig. 3B. 17).

**Entry 4k-(Table 3B. 2)**

![Structural formula](image)

**Molecular formula**: C₂₂H₂₇NO₃S

**IR Spectrum**: νₘₐₓ 3287, 1680, 1599, 1449, 1328 cm⁻¹.

**1H-NMR spectrum**: (300 MHz, CDCl₃):

δ 7.80 (2H, d, J = 8.0 Hz), 7.71 (2H, d, J = 8.0 Hz), 7.57 (1H, t, J = 8.0 Hz), 7.45 (2H, t, J = 8.0 Hz), 7.19 (2H, d, J = 8.0 Hz), 5.30 (1H, d, J = 8.0 Hz), 3.49 (1H, m), 3.18 (1H, dd, J = 17.0, 4.0 Hz), 2.99 (1H, dd, J = 17.0, 6.0 Hz), 2.35
(3H, s), 1.85 (1H, m), 1.72 – 1.43 (4H, m), 1.34 – 1.21 (2H, m), 1.19 – 1.04 (2H, m), 0.95 – 0.73 (2H, m) (**Fig. 3B. 18**).

**13C-NMR spectrum** : (75 MHz, CDCl₃)

δ 199.5, 143.3, 138.0, 136.2, 134.2, 130.0, 129.9, 128.7, 127.5, 126.8, 126.1, 55.2, 40.5, 39.9, 29.9, 29.2, 25.9, 25.7, 21.0 (**Fig. 3B. 19**).

**HRMS-spectrum** : 408.1607 (m/z calcd for C₂₂H₂₇NO₃SNa (M+Na)⁺ 408.1609).

**General experimental procedure for synthesis of N-tosyl azetidines:**

N- tosyl β-amino ketones 4 were reduced with NaBH₄ in MeOH at room temperature for 1h following the general procedure to form N-tosyl γ-amino alcohols 5. These compounds were subsequently utilised for the preparation N-tosyl azetidines.

To a suspension of powdered KOH (3.1 mmol), TsCl (1.2 mmol) in Dry THF (10 mL) was added N-tosyl γ-amino alcohol 5 (1.1 mmol) dropwise at room temperature. The mixture was refluxed for 45 min. After completion the reaction mixture was washed with water (20 mL) and extracted with EtOAc (30 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was subjected to column chromatography (silica gel, hexane-EtOAc) to furnish pure 2,4-disubstituted N-tosyl azetidines 6.
Entry 6a-(Table 3B. 3)

\[
\begin{align*}
\text{Molecular formula} & : \text{C}_{22}\text{H}_{21}\text{NO}_2\text{S} \\
\text{IR Spectrum} & : \nu_{\text{max}} 1600, 1455, 1341, 1156 \text{ cm}^{-1}.
\end{align*}
\]

\[
\begin{align*}
\text{\textsuperscript{1}H-NMR spectrum} & : (300 \text{ MHz, CDCl}_3): \\
& \delta 7.61 (2\text{H, d, } J = 8.0 \text{ Hz}), 7.48 (2\text{H, d, } J = 8.0 \text{ Hz}), 7.40 - 7.22 (10\text{H, m}), 4.92 (2\text{H, t, } J = 7.0 \text{ Hz}), 2.81 (1\text{H, m}), 2.41 (3\text{H, s}), 2.13 (1\text{H, m})
\end{align*}
\]

(Fig. 3B. 20).

\[
\begin{align*}
\text{\textsuperscript{13}C-NMR spectrum} & : (75 \text{ MHz, CDCl}_3) \\
& \delta 144.9, 141.2, 129.5, 128.6, 128.5, 127.5, 126.4, 62.1, 35.7, 21.0 \text{ (Fig. 3B. 21).}
\end{align*}
\]

\[
\begin{align*}
\text{HRMS-spectrum} & : 386.1200 \text{ (m/z calcd for } \text{C}_{22}\text{H}_{21}\text{NO}_2\text{SNa} (\text{M+Na})^+ \text{ 386.1190) (Fig. 3B. 22).}
\end{align*}
\]

Entry 6c-(Table 3B. 3)

\[
\begin{align*}
\text{Molecular formula} & : \text{C}_{26}\text{H}_{23}\text{NO}_2\text{S} \\
\text{IR Spectrum} & : \nu_{\text{max}} 1636, 1459, 1343, 1158 \text{ cm}^{-1}.
\end{align*}
\]

\[
\begin{align*}
\text{\textsuperscript{1}H-NMR spectrum} & : (300 \text{ MHz, CDCl}_3): \\
& \delta 7.89 - 7.80 (4\text{H, m}), 7.67 - 7.58 (3\text{H, m}), 7.55
\end{align*}
\]
- 7.42 (4H, m), 7.40 – 7.31 (3H, m), 7.28 - 7.19 (2H, m), 5.12 (1H, t, \( J = 7.0 \) Hz), 5.02 (1H, t, \( J = 7.0 \) Hz), 2.89 (1H, m), 2.35 (3H, s), 2.22 (1H, m) (Fig. 3B. 23).

\(^{13}\text{C-NMR spectrum} : \) (75 MHz, CDCl\(_3\))

\[ \delta 140.7, 137.5, 132.8, 132.0, 129.5, 128.7, 128.3, 128.0, 127.5, 127.1, 126.9, 126.2, 125.8, 125.4, 124.1, 61.8, 61.6, 35.1, 20.1 \]

(Fig. 3B. 24).

\( \text{HRMS-spectrum : } 436.1349 (m/z \text{ calcd for } C_{26}H_{23}NO_2SNa} (M+Na)^+ 436.1347). \)

**General experimental procedure for the synthesis of \( \alpha \)-aminonitriles:**

Tosylimine 7 (1mmol) was taken in CH\(_2\)Cl\(_2\) (2 mL) and I\(_2\) (15 mol %) was added. To this mixture trimethyl silyl cyanide 8 (1.3 mmol) was added dropwise at room temperature. The mixture was stirred at same temperature and the reaction was monitored by TLC. After completion the reaction was quenched with hypo solution (10 mL) and the mixture was extracted with CH\(_2\)Cl\(_2\) (30 mL). The extract was dried and concentrated in vacuo. The crude residue was subjected to column chromatography (silica gel, hexane- EtOAc) to obtain pure \( \alpha \)-aminonitrile 9.

*Entry 9a-(Table 3B. 5)*
Molecular formula : $C_{15}H_{14}N_2O_2S$

**IR Spectrum** : $\nu_{\text{max}}$ 3264, 2310, 1597, 1448, 1333, 1156 cm$^{-1}$.

**$^1$H-NMR spectrum** : (300 MHz, CDCl$_3$):

$\delta$ 7.82 (2 H, d, $J = 8.0$ Hz), 7.49–7.36 (7 H, m), 5.60 (1 H, d, $J = 10.0$ Hz), 5.47 (1 H, d, $J = 10.0$ Hz), 2.49 (3 H, s) (Fig. 3B. 25).

**$^{13}$C-NMR spectrum** : (75 MHz, CDCl$_3$)

$\delta$ 144.8, 136.1, 132.2, 130.0, 129.9, 129.4, 127.3, 127.1, 116.5, 48.3, 21.9. (Fig. 3B. 26).

**ESIMS-spectrum** : $m/z$ 309 [M+Na]$^+$ (Fig. 3B. 27).

**Entry 9b-(Table 3B. 5)**

Molecular formula : $C_{15}H_{13}ClN_2O_2S$

**IR Spectrum** : $\nu_{\text{max}}$ 3278, 2237, 1596, 1437, 1349, 1161 cm$^{-1}$.

**$^1$H-NMR spectrum** : (300 MHz, CDCl$_3$):

$\delta$ 7.78 (2 H, d, $J = 8.0$ Hz), 7.40–7.31 (6 H, m), 5.59 (1 H, d, $J = 10.0$ Hz), 5.39 (1 H, d, $J = 10.0$ Hz), 2.48 (3 H, s). (Fig. 3B. 28).
The provided text describes the spectroscopic data for two compounds, Entry 9e and Entry 9h, with specific details on their chemical structures and spectral properties.

**Entry 9e (Table 3B. 5)**

**Molecular formula**: $C_{15}H_{11}F_{3}N_{2}O_{2}S$

**IR Spectrum**: $\nu_{\text{max}}$ 3253, 2240, 1600, 1512, 1348, 1153 cm$^{-1}$.

**$^1$H-NMR spectrum**: (300 MHz, CDCl$_3$):

- $\delta$ 7.72 (2 H, d, $J = 8.0$ Hz), 7.38–7.19 (3 H, m),
- 7.00 (1H, m), 5.92 (1H, d, $J = 10.0$ Hz), 5.57 (1H, d, $J = 10.0$ Hz), 2.45 (3H, s) (Fig. 3B. 31).

**$^{13}$C-NMR spectrum**: (75 MHz, CDCl$_3$)

- $\delta$ 145.0, 135.9, 130.1, 127.2, 123.0, 122.9, 118.0, 117.9, 116.1, 113.1, 113.0, 42.4, 21.9 (Fig. 3B. 32).

**ESIMS-spectrum**: $m/z$ 343, 345 [M+Na]$^+$(Fig. 3B. 30).

**Entry 9h (Table 3B. 5)**

**Molecular formula**: $C_{15}H_{11}F_{3}N_{2}O_{2}S$

**IR Spectrum**: $\nu_{\text{max}}$ 3253, 2240, 1600, 1512, 1348, 1153 cm$^{-1}$.

**$^1$H-NMR spectrum**: (300 MHz, CDCl$_3$):

- $\delta$ 7.72 (2 H, d, $J = 8.0$ Hz), 7.38–7.19 (3 H, m),
- 7.00 (1H, m), 5.92 (1H, d, $J = 10.0$ Hz), 5.57 (1H, d, $J = 10.0$ Hz), 2.45 (3H, s) (Fig. 3B. 31).

**$^{13}$C-NMR spectrum**: (75 MHz, CDCl$_3$)

- $\delta$ 145.0, 135.9, 130.1, 127.2, 123.0, 122.9, 118.0, 117.9, 116.1, 113.1, 113.0, 42.4, 21.9 (Fig. 3B. 32).

**ESIMS-spectrum**: $m/z$ 363 [M+Na]$^+$. 
Molecular formula : $\text{C}_{22}\text{H}_{20}\text{N}_{2}\text{O}_{3}\text{S}$

IR Spectrum : $\nu_{\text{max}}$ 3258, 2238, 1606, 1513, 1329, 1247 cm$^{-1}$.

$^1$H-NMR spectrum : (300 MHz, CDCl$_3$): $\delta$ 7.81 (2H, d, $J = 8.0$ Hz), 7.46–7.31 (9H, m), 6.98 (2H, d, $J = 8.0$ Hz), 5.41 (1H, d, $J = 10.0$ Hz), 5.17 (1H, d, $J = 10.0$ Hz), 5.05 (2H, s), 2.46 (3H, s) (Fig. 3B. 33).

$^{13}$C-NMR spectrum : (75 MHz, CDCl$_3$)
$\delta$ 158.8, 145.5, 136.1, 130.1, 128.9, 128.8, 127.3, 124.6, 115.8, 70.1, 48.0, 21.8 (Fig. 3B. 34).

ESIMS-spectrum : $m/z$ 415 [M+Na]$^+$. 

Entry 9k-(Table 3B. 5)

Molecular formula : $\text{C}_{17}\text{H}_{18}\text{N}_{2}\text{O}_{2}\text{S}$

IR Spectrum : $\nu_{\text{max}}$ 3268, 2217, 1596, 1332, 1157 cm$^{-1}$.

$^1$H-NMR spectrum : (300 MHz, CDCl$_3$):
$\delta$ 7.80 (2H, d, $J = 8.0$ Hz), 7.35 (2H, d, $J = 8.0$ Hz), 7.28 (2H, d, $J = 8.0$ Hz), 5.70 (1H, d, $J = 10.0$ Hz), 5.05 (2H, s), 2.46 (3H, s) (Fig. 3B. 33).
Hz), 7.22 (1H, dd, \( J = 8.0, 2.0 \) Hz), 7.08 (2H, br s), 5.51 (1H, d, \( J = 10.0 \) Hz), 4.89 (1H, d, \( J = 10.0 \) Hz), 2.49 (3H, s), 2.38 (3H, s), 2.31 (3H, s) (Fig. 3B. 35).

**\(^{13}\)C-NMR spectrum**: (75 MHz, CDCl\(_3\))

δ 144.5, 136.8, 136.2, 133.1, 131.6, 130.8, 129.9, 128.2, 127.3, 116.8, 46.0, 21.5, 21.0, 18.2. (Fig. 3B. 36).

**ESIMS-spectrum**: \( m/z \) 337 [M+Na]\(^+\).

**Entry 9n-(Table 3B. 5)**

![Chemical structure diagram]

**Molecular formula**: \( C_{13}H_{12}N_2O_2S_2 \)

**IR Spectrum**: \( \nu_{\text{max}} \) 3238, 2217, 1600, 1333 cm\(^{-1}\).

**\(^1\)H-NMR spectrum**: (300 MHz, CDCl\(_3\)):

δ 7.81 (2H, d, \( J = 8.0 \) Hz), 7.40–7.34 (3 H, m), 7.20 (1 H, m), 6.98 (1H, m), 5.79 (1H, d, \( J = 10.0 \) Hz), 5.65 (1H, d, \( J = 10.0 \) Hz), 2.46 (3H, s) (Fig. 3B. 37).

**\(^{13}\)C-NMR spectrum**: (75 MHz, CDCl\(_3\))

δ 145.0, 136.2, 134.9, 130.2, 130.0, 128.2, 128.0, 127.3, 127.2, 126.4, 115.8, 43.9, 21.5
ESIMS-spectrum : $m/z$ 315 $[\text{M+Na}]^\text{+}$.

**Entry 9p-(Table 3B. 5)**

![Molecule Structure](Fig. 3B. 38).

Molecular formula : $\text{C}_{12}\text{H}_{16}\text{N}_{2}\text{O}_{2}\text{S}$

IR Spectrum : $\nu_{\text{max}}$ 3282, 2242, 1597, 1424, 1334, 1160 cm$^{-1}$.

$^1\text{H}-\text{NMR}$ spectrum : (300 MHz, CDCl$_3$):

$\delta$ 7.80 (2H, d, $J = 8.0$ Hz), 7.35 (2H, d, $J = 8.0$ Hz), 5.69 (1H, br s), 4.21 (1H, q, $J = 7.0$ Hz), 2.45 (3H, s), 1.81–1.72 (2H, m), 1.52–1.40 (2H, m), 0.92 (3H, t, $J = 7.0$ Hz) (Fig. 3B. 39).

$^{13}\text{C}-\text{NMR}$ spectrum : (75 MHz, CDCl$_3$)

$\delta$ 144.5, 136.0, 129.9, 127.0, 117.6, 44.0, 35.8, 21.7, 18.4, 13.0 (Fig. 3B. 40).

ESIMS-spectrum : $m/z$ 275 $[\text{M+Na}]^\text{+}$.