RING-SUBSTITUTION, ENLARGEMENT, AND CONTRACTION BY
BASE-INDUCED REARRANGEMENTS OF N-HETEROCYCLIC
AMMONIUM SALTS

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Abstract – An overview of the utility of base-induced Stevens, Sommelet–Hauser, and related sigmatropic rearrangements of N-heterocyclic ammonium salts into various types of N-heterocycles reported after 1970 will be described. The synthetic transformations are classified as N-heterocyclic ring-substitution, ring-enlargement, and ring-contraction.

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1. INTRODUCTION

1-1. Definitions

Ammonium ylide (R₃N⁺C⁻R₂) rearrangements, for example, [1,2] Stevens,¹ [2,3] sigmatropic (Stevens),² and Sommelet–Hauser³–⁵ (S–H) rearrangements are useful synthetic transformations because they convert a readily accessible C–N bond into a new C–C bond under mild and simple conditions to produce various types of nitrogen-containing compounds.⁵–⁸ As the representative synthetic application, the rearrangements of amino acid-derived ammonium ylides into unnatural amino acid analogs have been well-studied.

A [1,2] Stevens rearrangement is the [1,2] shift of an N-migrating group into a ylide carbon involving C–N bond cleavage followed by C–C bond formation to afford the corresponding α-substituted tertiary amine. A representative example is shown in Scheme 1.⁹ Based on depth studies, researchers believe that the [1,2] Stevens rearrangement mainly proceeds via a radical cleavage–recombination process. The preferred N-migrating group is benzylic, which stabilizes and generates the biradical intermediate. When a chiral N-benzylic migrating group is used, such as N-(R)-(α-methylbenzyl), as in salt (R)-1, the ylide (R)-2 generated with sodium methoxide in methanol was rearranged into product 3 in 80% yield, and the chirality was retained (>95%) at the carbon migrating center. A [1,2] rearrangement of non-benzylic migrating group is also possible; however, successful examples are limited unless the rearrangement is intramolecular.

Scheme 1. Representative example of a [1,2] Stevens rearrangement

A [2,3] sigmatropic (Stevens) rearrangement is performed using N-allylic ammonium ylides and proceeds via C–N bond cleavage and C–C bond formation at the N-allylic migrating group γ-carbon. A
A representative example is shown in Scheme 2. The rearrangement of \( N \)-crotyl ammonium ylide 5 generated from ammonium salt 4 afforded the \( \alpha \)-(but-3-en-2-yl)derivative 6 in 63\% yield. The [2,3] rearrangement mainly proceeds via a concerted pathway; however, when \( N \)-cinnamyl ammonium salt 7 was subjected to the same conditions, the generated ylide 8 provided the corresponding [2,3] rearrangement product 9 in 43\% yield and the [1,2] Stevens rearrangement product 10 in 34\% yield. This result indicates that radical cleavage–recombination process is also possible for \( N \)-allylic ammonium ylide rearrangements because the allylic moieties stabilize the biradical intermediate.

Scheme 2. Representative example of a [2,3] sigmatropic (Stevens) rearrangement

An S–H rearrangements is a [2,3] sigmatropic rearrangement with an aromatic double bond in the \( N \)-benzylic migrating group. The representative example includes transformation of benzyltrimethylammonium iodide 11 into (2-methylbenzyl)dimethylamine 14, which is depicted in Scheme 3. When treating 11 with sodium amide in liquid ammonia to generate ylide 12, a [2,3] sigmatropic rearrangement with an aromatic double bond occurred to afford the corresponding dearomatized 13. Finally, the isomerization of 13 leads to 14. This reaction resulted in enabling the conversion of a readily accessible C–N bond into a new C–C bond in an aromatic ring. This S–H rearrangement frequently competes with the [1,2] Stevens rearrangement.
Scheme 3. Representative example of an S–H rearrangement

1-2. Rearrangements of N-heterocyclic ammonium ylides

Rearrangements of N-heterocyclic ammonium ylides into other N-heterocycles are notable because the rearrangements not only facilitate N-heterocyclic ring-substitution but also ring-enlargement or ring-contraction; these transformations provide key building blocks for the synthesizing biologically active compounds, such as alkaloids. For example, the [2,3] sigmatropic rearrangement of N-allylic piperidinium ylide generated from salt 15 with a base afforded the α-substituted derivative 16 (Scheme 4, Eq. 1).\(^{11}\) However, 2-vinylpiperidinium salt 17 reacted to produce the 6-to-9 ring-enlarged 18 (Eq. 2).\(^{12}\) In another reaction, 1,2,3,6-tetrahydropyridinium salt 19 was rearranged into the 6-to-5 ring-contracted 20 (Eq. 3).\(^{13}\) The transformations depicted in Scheme 4 were successful due to the substrate ammonium salt structure design. In many cases, N-heterocyclic ammonium salts, such as 15, 17, and 19 are used as substrates; however, N-spirocyclic salts also have been employed for ring-enlarged rearrangements. For example, the [1,2] Stevens rearrangement of N-spiro ammonium salt 21 afforded a 5-to-6 ring-enlarged 22 in 41% yield (Scheme 5).\(^{14}\)

For these rearrangements, the desired ammonium ylide must be generated from the precursor.\(^{5,6,15-17}\) One of the standard methods used includes forming a base-induced ylide from a tetraalkylammonium salt; however, this method involves undesirable side reactions.\(^{7}\) When the N,N-dialkylpiperidinium salt 23 is used as a model ammonium salt (Scheme 6), the ylide 24 is generated through deprotonating the α-proton on the piperidine ring (Eq. 1). The ylide anion located on the N-heterocyclic ring is an ‘internal ylide’. However, ylide 25 is also formed under the same conditions through deprotonating the α-proton at the external N-alkyl substituent (Eq. 2). The ylide anion located outside of the N-heterocyclic ring is an ‘external ylide’. Furthermore, a Hoffmann elimination into 26 can also occur and is caused by deprotonation of the β-proton at the piperidine ring (Eq. 3).
To achieve regioselective deprotonation, an acidic proton at the $\alpha$-position of an ammonium nitrogen activated by carbonyl, benzylic, or allylic substituents is essential. For example, treatment of a model ammonium salt having a carbonyl substituent $27$ with base gives exclusively the stabilized ammonium ylide $28$ (Scheme 7).

Deprotonation of ammonium salts followed by the rearrangements of ammonium ylides is defined as the base-induced (or promoted) rearrangement of ammonium salts. The earlier works (prior to 1970) on the
rearrangements were fully summarized by Pine in Organic Reactions.\textsuperscript{2} For the purpose of this review, only the rearrangements of N-heterocyclic ammonium salts reported after 1970 will be described with the origin of each rearrangement.

Scheme 6. Possible reactions during base-induced generation of an ylide from an ammonium salt

\begin{align*}
\text{X}^- & \quad \text{base} \quad \text{internal ylide} \quad (1) \\
\text{X}^- & \quad \text{base} \quad \text{external ylide} \quad (2) \\
\text{X}^- & \quad \text{base} \quad \text{Hofmann elimination} \quad (3)
\end{align*}

Scheme 7. An example of stabilized ylide formation by regioselective deprotonation

1-3. Diastereoselective N-quaternization of N-heterocyclic tertiary amines

In base-induced rearrangements of N-heterocyclic ammonium ylides, a diastereoselective tetraalkylammonium salt preparation may be necessary to control the rearrangement pathway or the stereoselective product formation. In many cases, the pure diastereomeric salts could be obtained by diastereoselective N-quaternization of N-heterocyclic amines with alkyl electrophiles followed by fractional recrystallization of the resulting ammonium salts. In 1970, McKenna summarized stereochemistry studies on N-quaternization of N-heterocyclic amines.\textsuperscript{18} Several examples were reported thereafter; however, the results have not been summarized. In 2015, Dumbar and West reviewed diastereoselective N-quaternization of N-substituted piperidines (Table 1).\textsuperscript{19} The diastereoselectivity of N-quaternization can be partially controlled by adjacent substituents or alkylating reagents. Focusing on N-alkyl-2-methylpiperidines 29 as substrates, N-quaternization preferentially
gives the axial alkylated salts 30 over the equatorial alkylated salts 31; however, occasionally, the selectivity is turned over. The precise basis is difficult to explain; the conformational mobility of the piperidine rings may affect diastereoselective N-quaternization. In fact, N-quaternization of five- and four-membered N-heterocycles, such as N-substituted pyrrolidines or azetidines, proceeds with better to high diastereoselectivity due to less conformational mobility.

**Table 1.** Diastereoselectivity in 2-methylpiperidine N-alkylation

<table>
<thead>
<tr>
<th>R</th>
<th>R'X</th>
<th>solvent</th>
<th>% axial</th>
<th>% equatorial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Et$_3$OBF$_4$</td>
<td>CH$_2$Cl$_2$</td>
<td>62</td>
<td>38</td>
</tr>
<tr>
<td>Me</td>
<td>EtI</td>
<td>acetone</td>
<td>43–50</td>
<td>57–50</td>
</tr>
<tr>
<td>Me</td>
<td>CD$_3$I</td>
<td>acetone</td>
<td>66</td>
<td>34</td>
</tr>
<tr>
<td>Me</td>
<td>Br</td>
<td>MeCN</td>
<td>19</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>Mel</td>
<td>MeCN</td>
<td>62</td>
<td>38</td>
</tr>
</tbody>
</table>

2. RING-SUBSTITUTION

2-1. [1,2] Stevens rearrangement

The first example of ring-substitution of N-heterocycles by a base-induced [1,2] Stevens rearrangement of ammonium salts was reported by Wittig and Streib in 1953 (Scheme 8). Treatment of N-Benzyl isoindolinium salt 32 with sodium ethoxide to generate the semi-stabilized ylide 33 followed by a [1,2] rearrangement of the benzyl migrating group afforded 1-benzylated isoindolin 34 in 44% yield.

**Scheme 8.** Ring-substitution by a base-induced [1,2] Stevens rearrangement of an ammonium salt
In 1971, Mageswaran et al. examined the base-induced \([1,2]\) Stevens rearrangement of a stabilized ammonium ylide generated from N-benzyl isoquinolinium salt \(35\) and obtained 3-benzylated \(36\) in 60% yield (Scheme 9). In the ylide formation step, regioselective deprotonation at an acidic α-proton of the carbonyl minimized undesirable side reactions.

![Scheme 9. Regioselective deprotonation followed by a \([1,2]\) Stevens rearrangement](image)

This result was applied to the synthesis of α-quaternary amino acid derivatives. In 1999, Glaeske and West reported the asymmetric base-induced \([1,2]\) Stevens rearrangement of L-proline-derived ammonium salt \(38\) prepared by diastereoselective quaternization of N-benzyl-L-proline ester \(37\) with methyl iodide (Scheme 10). Diastereoselective N-methylation is controlled by the adjacent ester moiety as in \(37\). The \([1,2]\) rearrangement of the single diastereomer \(38\) proceeded with a moderate level of N-to-C chirality transmission to yield the α-benzylated proline \(39\) with a 3.3/1 enantiomeric ratio (54% ee). The lack of the stereoisomeric ratio (100% de to 54% ee) could be explained that this \([1,2]\) Stevens rearrangement proceeded via a radical cleavage–recombination mechanism.

![Scheme 10. Asymmetric base-induced \([1,2]\) Stevens rearrangement via N-to-C chirality transmission](image)

The rate of chirality transmission for this rearrangement improved under solid–liquid biphasic conditions using a halogenated solvent as the liquid phase. When the rearrangement of tert-butyl ester derivative \(40\) was performed with cesium hydroxide monohydrate in 1,2-dichloroethane, 92% ee of α-benzylated \(41\) was obtained (Scheme 11). Under these biphasic conditions, recombination of the radical pair \(43\) initially formed from the \(N\)-ylide \(42\) occurs more rapidly in a solvent cage and preferentially in a retentive
fashion (on the bottom side) to give 41 with high N-to-C chirality transmission. Recombination outside the solvent cage that decreases the % ee would be suppressed.

\[
\begin{align*}
\text{40} & \quad \text{single stereoisomer} \\
\text{42} & \quad \text{radical pair} \\
\text{43} & \quad \text{in solvent cage} \\
\end{align*}
\]

**Scheme 11.** Asymmetric [1,2] Stevens rearrangement under solid–liquid biphasic conditions

Although not a base-induced rearrangement, the author would like to introduce a closely related work developed by Palombi (Scheme 12). The rearrangement described in Scheme 10 was applied to an electrochemically promoted version. Ylide generation by electrolysis of 38 in propionitrile at 45 °C followed by a [1,2] Stevens rearrangement yielded the α-benzylated 39 in 92% yield with 84% ee.

\[
\begin{align*}
\text{38} & \quad \text{single stereoisomer} \\
\text{39} & \quad \text{92%, 84% ee} \\
\end{align*}
\]

**Scheme 12.** Electrochemically promoted asymmetric [1,2] Stevens rearrangement

The rearrangements of six- and four-membered cyclic amino acid-derived ammonium salts were also reported (Scheme 13). N-Benzyllic pipercolinic and azetidinic acid-derived ammonium salts 44 and 46 were rearranged into the corresponding α-substituted 45 and 47 in moderate yields. Pacheco et al. employed the ring-substitution for the synthesis of alkaloid derivatives (Scheme 14). Deprotonation of α-cyano ammonium salt 48 with potassium bis(trimethylsilyl)amide followed by a [1,2] rearrangement afforded a solution of α-aminonitrile 49. The nitrile substituent, as in 49, was eliminated in situ by treatment with sodium cyanoborohydride to produce (±)-laudanosine (50).
Scheme 13. Rearrangement of six- and four-membered cyclic amino acid-derived ammonium salts

Scheme 14. Synthesis of (±)-laudanosine (50)

Valpuesta et al. succeeded with a regioselective deprotonation of ammonium salt 51 without an efficient electron-withdrawing group (EWG) followed by a [1,2] Stevens rearrangement (Scheme 15).28 Their group tested various bases and solvents and found that the use of dimsylsodium in DMSO afforded the desired polycyclic 52 in 45% yield.

Scheme 15. Regioselective deprotonation with dimsylsodium followed by a [1,2] Stevens rearrangement
This results was applied to a total synthesis of an alkaloid natural product (Scheme 16).\textsuperscript{29} The reactions of diastereomically pure berbinium salt \textit{trans}-53 stereoselectively yielded 8-(arylmethyl)derivative \textit{trans}-54. Hydrogenation of \textit{trans}-54 provided (\textpm)-8-(arylmethyl)berbine (55), which has been isolated from the aerial part of \textit{Aristolochia constria}. Later, their group reported a regioselective deprotonation of a dibenzylic methine proton, as in salts 56, followed by a rearrangement to give 1,1-disubstituted isoquinolines 57 in good yields (Scheme 17).\textsuperscript{30}

Scheme 16. Synthesis of (\textpm)-8-(arylmethyl)berbine (55)

Scheme 17. Deprotonation of a dibenzylic methine proton followed by a rearrangement

\textbf{2-2. \textsuperscript{[2,3]} Sigmatropic (Stevens) rearrangement}

When allyl (CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}) or methallyl (CH\textsubscript{2}C(Me)\textsubscript{2}CH\textsubscript{2}) substituents are used as a migrating group, the exact pathway of \textsuperscript{[2,3]} or [1,2] cannot be identified from the products; however, the rearrangements are summarized in this section.

As already mentioned in introduction, the ring-substitution of \textit{N}-heterocycles by base-induced \textsuperscript{[2,3]} rearrangement were employed by Ollis’s group in 1971 using amino ketone-derived ammonium salts 15
as the substrate (Scheme 18). $^{11}$ α-Substituted 16 was obtained in 88% yield as a single diastereomer.

\[ \begin{array}{c}
\text{Scheme 18. Ring-substitution by a [2,3] rearrangement of an amino ketone-derived ammonium salt}
\end{array} \]

Their group investigated the rearrangement of N-cinnamyl-1-azabicyclo[3.3.1]nonanum salt 58 to clarify the stereochemical mechanism (Scheme 19). The [2,3] rearrangement proceeded on the sterically less hindered face of the ylide 59 through an exo transition state (exo-TS) to afford the diastereomerically pure rearranged product 60.

\[ \begin{array}{c}
\text{Scheme 19. Ring-substitution by a [2,3] rearrangement of 1-azabicyclo[3.3.1]nonanum salt}
\end{array} \]

Later, the [2,3] rearrangement of N-propargyl ammonium ylides was also examined to expand the scope and highlight its limitations (Scheme 20). $^{31}$ On treatment of N-3-phenylpropargyl salt 61 with sodium hydride in DMSO provided the α-allenyl derivative 62 in 86% yield. In contrast, the reaction of 1-azabicyclo[3.3.1]nonanum salt 63 under similar conditions afforded the furan derivative 65 in 99% yield via formation of the α-allenyl derivative 64 followed by adding an enolate O-anion generated by excess base to a central allenyl carbon. The product 62 was unreacted under the same conditions at room temperature because an enolate O-anion derived from aromatic ketone 62 is less nucleophilic than aliphatic ketone 64.

The asymmetric [2,3] rearrangement via N-to-C chirality transmission was demonstrated by Glaeske and West as well as the [1,2] rearrangement described in Scheme 10. $^{22}$ The concerted [2,3] rearrangement from the single diastereomer of chiral cyclic amino acid-derived ammonium salts 66 and 68 proceeded with excellent levels of N-to-C chirality transmission (Scheme 21). The diastereomeric ratios of 66 or
were converted into the enantiomeric ratios of rearrangement products 67 or 69, respectively. This method provides efficient access to the optically active \(\alpha\)-quaternary amino acid derivatives.

**Scheme 20.** Ring-substitution through a [2,3] rearrangement of \(N\)-propargyl ammonium salts

Arboré et al. reported a similar rearrangement without isolation of the ammonium salt derived from \(N\)-benzyl \(L\)-proline ester 37 (Scheme 22).\(^{32}\) Diastereoselective quaternization of 37 with allyl iodide followed by generation of the ylide 70 in a one-pot synthetic approach gave \(\alpha\)-allylated proline ester 71 in 48% yield with 86% ee.

Smith and Bentley applied this protocol for the diastereoselective synthesis of 5-disubstituted proline analog 73 (Scheme 23).\(^{33}\) One-pot quaternization and [2,3] rearrangement of 5-substituted proline ester...
72 (cis/trans = 3/1) afforded α-allylated 73 in 42% yield (cis/trans = 4/1). The product 73 was successfully converted into diazabicyclo[3.2.1]octane 74, which acts as a key building block for alkaloid synthesis.

Scheme 22. One-pot diastereoselective quaternization and asymmetric [2,3] rearrangement

Scheme 23. Diastereoselective synthesis of a trisubstituted proline analog

In the base-induced [2,3] rearrangement of 75, the use of [BMIm][PF₆] (1-butyl-3-methylimidazolium hexafluorophosphate) as an additive improved the yields of the rearrangement product 71, as proposed by Duran-Lara et al. (Table 2). This effect was observed under various reaction conditions.

Table 2. Effect of [BMIm][PF₆] as an additive in base-induced [2,3] rearrangements

<table>
<thead>
<tr>
<th>conditions</th>
<th>with [BMIm][PF₆]</th>
<th>without [BMIm][PF₆]</th>
</tr>
</thead>
<tbody>
<tr>
<td>K₂CO₃, DMF, rt</td>
<td>50%, 85% ee</td>
<td>40%, 85% ee</td>
</tr>
<tr>
<td>tBuOK, DMF, rt</td>
<td>50%, 85% ee</td>
<td>40%, 85% ee</td>
</tr>
<tr>
<td>DBU, MeCN, 0 °C</td>
<td>80%, 65% ee</td>
<td>55%, 50% ee</td>
</tr>
</tbody>
</table>

The asymmetric [2,3] rearrangement involving N-to-C chirality transmission was applied to other cyclic amino acid-derived ammonium ylides. Quaternization of (R)-5-phenylmorpholin-2-one 76 with methyl
tosylate gave the salt 77 as a trans/cis = 2/1 mixture of diastereomers (Scheme 24). The [2,3] rearrangement of diastereomixture salts 77 with potassium tert-butoxide in THF–DME at −78 °C afforded 3-allylated (3R)-78 and (3S)-78 in 44% combined yield with 3R/3S = 7/1 ratio. During this rearrangement, kinetic resolution occurs to improve the diastereomeric ratio from 2/1 to 7/1.

Couty’s group demonstrated the successive diastereoselective transformations from substituted azetidine derivatives (Scheme 25). Quaternization of N-allyl azetidinic nitrile 79 with methyl triflate proceeded with high diastereoselectivity to yield the salt 80a as a single isomer. The [2,3] rearrangements of 80a gave α-allylated 81a in 93% yield with 96% de via N-to-C chirality transmission. When N-methyl azetidinic nitriles 82 and allyl triflate were used as the starting materials, the other diastereomers 80b and 81b were obtained.

Scheme 24. Kinetic resolution via a [2,3] rearrangement

Scheme 25. Successive diastereoselective quaternization and [2,3] rearrangements
An example of bicyclic ring-substitution through a base-induced [2,3] rearrangement was reported by Hanessian et al. (Scheme 26).\textsuperscript{12} Treating the N-allylic-1-azabicyclo[3.3.1]nonanium salts 83 with potassium tert-butoxide generated ylide 84 or 85 as a [2,3] rearrangement intermediate. The rearrangement proceeded preferentially from less sterically hindered site and face of the ylide 84 via an endo transition state (endo-TS) to give α-substituted 86 in moderate yields.

![Scheme 26. Bicyclic ring-substitution through a base-induced [2,3] rearrangement](image)

The synthesis of alkaloid natural products or their key building blocks has been investigated by Li and Wang in 2003 (Scheme 27).\textsuperscript{18} Quaternization of 1,2,3,4-tetrahydroisoquinoline derivative 87 with allyl bromide followed by [2,3] rearrangement of the salt 88 in one-pot produced 1-allylated 89. The product 89 was successfully converted into cephalotaxine (90), which is the parent member of cephalotaxus alkaloids.

In 2009, a formal synthesis of cephalotaxine (90) via the [2,3] rearrangement was reported by Sun et al. (Scheme 28).\textsuperscript{39} One-pot quaternization and ylide generation from N-substituted proline ester 91 followed by a [2,3] rearrangement of the ylide 92 yielded the α-allylproline ester derivative 93. Further synthetic transformation produced spirocyclopentenone 94, which is a known intermediate leading to 90.
Scheme 27. Synthesis of cephalotaxine (90)

Scheme 28. A formal synthesis of cephalotaxine (90)

2-3. Sommelet–Hauser rearrangement

The first example of ring-substitution of N-heterocycles by base-induced S–H rearrangement was reported by Wittig and Streib in 1953 (Scheme 29). Treatment of N-benzylic-1-isoindolinium salts 32 or 96 with sodium amide in liquid ammonia or phenyllithium in diethyl ether gave 1-(o-tolylic)isoindolines 95 or 97 in acceptable yields without formation of competitive [1,2] Stevens rearrangement products.
In 2006, Hanessian et al. reported the rearrangement of *N*-benzyl-1-azabicyclo[3.3.1]nonanium salt 98 into *o*-tolyl substituted 99 (Scheme 30). Their group examined additional reactions to investigate the substituent effect on the migrating aromatic ring; however, the maximum yield of the S–H rearrangement product was 50%.

Although only one example, the successful demonstration of ring-substitution by base-induced asymmetric S–H rearrangement was reported in 2007 (Scheme 31). On treatment of diastereomerically pure *L*-proline ester-derived ammonium salt 100 with potassium *tert*-butoxide in THF at −40 °C, S–H rearrangement proceeded exclusively with a perfect level of N-to-C chirality transmission to give *α*-arylated 101 in 96% yield with >99% ee. An EWG, such as *para*-tert-butoxycarbonyl, on the aromatic ring improved the yield of S–H rearrangement product.
Similarly, a reaction of \( N \)-benzylpipecolinic acid-derived ammonium salt 102 (racemic, 91/9 diastereomeric mixture) also gave the S–H rearrangement product 103 (Scheme 32). An EWG on the \( N \)-benzylic aromatic ring and a lower reaction temperature (–40 °C) were necessary for sufficient yield (76%) of 103. These conditions minimized competitive [1,2] Stevens rearrangements that would lead to \( \alpha \)-benzylated 104.

Although the cause was not identified, on treatment of diastereomerically pure \( N \)-benzylazetidine-2-carboxylic acid ester-derived ammonium salt 105 with potassium tert-butoxide, a S–H rearrangement occurred exclusively to afford 106 as the sole product, even at 0 °C, without an EWG on the aromatic ring (Scheme 33).

Scheme 32. Ring-substitution of pipercolinic acid ester-derived ammonium salt

\[
\begin{align*}
\text{102} & \quad \text{91/9 dr} \\
\text{103} & \quad 23\% \\
\text{104} & \quad 54\% \\
\end{align*}
\]

Scheme 33. Ring-substitution of azetidinic acid derivative by a base-induced S–H rearrangement

3. RING-ENLARGEMENT

3-1. [1,2] Stevens rearrangement

The first example of ring-enlargement of \( N \)-heterocycles by base-induced [1,2] Stevens rearrangement was reported by Wittig et al. in 1951 (Scheme 34). As already mentioned in Scheme 5, when \( N \)-spiro ammonium salt 21 was treated with phenyllithium in diethyl ether, a 5-to-6 ring-enlargement by a [1,2] shift gave [5,6]-fused \( N \)-heterocycle 22 in 41% yield. Similarly, polycyclic ammonium salt 107 rearranged into dibenzo-9-azabicyclo[3.3.1]nonane derivative 109 in 35% yield via the formation of the internal ylide 108.
Scheme 34. Ring-enlargement of N-heterocycles by a base-induced [1,2] Stevens rearrangement

Chicharro et al. examined the ring-enlarged rearrangement of N-spiro ammonium salt 110 via the formation of the stabilized ammonium ylide 111 to afford a 6-to-7 ring-enlarged polycyclic quinoxaline-2-one 112 in 96% yield (Scheme 35). 41

Scheme 35. 6-to-7 Ring-enlarged [1,2] Stevens rearrangement of a stabilized internal ylide

Ring-enlargement via the formation of an external ylide 114 were reported by Gimranova et al. (Scheme 36). 42 Treatment of 1,2,3,4-tetrahydroisoquinolinium salts 113 with sodium hydride in boiling 1,4-dioxane gave benzo-fused azepane-2-carboxylic acid esters 115 in moderate yields.
Scheme 36. 6-to-7 Ring-enlarged [1,2] Stevens rearrangement of external ylides

Valpuesta et al. applied this protocol to diastereoselective transformations (Scheme 37). Diastereoselective quaternization of 1-phenylisoindolin derivative 116 controlled by the adjacent 1-phenyl substituent produced 1-phenyl-1,2,3,4-tetrahydroisoquinolinium salt 117 as a single stereoisomer. The rearrangement of 117 afforded ring-enlarged trans-118 in good yields.

Scheme 37. Successive diastereoselective quaternization followed by a 6-to-7 ring-enlargement

Their group investigated the reaction using various types of 1-substituted-1,2,3,4-tetrahydroisoquinolinium salts to clarify its scope and limitations (Scheme 38). As an example of an asymmetric reaction, an enantiomerically pure salt 119 prepared from chiral tertiary amine rearranged into optically active azepanyl derivative 120 in 85% yield. The enantiopurity of the ring-enlarged product 120 was not determined.
Kowalkowska and Jończyk examined a similar transformation using five-membered N-heterocyclic ammonium salts (Scheme 39)\textsuperscript{44}. A cis/trans mixture of N-cyanomethyl-2-arylpyrrolidinium salts 121 were transferred into the 5-to-6 ring-enlarged piperidinyl derivatives 122 as a mixture of cis/trans diastereomers.

The synthesis of polycyclic alkaloids via ring-enlarged [1,2] Stevens rearrangements were demonstrated by Pacheco et al. (Scheme 40)\textsuperscript{27}. The rearrangement of N-spiro-α-cyanopiperidinium salt 123 via the formation of nitrile ylide 124 gave the 5-to-6 ring-enlarged 125. One-pot reductive elimination of the nitrile substituent, as in 125, afforded (±)-7-methoxycryptopleurine (126).

Couty’s group examined the ring-enlargement of four-membered N-heterocyclic ammonium ylides. Deprotonation of the sterically less hindered benzylic methylene proton, as in salt 127, to generate the external ylide 128 followed by a [1,2] shift afforded the 4-to-5 ring-enlarged 2,3-diphenylpyrrolidines 129a and 129b in 48% yields (Scheme 41)\textsuperscript{26}. Similarly, deprotonation of a diphenylmethine proton, as in salt 130, to generate ylide 131 followed by a [1,2] shift gave the ring-enlarged 132 in 25% yield. The ring-enlarged base-induced [1,2] Stevens rearrangement occurs not only for the benzylic migrating group but also the alkyl migrating group.
An allylic migrating group also undergoes a ring-enlarged [1,2] Stevens rearrangement depending on the structure of the ammonium ylides or the electronic effect of the substituents. 2,5-Dihydro-1H-pyrrolidinium ylide 134, which has an internal N-allylic migrating group, was generated from the salt 133 (Scheme 42). The C–N bond cleavage of 134 to form the biradical intermediate 135 followed by recombination between the α-carbonyl radical and the allylic radical afforded the 5-to-6 ring-enlarged 136. The [2,3] rearrangement from 134 between the external ylide anion and the internal
N-allylic double bond (ring-contraction) did not proceed because of strain in the four-membered heterocycle.

![Chemical structure](image1)

**Scheme 42.** 5-to-6 Ring-enlarged [1,2] Stevens rearrangement involving an internal N-allylic group

Soldatova et al. reported similar ring-enlarged [1,2] Stevens rearrangements involving an internal N-allylic migrating group (Scheme 43).\(^{45}\) A reaction of 4-aryl-1,2,3,6-tetrahydropyridinium salt 137 proceeded via the formation of ylide 138 followed by a [1,2] shift to give 6-to-7 ring-enlarged 139. In this reaction, the [2,3] rearrangement toward the internal double bond was accompanied. An electron-deficient aryl group attached at the 4-position preferred the ring-enlarged [1,2] Stevens rearrangement. The details are described in section 4 (Table 3).

![Chemical structure](image2)

**Scheme 43.** 6-to-7 Ring-enlarged [1,2] Stevens rearrangement involving an internal N-allylic group

Rearrangement of 1,3-oxazolidinium salts 140 via forming external ylides 141 was followed by the biradical intermediate 142, which afforded 5-to-6 ring-enlarged 143 and 144 through [1,2] shifts with chirality retained at the 2-position carbon migrating center, as in 140 (Scheme 44).\(^{46}\) The corresponding [2,3] rearrangement products derived through C–C bond formation between the ylide anion and external double bond, as in 141, were not obtained.

Couty’s group reported a similar result with a sufficient explanation using azetidinium salt as the
substrate (Scheme 45). When a diastereomerically pure N-benzyl-2-vinylazetidinium salt 145 was treated with KHMDS, the 4-to-5 ring-enlarged [1,2] rearrangement product 148 was obtained in 83% yield via the formation of the biradical intermediate 147. The [2,3] rearrangement between the external ylide anion and the external N-allylic double bond, as in 146, did not proceed because the two reacting centers adopt a trans-relationship and did not overlap for the [2,3] rearrangement.

Scheme 44. 5-to-6 ring-enlarged [1,2] Stevens rearrangement involving an external double bond

Scheme 45. 4-to-5 Ring-enlarged [1,2] Stevens rearrangement involving an external N-allylic group

3-2. [2,3] Sigmatropic (Stevens) rearrangement

The ring-enlarged [2,3] rearrangement of N-heterocyclic ammonium ylides has been achieved by a C–C bond formation between an external ammonium ylide anion and an external allylic double bond, which enables the reaction of N-heterocycles with three carbons. Earlier studies on this transformation were investigated by Vedejs et al. in 1978 (Scheme 46). Diastereoselective quaternization of
2-vinylpiperidine 149 followed by deprotonation of piperidinium salt 17 generated ylide 150. The cisoid ylide 150 underwent a 6-to-9 ring-enlarged [2,3] rearrangement to produce the nine-membered N-heterocycle 18 in 90% yield as a single isomer. Their group also examined a similar reaction of five-membered N-heterocyclic ammonium salts prepared from tertiary amine 151 (Scheme 47). The rearrangement of 2-vinylpyrrolidinium salts 152a or 152b yielded the 5-to-8 ring-enlarged cis-153 as the only isolatable product (48% yield from 152a, 28% from 152b). As an unstable product, trans-153 was observed by $^1$H NMR analysis of the crude product.

Scheme 46. 6-to-9 Ring-enlargement of N-heterocycle by a base-induced [2,3] rearrangement

Scheme 47. 5-to-8 Ring-enlarged base-induced [2,3] rearrangement
Couty’s group reported a 4-to-7 ring-enlargement (Scheme 48). Deprotonation of diastereomerically pure 2-vinylazetidinium salt 154 followed by a [2,3] rearrangement of the ylide 155 produced azepanyl derivative 156 in 93% yield. A cis-relationship between the external ylide anion and the external alkenyl substituent, as in 155, is favored for this transformation because the two reacting centers can overlap for the [2,3] rearrangement.

Scheme 48. 4-to-7 Ring-enlarged [2,3] rearrangement of azetidinic ammonium salt

3-3. [1,4] Sigmatropic rearrangement

In the ammonium ylide rearrangement, a [1,4] rearrangement is one possible pathway; however, previous examples and synthetic applications have been limited. Recently, Pacheco and Opatz successfully demonstrated the first example of a 6-to-9 ring-enlarged base-induced [1,4] rearrangement of N-cyano(phenyl)methyl isoquinolinium salt 157 into dibenzo[c,f]azonine 161 (Scheme 49).

Scheme 49. Ring-enlargement of an N-heterocycle by a base-induced [1,4] sigmatropic rearrangement
They proposed that the reaction proceeds as follows: (i) ammonium ylide 158 formation, (ii) isomerization to the zwitterionic intermediate 159, (iii) ring-enlarged concerted [1,4] rearrangement into the dearomatized 160 involving a six-electron aromatic transition state with suprafacial–suprafacial characteristics, and (iv) aromatization to 161. Finally, hydride reduction of the product 161 yielded decyanated dibenzo[c,f]azonine 162. The [1,2] Stevens rearrangement from 158 did not proceed because of strong stabilization by an electron-withdrawing cyano group. In addition, the substituent would aid in forming dearomatized 159.

3-4. Sommelet–Hauser rearrangement

The first example of a ring-enlarged S–H rearrangement was reported by Lednicer and Hauser in 1957 (Scheme 50). Treatment of 2-phenylpiperidinium salt 163 with sodium amide in liquid ammonia gave a nine-membered N-heterocycle 166 via the formation of unstabilized ammonium ylide 164 followed by dearomatized 165. However, further studies on this transformation have not been advanced because of the difficulty of regioselective deprotonation to generate the unstabilized ammonium ylide.

Although not a base-induced rearrangement, the author would like to introduce a closely related work reported by Sato and Shirai’s group. In 1979, Vedejs et al. developed the fluoride-induced regioselective formation of an ammonium ylide from N-silylmethylammonium salts. This method enables the formation of the desired ammonium ylide at the silylated carbon without base. Nakano and Sato focused on this method and developed the fluoride-induced S–H rearrangement and reported ring-enlargement of N-heterocycles (Scheme 51). For example, treatment of 2-phenyl-N-silylmethylpiperidinium salt 167 with cesium fluoride in DMF generated ylide 164. Subsequent S–H rearrangement afforded the dearomatized 165 in 74% yield. Aromatization to benzo-fused 166 proceeded by treatment with potassium hydroxide in ethanol. Their further investigation on this fluoride-induced S–H rearrangement produced various types of benzo-fused N-heterocycles.
Scheme 51. Ring-enlargement of an N-heterocycle by a fluoride-induced S–H rearrangement

4. RING-CONTRACTION

The ring-contractive rearrangement of N-heterocyclic ammonium ylides have been achieved by a C–C bond formation between an external ylide anion and an internal allylic migrating group. To the best of my knowledge, the first observation of a ring-contraction by base-induced rearrangements of ammonium salts was reported by Maeda and Ohsugi in 1968 (Scheme 52). A reaction of N-benzyl-1,2,3,6-tetrahydropyridinium salt 168 with phenyllithium in diethyl ether generated ylide 169 and that produced various rearrangement products. As a minor product, the 6-to-5 ring-contracted spiro-pyrrolidine 170 derived by a [2,3] rearrangement was isolated in 1.5% yield.

Scheme 52. The first observation of a ring-contractive ammonium ylide rearrangement

In 1973, Ollis’s group demonstrated a successful example of a 6-to-5 ring-contraction from N-benzoylethyl tetrahydropyridinium ylide 171 prepared from salt 19 (Scheme 53). The 2,3-disubstituted pyrrolidinyl derivative 20 was obtained in 90% yield via a [2,3] rearrangement. Sweeney’s group applied this method to the synthesis of 3-substituted proline ester 173 from salt 172 (Scheme 54). The use of sodium hydride in DME minimized the potential for a competing Hofmann elimination to lead to diene 174. The same reaction was performed in sodium methoxide in methanol, and the formation of the undesiread 174 product proceeded exclusively. Later, their group attempted an asymmetric version of this rearrangement using chiral auxiliaries, as in the N-alkoxycarbonylmethyl substituent; however, the reaction resulted in almost no stereocontrol.
Scheme 53. 6-to-5 Ring-contraction of an N-heterocycle by a [2,3] rearrangement

Scheme 54. Effects of base and solvent in a 6-to-5 ring-contractive [2,3] rearrangement

Notably, α-arylproline ester derivatives 178 could be prepared by this protocol (Scheme 55). Quaternization of N-methyl-1,2,3,6-tetrahydropyridine 175 with α-bromoacetate 176 followed by a ring-contractive base-induced [2,3] rearrangement of the resulting salts 177 produced 2-aryl-3-vinylproline esters 178 as the main product.

Scheme 55. Synthesis of 2-aryl-3-vinylproline esters by a 6-to-5 ring-contraction

Soldatova et al. studied the substituent effect in ring-contractive [2,3] rearrangements. A reaction of 4-arylpiperidinium salts 137 afforded the ring-contracted 179 and 180 or the ring-enlarged 139 (Table 3). As already mentioned in section 3-1 (Scheme 43), when an electron-deficient aryl group such as
p-bromophenyl was attached at the 4-position (137b), a cooperative ring-enlarged [1,2] Stevens rearrangement proceeded to afford 139.

Table 3. Substituents effects for ring-enlargement and contraction reactions

<table>
<thead>
<tr>
<th>Substituents</th>
<th>Ring-enlargement</th>
<th>Ring-contraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>R = OEt, Ar = Ph, X = Cl (a)</td>
<td>31%</td>
<td>8%</td>
</tr>
<tr>
<td>R = OEt, Ar = p-Br-C₆H₄, X = Cl (b)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>R = OEt, Ar = p-tolyl, X = Cl (c)</td>
<td>58%</td>
<td>–</td>
</tr>
<tr>
<td>R = Ph, Ar = Ph, X = Br (d)</td>
<td>18%</td>
<td>18%</td>
</tr>
<tr>
<td>R = Ph, Ar = p-tolyl, X = Br (e)</td>
<td>9%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Additionally, Neeson and Stevenson demonstrated a 7-to-6 ring-contraction by a [2,3] rearrangement (Scheme 56). Treatment of azepinium salt 181 with LDA to generate ylide 182 followed by a [2,3] Stevens rearrangement afforded substituted pipecolinic acid analogs 183.

Scheme 56. 7-to-6 Ring-contraction of N-heterocycles by a [2,3] rearrangement

5. RING SYSTEM TRANSFORMATION OF BICYCLIC COMPOUNDS

Ammonium ylides derived from azabicyclic compounds enable the transformation of ring systems by simultaneous ring-enlargement/contraction. In 2000, Liou and Cheng applied this protocol to the total synthesis of (±)-desoxycodeine-D (186) (Scheme 57). Quaternization of tertiary amine 184 followed by a base-induced [1,2] Stevens rearrangement of azabicyclic ammonium salt 185 provided the desired 186 in 83% yield.
In addition, Hanessian et al. reported a similar transformation in 2001. A reaction of 1-azabicyclo[3.3.1]nonanium salt 187 proceeded via the formation of ylide 188 to afford 2-azabicyclo[3.2.2]nonane derivative 189 in 85% yield (Scheme 58)."
rearrangements, or Lewis acid-mediated rearrangements of tertiary amines. New synthetic transformations into \(N\)-heterocycles by these rearrangements will be demonstrated in the future.

**REFERENCES**


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