INTRODUCTION OF AN N1 UNIT TO MONOENES OR 1,6-DIENES USING CHLORAMINE-T-SILVER NITRATE: A NEW ROUTE TO AZIRIDINES OR BICYCLIC PYRROLIDINES

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Abstract - Aziridine derivatives are synthesized from a variety of olefins using commercially available Chloramine-T as a nitrogen source in the presence of AgNO3. The method is applicable to a tandem cyclization of 1,6-dienes accompanied by an N1 unit incorporation to afford bicyclic pyrrolidine derivatives.

Nitrogen-containing heterocycles, such as aziridines,1 pyrrolidines,2 and related compounds frequently confer potent and diverse biological activities as substructures of natural products. Thus, their syntheses have attracted considerable attention over the years.1,3 An N1 unit introduction to organic molecules is one of the effective routes for producing such heterocycles.1,3,4 Commercially available Chloramine-T (CT) is known not only as a versatile oxidizing reagent but also as a nitrogen source in organic synthesis.5
We, and other groups, have previously reported on several methods for the construction of nitrogen-containing heterocycles utilizing CT as an N1 unit. To further extend this strategy, AgNO₃, a potent reagent for capture of halide ions, was applied to the synthesis of aziridines and bicyclic pyrrolidines involving the generation of a nitrene species from CT. During the course of our studies in this area, Rai et al. reported on the aziridination of olefins using CT in the presence of AgNO₃ in THF, in which the substrates were restricted to styrene, acrylonitrile, and ethyl acrylate. Although we investigated the same reaction, no reproducibility was observed (vide infra). Here, we report on the aziridination of olefins utilizing CT as an N1 unit in the presence of AgNO₃, and on the finding that this system is applicable to the synthesis of bicyclic pyrrolidines from 1,6-dienes via a tandem cyclization (Scheme 1).

When styrene (1.5 mmol) was treated with CT (0.5 mmol) and AgNO₃ (0.5 mmol) in CH₂Cl₂ (2.0 mL) at room temperature for 3 h, N-(p-toluenesulfonyl)-2-phenylaziridine (2a) was obtained in 70% yield (Scheme 2). Since a similar aziridination was reported by Rai’s group, as mentioned above, during the course of our research, we reinvestigated the aziridination of styrene using their method. However, the corresponding aziridine was not produced at all. The result well agreed with our preliminary experiment showing that the aziridination did not proceed when THF was used as a solvent, instead of CH₂Cl₂ or

![Scheme 1. Generation of a nitrene species from Chloramine-T and its application to the synthesis of aziridines and pyrrolidines](image-url)
benzene.

\[
\begin{align*}
\text{Ph} & \quad + \quad \text{Cl} \quad \text{N-Ts} \\
\text{1a (1.5 mmol)} & \quad \text{Na} \quad \text{(0.5 mmol)} \quad \text{AgNO}_3 \quad \text{(0.5 mmol)} \quad \text{CH}_2\text{Cl}_2, \text{rt}, \text{3 h} \\
\text{2a 70%}
\end{align*}
\]

**Scheme 2.** Aziridination of styrene using CT and AgNO₃

The aziridination of a variety of olefins other than styrene was also successful using the CT\[\text{[]AgNO}_3\] system (Table 1). *trans*-\[\text{[]}-\text{Methylstyrene was converted to the corresponding aziridine in 59% yield under the same conditions as were used for the reaction of styrene (method A; run 1). When the reaction was carried out with two equivalents of both CT and AgNO₃ in benzene at 60 °C for 3 h (method B), the

### Table 1. Aziridination of olefins using Chloramine-T and AgNO₃

<table>
<thead>
<tr>
<th>run</th>
<th>substrate</th>
<th>method</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>(cis/trans)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph-Me</td>
<td>A</td>
<td>3</td>
<td>59</td>
<td>(14 / 86)</td>
</tr>
<tr>
<td>2</td>
<td>Ph-Me</td>
<td>B</td>
<td>3</td>
<td>92</td>
<td>(6 / 94)</td>
</tr>
<tr>
<td>3</td>
<td>Ph-Me</td>
<td>B</td>
<td>3</td>
<td>89</td>
<td>(7 / 93)</td>
</tr>
<tr>
<td>4</td>
<td>Ph-Me</td>
<td>B</td>
<td>8</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(n-C_5H_{11})-Me</td>
<td>B</td>
<td>14</td>
<td>43</td>
<td>(38 / 62)</td>
</tr>
<tr>
<td>6</td>
<td>(n-C_5H_{11})-Me</td>
<td>B</td>
<td>14</td>
<td>53</td>
<td>(43 / 57)</td>
</tr>
<tr>
<td>7</td>
<td>Ph-CO-OMe</td>
<td>Aᵇ</td>
<td>6</td>
<td>54</td>
<td>(0 / 100)</td>
</tr>
<tr>
<td>8</td>
<td>Ph-CO-OPh</td>
<td>A</td>
<td>5</td>
<td>47</td>
<td>(0 / 100)</td>
</tr>
</tbody>
</table>

\(a\) Method A: olefin (1.5 mmol), CT (0.5 mmol), AgNO₃ (0.5 mmol), CH₂Cl₂ (2.0 mL), rt, under Ar. Method B: olefin (0.5 mmol), CT (1.0 mmol), AgNO₃ (1.0 mmol), benzene (5.0 mL), 60 °C, under Ar. \(b\) Solvent: benzene (2.0 mL).
yield was improved to 92% with high diastereoselectivity (cis/trans = 6/94) (run 2). Methylstyrene was also aziridinated in excellent yield to afford the predominantly trans-isomer (run 3). cis-1,2-Dihydronaphthalene and aliphatic olefins, such as trans- and cis-2-octenes, could be converted to the corresponding aziridines in moderate yields (runs 4-6). Although our alternative methods of aziridination catalyzed by CuCl or I are not suitable for the synthesis of aziridines from electron-deficient olefins, the present system permits the aziridination of methyl cinnamate and trans-chalcone with the conservation of the stereochemistry of the starting olefins (runs 7 and 8).

In order to clarify the most likely reaction pathway for this reaction, the following experiments were carried out (Scheme 3). When three equivalents of 1,4-dioxane were treated with CT and AgNO3 in CH2Cl2 at room temperature for 24 h, C-H insertion of an NTs unit to the oxygen of 1,4-dioxane proceeded to provide 3 in 34% yield. The aziridination of methyl cinnamate did not take place when the argon atmosphere was changed to oxygen. In addition, from the results of stereochemistry of the reactions as shown Table 1 (runs 1-3, 5, and 6), it is likely that the reactions proceed via a stepwise cyclization. These experimental facts suggest that the present reaction might involve a nitrogen radical species (a triplet state nitrene).

**Scheme 3.** Experiments designed to identify the reaction intermediates.
This prediction prompted us to propose the following radical reaction (Scheme 4). If 1,6-diene (4) is employed in the present system, a tandem cyclization would occur via biradical intermediates (5 and 6) to afford the bicyclic pyrrolidine derivative (7).

![Scheme 4. Reaction scheme for a tandem cyclization of 1,6-diene with a triplet state N-tosyl nitrene](image)

In fact, when 1,6-heptadiene (4a) was treated with CT and AgNO₃ under the conditions used in method B for 14 h, the anticipated bicyclic pyrrolidine derivative (7a) was obtained in 42% yield along with \textit{trans}-substituted cyclopentane derivative (8a) (Scheme 5). The substituted bicyclic pyrrolidine derivative (7b) was also formed from 4b. Evidence of the formation of by-product (8) would confirm the generation of intermediate (6) shown in Scheme 4. Although 5-\textit{exo}-cyclization in a \textit{cis}-fashion from 5 to 6 would readily provide bicyclic products (7) \textit{via} the second cyclization, the recombination of the biradical of the resulting \textit{trans}-isomer would be rather difficult and, as a result, compounds (8) were formed. In general, the 5-\textit{exo}-cyclization of the 1-methyl-5-hexenyl radical at 60 °C gives a mixture of \textit{cis}- and \textit{trans}-diastereomers of (2-methylcyclopentyl)methyl radical (\textit{cis}/\textit{trans} = 3.2/1), the ratio of which is in good agreement with that of 7:8. This provides support for the present reaction proceeding \textit{via} a tandem radical cyclization.
In summary, we reported that the CT-AgNO₃ system is applicable to the synthesis of not only aziridines from monoenes including electron-deficient olefins but also bicyclic pyrrolidines from 1,6-dienes. The finding herein suggests that a nitrogen radical species (a triplet state nitrene) is involved, when the reaction is conducted using CT and AgNO₃. Further applications of the method to the synthesis of other heterocycles are currently in progress.

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REFERENCES AND NOTES


8. **General procedure for the synthesis of aziridines using CT and AgNO₃**

**Method A:** Olefins (1.5 mmol) were added to a suspension of Chloramine-T (141 mg, 0.5 mmol) and AgNO₃ (85 mg, 0.5 mmol) in distilled CH₂Cl₂ (2.0 mL). The mixture was stirred at room temperature for the times indicated in Table 1 under an atmosphere of argon. After the addition of Et₂O (10 mL), the mixture was passed through a short silica gel column using Et₂O (80 mL) as an eluent. The filtrate was concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc).

**Method B:** Olefins (0.5 mmol) were added to a suspension of Chloramine-T (282 mg, 1.0 mmol) and AgNO₃ (170 mg, 1.0 mmol) in distilled benzene (5.0 mL). The mixture was stirred at 60 °C for the times indicated under an atmosphere of argon. After the addition of Et₂O (10 mL), the mixture was passed through a short silica gel column using Et₂O (80 mL) as an eluent. The filtrate was concentrated *in vacuo*, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc).

The characteristics of all the aziridines reported here (aziridines from olefins (1a-d and 1g, 1e and 1f, 6b and 1h)) were found to be identical to those published previously.

9. ¹H NMR spectral data of aziridines reported by Rai’s group are not identical with those published by Evans¹⁵ and Sharpless⁶c groups which were also confirmed by us.⁶a

10. The stereochemistry of the olefins recovered was investigated. When *trans*- and *cis*-octenes and *trans*-[ α- methylstyrene were employed in the present reaction, isomerizations of the olefins were not
observed at all in the reaction mixture. In the case of cis-\(\pi\)-methylstyrene, the trans-olefin was detected in the reaction mixture (\(\text{cis} / \text{trans} = 91 / 9\)).


12. Methyl cinnamate (100%) and \(p\)-toluenesulfonamide (17%) derived from CT were detected in an ethereal extract from the reaction mixture. Although iodometry on an aqueous extract showed oxidizing activity (71% based on CT employed in the reaction), the structure(s) of the oxidizing species is uncertain at the present stage.

13. Similar to the procedure of Method B given in ref. 8.

\textbf{3-\((p\)-Toluenesulfonyl\)-3-azabicyclo[3.3.0]octane (7a).} white solid; mp 75-77 \(^\circ\)C; TLC \(R_f\) 0.43 (hexane/EtOAc, 7:3); IR (KBr) 1342, 1163 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 270 MHz) \(\delta\) 1.34-1.77 (m, 6H, \((CH_2)_3\)), 2.43 (s, 3H, Ar-\(CH_3\)), 2.51-2.58 (m, 2H, \(CH\)), 2.88 (dd, 2H, \(J = 3.5, 9.9\) Hz, CHCHH), 3.11 (dd, 2H, \(J = 7.8, 9.9\) Hz, CHCHH), 7.33 (d, 2H, \(J = 8.1\) Hz, Ar-\(H\)), 7.68 (d, 2H, \(J = 8.1\) Hz, Ar-\(H\)); \(^{13}\)C NMR (CDCl\(_3\), 68 MHz) \(\delta\) 21.6, 23.2, 32.8, 42.6, 54.6, 127.9, 129.4, 132.2, 143.3; MS (EI): \(m/z\) (%) = 265 (5) [M]\(^+\), 155 (5), 110 (45), 91 (24), 42 (100); Anal. Calcd for C\(_{14}\)H\(_{19}\)NO\(_2\)S: C, 63.36; H, 7.22; N, 5.28. Found: C, 63.19; H, 7.13; N, 5.13.

\textbf{trans-1-Chloromethyl-2-(p-toluenesulfonylaminomethyl)cyclopentane (8a).} yellow oil; TLC \(R_f\) 0.35 (hexane/EtOAc, 7:3); IR (neat) 3278, 1329, 1161 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 270 MHz) \(\delta\) 1.23-1.97 (m, 6H, \((CH_2)_3\)), 2.43-2.48 (m, 5H, \(CH\) and Ar-\(CH_3\)), 2.83-2.90 (m, 1H, CHHNHTs), 2.95-3.02 (m, 1H, CHHNHTs), 3.48 (d, 2H, \(J = 5.9\) Hz, -\(CH_2\)Cl), 4.43 (br t, 1H, \(J = 3.1\) Hz, NHNTs), 7.32 (d, 2H, \(J = 7.3\) Hz, Ar-\(H\)), 7.74 (d, 2H, \(J = 7.3\) Hz, Ar-\(H\)); \(^{13}\)C NMR (CDCl\(_3\), 68 MHz) \(\delta\) 21.6, 24.2, 30.7, 42.9, 45.2, 47.2, 48.7, 126.9, 129.6, 136.6, 143.3; MS (CI, isobutane): \(m/z\) (%) = 302 (100) [M+1]\(^+\), 155 (30), 110 (26); HRMS (CI, methane): \(m/z\) Calcd for C\(_{14}\)H\(_{21}\)NO\(_2\)ClS [(M + H)\(^+\)]: 302.0982. Found: 302.0984.

\textbf{3-\((p\)-Toluenesulfonyl\)-7,7-bis(ethoxycarbonyl)-3-azabicyclo[3.3.0]octane (7b).} white solid; mp
105 °C; TLC Rf 0.20 (hexane/EtOAc, 7:3); IR (KBr) 1726, 1344, 1168 cm⁻¹; ¹H NMR (CDCl₃, 270 MHz) δ 1.19-1.27 (m, 6H, CH₂C₃H₇), 1.95 (dd, 2H, J = 7.0, 13.5 Hz, (EtOCO)₂CCHH), 2.44 (s, 3H, Ar-CH₃), 2.52 (dd, 2H, J = 8.1, 13.5 Hz, (EtOCO)₂CCHH), 2.67 (dddd, 2H, J = 1.4, 7.0, 7.0, 13.5 Hz, CH), 2.85 (dd, 2H, J = 7.0, 9.6 Hz, CHHNTs), 3.16 (dd, 2H, J = 1.4, 9.6 Hz, CHHNTs), 4.11-4.20 (m, 4H, CH₂CH₃), 7.33 (d, 2H, J = 8.4 Hz, Ar-H), 7.76 (d, 2H, J = 8.4 Hz, Ar-H); ¹³C NMR (CDCl₃, 68 MHz) δ 14.0, 14.0, 39.6, 41.7, 53.5, 61.5, 62.2, 127.8, 129.4, 131.7, 143.5, 170.5, 171.4; MS (CI, isobutane): m/z (%) = 410 (100) [M+1]⁺, 254 (21); Anal. Calcd for C₂₀H₂₇NO₆S: C, 58.66; H, 6.65; N, 3.42. Found: C, 58.43; H, 6.61; N, 3.36.

trans-1-Chloromethyl-2-(p-toluenesulfonylaminomethyl)-4,4-bis(ethoxycarbonyl)cyclopentane (8b). yellow oil; TLC Rf 0.21 (hexane/EtOAc, 7:3); IR (neat) 3288, 1726, 1367, 1163 cm⁻¹; ¹H NMR (CDCl₃, 270 MHz) δ 1.21-1.27 (m, 6H, CH₂C₃H₇), 2.06-2.18 (m, 2H, (EtOCO)₂CCHH), 2.38-2.53 (m, 7H, (EtOCO)₂CCHH, CH, and Ar-CH₃), 2.88-2.97 (m, 1H, CHHNTs), 3.00-3.09 (m, 1H, CHHNTs), 3.46-3.58 (m, 2H, CH₂Cl), 4.12-4.23 (m, 4H, CH₂CH₃), 4.69 (br t, 1H, J = 6.2 Hz, NHTs), 7.31 (d, 2H, J = 8.0 Hz, Ar-H), 7.73 (d, 2H, J = 8.0 Hz, Ar-H); ¹³C NMR (CDCl₃, 68 MHz) δ 14.1, 21.6, 37.6, 38.0, 41.7, 43.9, 45.6, 46.8, 58.4, 61.7, 61.9, 126.9, 129.7, 136.6, 143.4, 171.4, 171.9; MS (CI, isobutane): m/z (%) = 446 (100) [M+1]⁺, 290 (10), 155 (4); HRMS (CI, methane): m/z Calcd for C₂₀H₂₉NO₆ClS [(M + H)⁺]: 446.1404. Found: 446.1400.