CONVENIENT PREPARATION OF 1-AZAAZULENE DERIVATIVES BY THE REACTION OF TROPONIMINES WITH ENAMINES

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Abstract—Troponimines having OH, OMe, OMs, and OTs group on the nitrogen atom react with pyrrolidine enamines to give formal [8+2] cycloadducts, which undergo spontaneous aromatization to give 1-azaazulene derivatives in good to moderate yields.

The chemistry of azaazulenes has attracted considerable attention for several decades. In a series of studies concerning (vinylimino)phosphoranes, we have demonstrated convenient methodology synthesizing 1-azaazulenes and 5-azaazulenes. Since 1-azaazulenes and 1-azaazulene-2-ones have also attracted much attention from the viewpoint of their pharmacological activities, we have embarked on the exploration of the methodology for synthesizing versatile 1-azaazulenes. Although cycloaddition reaction of troponimines with electron-deficient acetylene and cumulenes has been studied extensively, no reaction with electron-rich olefins has been reported. Thus, we have found previously that N-diphenylphosphinoyl-, N-benzenesulfonyl-, and N-methanesulfonyliminoimines (1a-c) react with enamines (2) to give 1-azaazulene derivatives in low to modest yields. In the reactions, the yields of 1-azaazulenes would be dependent on the aromatization process of the intermediates (3a-c) (Scheme 1).

In this paper, we wish to describe the reaction of N-hydroxy-, N-methoxy-, N-mesyloxy, and N-tosyloxytroponimines (4-7), all of which have suitable leaving group on the nitrogen atom, with pyrrolidine
enamines (8a-g) to give 2,3-ring-annulated and 2,3-disubstituted 1-azaazulenes in good to moderated yields.

General procedure for the reaction of 4-7 with 8a-g was as follows. A solution of the troponimines (4-7) (1 mmol) and the enamins (8a-g) (2 mmol) reacted under nitrogen atmosphere until almost all of troponimine (4-7) disappeared. The separation of the products of 1-azaazulenes (9a-g) was performed through TLC on silica gel (hexane/AcOEt : 1/1). The reaction conditions and the yields of the products are summarized in Table 1.

The postulated pathways for the formation of 9a-g are shown in Scheme 2. The enamine alkylation of 8a-g onto C-2 of troponimines (4-7) gives the intermediates (10a-g), which undergo cyclization to give 11a-g. The facile aromatization eliminating HOR and pyrrolidine results in the formation of 1-azaazulenes (9a-g). The reddish color of 9a-g and the formation of the corresponding picrates are characteristic for 1-azaazulenes.11,12 The structures of 9a-c were confirmed on the basis of comparison of the spectral data with those of the authentic specimens.11,12 The proton assignments of 1H-NMR spectra of new compounds (9d-g)16 were made by aid of Eu(fod)3. On the basis of the spectral data and picrate formations (Table 2), as well as on consideration of the structural relation with enamine (8d-g), the structures of 1-azaazulenes (9d-g) were assigned.

Scheme 2.

The present reaction of 4 and 5 with 8c-g proceeded under reflux in benzene, while those of 6 and 7 with 8b-g proceeded even at rt (Table 1). The MNDO calculations17 suggest that the energy levels of LUMO of 4 (-0.48 eV) and 5 (-0.48 eV) are higher than those of 6 (-0.79 eV) and 7 (-0.70 eV). The energy level of LUMO of tropone (-0.82 eV), which is known to react with enamine to give [8+2] cycloaducts,18 is slightly lower than those of 6 and 7.19 The charge densities on the nitrogen and imine-carbon atoms of 4 (-1.2 and +0.04), 5 (-1.2 and +0.05), 6 (-1.2 and +0.11), and 7 (-1.6 and +0.09) are lower than those on the oxygen and carbonyl-carbon atoms of tropone (-0.31 and +0.29), respectively, suggesting less polarized nature of 4-7 as
compared with tropone. Thus, the troponimines (6) and (7), both of which have electron-withdrawing substituent on the nitrogen atom and thus low lying LUMO, would react with HOMO of enamines under mild conditions, as compared with 4 and 5.

Troponimines (4) and (5) did not react with 8a,b under reflux in benzene and 6 and 7 did not react also with 8a at rt, and forcing conditions were required (Table 1). Thus, it is clear that the reaction conditions are sensitive to the ring size of enamines. This feature is presumably ascribed to the ring strain in the cyclization step of the intermediate(10) giving 11, aromatization of which gives the final products (9a-c). The ring strain originating from the reaction of 8a to give 11a is considered to be larger than those for the others.

Table 1. Reaction of troponimines (4-7) with enamines (8a-g)

<table>
<thead>
<tr>
<th>Enamine</th>
<th>Product</th>
<th>Yield/% (Reaction time/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Method A\textsuperscript{a} for 4</td>
</tr>
<tr>
<td>8a</td>
<td>9a</td>
<td>64 (6)\textsuperscript{e}</td>
</tr>
<tr>
<td>8b</td>
<td>9b</td>
<td>89 (2)\textsuperscript{e}</td>
</tr>
<tr>
<td>8c</td>
<td>9c</td>
<td>100 (2)</td>
</tr>
<tr>
<td>8d</td>
<td>9d</td>
<td>83 (4)</td>
</tr>
<tr>
<td>8e</td>
<td>9e</td>
<td>98 (4)</td>
</tr>
<tr>
<td>8f</td>
<td>9f</td>
<td>65 (6)</td>
</tr>
<tr>
<td>8g</td>
<td>9g</td>
<td>42 (6)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} A mixture of 4 (1 mmol), 8 (2 mmol), and 0.4 nm molecular seaves (100 mg) in benzene (1 mL) was heated under reflux. b. A solution of 5 (1 mmol) and 8 (2 mmol) in benzene (1 mL) was heated under reflux. c. A solution of 6 (1 mmol), 8 (2 mmol), and NEt\textsubscript{3} (101 mg, 1 mmol) in benzene (1 mL) was stirred at rt. d. A solution of 7 (1 mmol), 8 (2 mmol), and NEt\textsubscript{3} (101 mg, 1 mmol) in benzene (1 mL) was stirred at rt. e. Heated under reflux in xylene. f. Heated under reflux in benzene.

Table 2. Physical data of new compounds (9d-g)

9d: red oil, \textsuperscript{1}H-NMR (CDCl\textsubscript{3}, 400 MHz) \textdelta 1.35-1.40 (2H, m), 1.42-1.47 (2H, m), 1.73-1.79 (2H, m), 1.83-2.00 (2H, m), 3.11 (2H, t, J=6.4 Hz), 3.25 (2H, t, J=6.4 Hz), 7.51
(1H, dd, J=9.5, 10.1 Hz), 7.61 (1H, dd, J=9.4, 10.5 Hz), 7.71 (1H, dd, J=9.5, 10.5 Hz), 8.26 (1H, d, J=10.1 Hz), 8.49 (1H, d, J=9.4 Hz). Picrate: mp 202-205°C (from MeOH).

**9e**: red oil; $^1$H-NMR (CDCl$_3$, 400 MHz) δ 1.26-1.60 (12H, m), 1.80-2.10 (4H, m), 3.02 (2H, t, J=7.0 Hz), 3.07 (2H, t, J=7.5 Hz), 7.54 (1H, dd, J=9.5, 9.9 Hz), 7.63 (1H, dd, J=9.7, 9.9 Hz), 7.73 (1H, dd, J=9.7, 9.9 Hz), 8.33 (1H, d, J=9.9 Hz), 8.51 (1H, d, J=9.5 Hz). Picrate: mp 177-178°C (from MeOH).

**9f**: reddish orange oil; $^1$H-NMR (CDCl$_3$, 400 MHz) δ 1.42 (3H, t, J=7.7 Hz), 2.50 (3H, s), 3.11 (2H, q, J=7.7 Hz), 7.52 (1H, dd, J=9.2, 9.9 Hz), 7.60 (1H, dd, J=9.5, 9.9 Hz), 7.71 (1H, dd, J=9.5, 9.9 Hz), 8.25 (1H, d, J=9.9 Hz), 8.49 (1H, d, J=9.2 Hz). Picrate: mp 188-190°C (from MeOH).

**9g**: reddish orange oil; $^1$H-NMR (CDCl$_3$, 400 MHz) δ 1.05 (3H, t, J=7.3 Hz), 1.25 (3H, t, J=7.3 Hz), 1.92 (2H, t, J=7.3, 7.7 Hz), 2.97 (2H, q, J=7.3 Hz), 3.05 (2H, t, J=7.7 Hz), 7.51 (1H, dd, J=9.5, 9.9 Hz), 7.60 (1H, dd, J=9.5, 9.9 Hz), 7.71 (1H, dd, J=9.5, 10.3 Hz), 8.28 (1H, d, J=10.3 Hz), 8.48 (1H, d, J=9.5 Hz). Picrate: mp 190-191°C (from MeOH).

In summary, the present method using troponimines (4-7) and enamines provides an efficient route to the synthesis of 1-azaazulenes. This methodology establishes the experimental framework for a new approach to 1-azaazulenes, just like as the so called enamine method synthesizing azulenoid compounds established by Takase, Yasunami, and coworkers. Scope and limitations of the methodology as well as the preparation of theoretically interesting molecules involving 1-azaazulene are under investigations in our laboratory.

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**REFERENCES**

16. All new compounds gave satisfactory spectral data and analytical data of their picrates.
17. The MNDO calculations were carried out by using MOPAC Ver. 6.12 program.

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