Preparation of Cyclic N-tert-Butylsulfonyl Enamines by Rh(II)-Mediated Ring Expansion of α-Diazoesters

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Received 23 February 2006

Abstract: The anion derived from ethyl diazoacetate adds to N-tert-butylsulfonyl ketimines to give β-tert-butylsulfonylamino α-diazoesters, which are further transformed into cyclic enamine by treatment with Rh2(OAc)4, through 1,2-C–C bond migration of a Rh(II) carbene intermediate.

Key words: diazo compounds, Rh(II) carbene, 1,2-C–C bond migration, ring expansion

Among the various catalytic transformations of α-diazo-carbonyl compounds, the C–C bond migration is a unique process.1 Although C–C bond migration is a less favorable process and in most cases is associated with other competing reactions, it may find application in organic synthesis in some special cases. For example, the C–C bond migration has been nicely utilized in the ring expansion of cyclic ketones via base-promoted aldol-type reaction with ethyl diazoacetate (EDA), followed by Rh2(OAc)4-catalyzed diazo decomposition (Scheme 1).2

We have recently studied the similar nucleophilic addition of the EDA-derived anion with aromatic N-tosylimines. Further treatment of the addition products with catalytic Rh2(OAc)4 resulted in the predominant formation of the 1,2-C–C migration products. The products which could result from the competing 1,2-C–H migration, a very feasible process, are not observed.3,4 On the other hand, in the Rh(II)-catalyzed reaction of α-hydroxy α-diazoesters, only 1,2-C–H migration products are formed.5 The results demonstrate a remarkable non-migrating group effect.

In this paper, we report further investigations along this line by extending a similar reaction to cyclic imines, as shown in Scheme 2. We demonstrate here that nucleophilic addition to cyclic imines works well to give the corresponding addition products, which can undergo ring expansion to afford cyclic enamines when treated with Rh2(OAc)4.

The cyclic N-tert-butylsulfonyl ketimines 4a–g were prepared from the corresponding cyclic ketones 1a–g by a two-step procedure recently reported by Ruano and co-workers.6 The overall yields for the two-step procedure range from 51–62% (Table 1). The cyclic ketimines have sufficient stability to withstand purification by column chromatography.

We then studied the reaction of the cyclic N-tert-butylsulfonyl ketimines 4a–g with EDA under basic conditions. Previously, we reported the reaction of EDA with aromatic N-tosylimines promoted by a catalytic amount of DBU.7 However, the DBU-promoted reaction of cyclic N-tert-butylsulfonyl ketimines 4a with EDA was very slow. We then used the strong base, LDA, to generate the anion from EDA at –78 °C.8 The EDA-derived anion added to cyclic ketimines 4a to afford the diazo product 5a. It was found that the addition of excess HMPA could improve the yields and shorten the reaction time (Table 2).

With the addition products 5a–g in hand, we then proceeded to study their Rh2(OAc)4-catalyzed diazo decomposition reaction. For diazo compounds 5a–d, the Rh2(OAc)4-catalyzed reaction proceeded efficiently in refluxing dichloromethane to afford the corresponding ring expansion products cyclic enamines 6a–d in excellent yields (Scheme 3).

For the diazo compounds 5e and 5f, the corresponding Rh2(OAc)4-catalyzed reaction was very slow. This may be due to the steric hindrance around the diazo group, which may impede access of the Rh(II) catalyst. The diazo decomposition could occur at elevated temperatures by car...
In summary, we have demonstrated that EDA could add to cyclic N-tert-butylsulfonyl ketimines with LDA as the deprotonating agent; the addition product was treated with a catalytic amount of Rh$_2$(OAc)$_4$ to effect 1,2-C–C bond migration and afford the ring-expansion product. The two-step procedure represents an efficient method to access cyclic enamines.

All solvents were distilled prior to use. $^1$H NMR and $^{13}$C NMR spectra were measured at 300 MHz and 75 MHz, respectively, on a Varian Mercury 300 spectrometer or at 200 MHz and 50 MHz, respectively, on a Varian Mercury 200 spectrometer. IR spectra were recorded with a Nicolet AVATAR 330 FT-IR infrared spectrometer. Mass spectra were obtained on a VG ZAB-HS mass spectrometer. Elemental analyses were carried out on a Elementar Vario EL Instrument. Column chromatography was performed on 100–200 mesh silica gel (Qingdao, P. R. of China) employing PE–EtOAc eluent. PE with a bp range 30–60 °C was used; EtAOc was distilled prior to use.

Caution: All diazo compounds are highly toxic or presumed to be toxic. Diazoo compounds are potentially explosive. They should be handled with care in a well-ventilated fume hood.

**Table 2** Reaction of EDA with Cyclic Ketimines 4a–g

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketimines 4</th>
<th>Reaction time (h) Yield (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>7</td>
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<tr>
<td>4</td>
<td>4d</td>
<td>24</td>
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<tr>
<td>5</td>
<td>4e</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>4f</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>4g</td>
<td>8</td>
</tr>
</tbody>
</table>

*a Isolated yield after column chromatography.

**SPECIAL TOPIC**

**Cyclic N-tert-Butylsulfonyl Enamines**


1H NMR (300 MHz, CDCl3): \( \delta = 1.46 \) (s, 9 H), 1.63–1.81 (m, 8 H), 2.61 (t, \( J = 6.2 \) Hz, 2 H), 3.11 (t, \( J = 6.0 \) Hz, 2 H).

13C NMR (75 MHz, CDCl3): \( \delta = 23.7, 24.6, 25.8, 29.5, 29.9, 37.1, 42.0, 58.5, 196.2 \).

EI-MS: \( m/z \) (%) = 231 (M+, 3), 57 (100).

Anal. Calcd for C11H21NO2S: C, 57.11; H, 9.15; N, 6.05. Found: C, 57.06; H, 8.94; N, 5.94.

N-Cyclooctylidine-tert-butanesulfonamide (4d)

Mp 153–154 °C; \( R_f = 0.56 \) (PE–EtOAc, 10:1).

IR (neat): 1614, 1296, 1122 cm–1.

1H NMR (200 MHz, CDCl3): \( \delta = 1.46 \) (s, 9 H), 1.51–1.56 (m, 5 H), 1.80–1.98 (m, 5 H), 2.52 (t, \( J = 6.2 \) Hz, 2 H), 2.96 (t, \( J = 6.2 \) Hz, 2 H).

13C NMR (50 MHz, CDCl3): \( \delta = 23.7, 23.9, 24.6, 26.1, 27.6, 29.0, 36.9, 39.4, 58.5, 199.2 \).

EI-MS: \( m/z \) (%) = 245 (M+, 4), 57 (100).


N-2-Methylcyclopentylidine-tert-butanesulfonamide (4e)

Mp 158–159 °C; \( R_f = 0.44 \) (PE–EtOAc, 10:1).

IR (neat): 1640, 1300, 1121 cm–1.

1H NMR (200 MHz, CDCl3): \( \delta = 1.18 \) (d, \( J = 6.8 \) Hz, 3 H), 1.48 (s, 9 H), 1.57–1.87 (m, 2 H), 1.93–2.16 (m, 2 H), 2.68–2.88 (m, 2 H), 2.99–3.13 (m, 1 H).

13C NMR (50 MHz, CDCl3): \( \delta = 15.5, 22.8, 23.8, 32.0, 34.4, 45.1, 58.4, 202.2 \).

EI-MS: \( m/z \) (%) = 217 (M+, 8), 57 (100).

Anal. Calcd for C10H19NO2S: C, 55.27; H, 8.81; N, 6.44. Found: C, 55.28; H, 8.82; N, 6.36.

N-2-Methylcyclohexylidine-tert-butanesulfonamide (4f)

Mp 133–134 °C; \( R_f = 0.41 \) (PE–EtOAc, 10:1).

IR (neat): 1627, 1297, 1117 cm–1.

1H NMR (300 MHz, CDCl3): \( \delta = 1.06 \) (d, \( J = 6.3 \) Hz, 3 H), 1.49 (s, 9 H), 1.57–1.85 (m, 4 H), 2.03–2.15 (m, 2 H), 2.29–2.39 (m, 1 H), 2.45–2.53 (m, 1 H), 2.83–3.57 (m, 1 H).

13C NMR (75 MHz, CDCl3): \( \delta = 16.3, 23.8, 24.9, 27.9, 36.3, 37.1, 43.9, 58.8, 195.6 \).

EI-MS: \( m/z \) (%) = 231 (M+, 4), 57 (100).

Anal. Calcd for C11H21NO2S: C, 57.11; H, 9.15; N, 6.05. Found: C, 56.93; H, 8.95; N, 5.94.

N-2-Phenylcyclohexylidine-tert-butanesulfonamide (4g)

Mp 133–134 °C; \( R_f = 0.70 \) (PE–EtOAc, 10:1).

IR (neat): 1627, 1284, 1120 cm–1.

1H NMR (200 MHz, CDCl3): \( \delta = 1.18 \) (s, 9 H), 1.50–2.33 (m, 6 H), 2.48–2.63 (m, 1 H), 2.52–3.68 (m, 2 H), 7.11–7.35 (m, 5 H).

13C NMR (50 MHz, CDCl3): \( \delta = 23.47, 25.10, 27.69, 34.59, 36.43, 55.24, 58.83, 126.80, 127.94, 128.63, 139.32, 193.35 \).

EI-MS: \( m/z \) (%) = 293 (M+, 8), 57 (100).

Anal. Calcd for C16H23NO2S: C, 65.49; H, 7.90; N, 4.77. Found: C, 65.63; H, 7.95; N, 4.72.

Scheme 4  Rh2(OAc)4-catalyzed reaction of 5e–g.
Reaction of EDA with Ketimines; General Procedure
A dry 50-mL flask equipped with a 10-mL dropping funnel was charged with anhyd THF (8 mL) under Ne, t-BuLi (1.3 mmol) and n-ButLi (2.0 M, hexane; 1.3 mmol) were added sequentially via syringe at –78 °C (dry ice–acetone). A solution of EDA (1.3 mmol) in anhyd THF (5 mL) was added dropwise over 5 min at the same temperature. After the resulting solution was stirred for 5 min, HMPA (6.5 mmol) was introduced, and the solution was stirred for another 5 min. Then a solution of N-tert-butanesulfonylimine (1 mmol) in anhyd THF (8 mL) was added dropwise over 30 min via the dropping funnel at –78 °C. The reaction continued for 4–24 h at the same temperature until the imine was no longer present (TLC). The reaction was quenched with a sat. aq solution of NH4Cl (3 mL) at –78 °C. The resulting mixture was extracted with CH2Cl2 (3 × 15 mL) and the combined organic layers were dried over anhyd Na2SO4. The solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography.

Ethyl 2-Diazo-2-[1’-(tert-butylsulfonyl)amino]cyclohexylacetate (5a)
Mp 80–81 °C; Rf = 0.39 (PE–EtOAc, 5:1).
IR (neat): 3272, 2920, 1661, 1318, 1302, 1125 cm⁻¹.
1H NMR (300 MHz, CDCl3): δ = 1.28 (t, J = 7.2 Hz, 3 H), 1.39 (s, 9 H), 1.65–1.75 (m, 2 H), 1.77–1.87 (m, 2 H), 2.05–2.19 (m, 4 H), 4.23 (q, J = 7.2 Hz, 2 H), 4.37 (br s, 1 H).
13C NMR (75 MHz, CDCl3): δ = 14.37, 22.31, 23.88, 24.18, 38.11, 59.62, 60.62, 64.14, 166.23.
EI-MS: m/z (%) = 317 (M⁺, 7), 289 (M – 28)+, 18, 57 (100).
Anal. Calcd for C15H27N3O4S: C, 52.15; H, 7.87; N, 12.16. Found: C, 52.28; H, 7.79; N, 12.01.

Ethyl 2-Diazo-2-[1’-(tert-butylsulfonyl)amino]cyclohexylacetate (5e)
Mp 102–103 °C; Rf = 0.43 (PE–EtOAc, 5:1).
IR (neat): 3291, 2904, 1684, 1315, 1127 cm⁻¹.
1H NMR (200 MHz, CDCl3): δ = 1.05 (d, J = 6.8 Hz, 3 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.40 (s, 9 H), 1.64–2.12 (m, 5 H), 2.26–2.36 (m, 1 H), 2.56–2.64 (m, 1 H), 4.24 (q, J = 7.2 Hz, 2 H), 4.89 (br s, 1 H).
13C NMR (50 MHz, CDCl3): δ = 14.4, 16.9, 20.3, 24.1, 30.3, 32.3, 43.1, 59.9, 60.8, 65.4, 166.5.
EI-MS: m/z (%) = 331 (M⁺, 6), 303 (M – 28)+, 21, 57 (100).
Anal. Calcd for C13H23N3O4S: C, 50.73; H, 7.60; N, 12.68. Found: C, 50.98; H, 7.70; N, 12.55.

Ethyl 2-Diazo-2-[1’-(tert-butylsulfonyl)amino]cyclohexylacetate (5f)
Mp 111–112 °C; Rf = 0.65 (PE–EtOAc, 5:1).
IR (neat): 3291, 2904, 1684, 1315, 1127 cm⁻¹.
1H NMR (200 MHz, CDCl3): δ = 1.17 (d, J = 7.2 Hz, 6 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.38 (s, 9 H), 1.46–1.78 (m, 7 H), 2.45–2.52 (m, 1 H), 2.77–2.79 (m, 1 H), 4.22 (q, J = 7.2 Hz, 2 H), 4.34 (br s, 1 H).
13C NMR (75 MHz, CDCl3): δ = 13.7, 14.3, 18.3, 22.4, 23.9, 27.8, 28.9, 34.2, 60.0, 60.4, 61.8, 166.1.
EI-MS: m/z (%) = 345 (M⁺, 5), 317 (M – 28)+, 31, 57 (100).

Ethyl 2-Diazo-2-[1’-(tert-butylsulfonyl)amino]cyclohexylacetate (5g)
Oil; Rf = 0.27 (PE–EtOAc, 5:1).
IR (neat): 2908, 1686, 1289, 1129 cm⁻¹.
1H NMR (300 MHz, CDCl3): δ = 1.22 (t, J = 7.2 Hz, 3 H), 1.30 (s, 9 H), 1.41–1.69 (m, 2 H), 1.85–1.87 (m, 2 H), 1.98–2.07 (m, 2 H), 2.20–2.27 (m, 1 H), 2.58–2.65 (m, 1 H), 3.44–3.45 (m, 1 H), 4.12 (q, J = 7.2 Hz, 2 H), 4.59 (br s, 1 H), 7.28–7.34 (m, 5 H).
13C NMR (75 MHz, CDCl3): δ = 14.4, 21.8, 23.1, 24.1, 28.3, 31.5, 50.9, 59.8, 60.3, 60.5, 127.4, 128.5, 129.2, 140.9, 166.2.
EI-MS: m/z (%) = 407 (M⁺, 2), 57 (100).
HRMS: m/z calc for C15H29N3O4S: 407.1879; found: 407.1879.

Rh2(OAc)4-Catalyzed Reaction of Diazocompounds 4a–g; General Procedure
In a three-necked round-bottom flask equipped with a dropping funnel and a condenser, Rh2(OAc)4 was dissolved in anhyd CH2Cl2 or DCE. The resulting solution was heated under reflux until the reagent was completely consumed. Reduction of diazo substrate in anhyd CH2Cl2 or DCE (5 mL) was added dropwise, and the resulting solution was heated under reflux until the reaction was complete (IR and TLC). The solvent was removed under reduced pressure to give the crude residue, which was purified by column chromatography.

1[(tert-Butylsulfonyl)amino]-2-carboethoxycyclohexene (6a)
Mp 65–66 °C; Rf = 0.62 (PE–EtOAc, 10:1).
IR (neat): 1659, 1606, 1235, 1132 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 1.30 (t, J = 7.2 Hz, 3 H), 1.44 (s, 9 H), 1.47–1.60 (m, 6 H), 1.80–1.82 (m, 2 H), 2.47 (t, J = 6.1 Hz, 2 H), 2.85 (t, J = 6.1 Hz, 2 H), 4.21 (q, J = 7.2 Hz, 2 H), 6.02 (s, 1 H).

13C NMR (75 MHz, CDCl₃): δ = 14.1, 22.9, 24.2, 25.5, 25.7, 28.0, 29.3, 30.3, 33.6, 60.8, 61.1, 120.9, 158.8, 165.6.

EI-MS: m/z (%) = 331 (M⁺, 2), 57 (100).

Anal. Calc'd for C₆H₁₂N₃O₅S: C, 55.42; H, 8.82; N, 4.23. Found: C, 55.79; H, 8.74; N, 4.14.

N-2-Butyroxy-7-methylcycloheptylidine-tert-butan sulfonylamine (7f)

Mp 165-166 °C; Rf = 0.32 (PE–EtOAc, 10:1).

IR (neat): 1736, 1621, 1304, 1122 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 1.27 (t, J = 7.2 Hz, 3 H), 1.51 (s, 9 H), 1.57–1.72 (m, 2 H), 1.81–2.22 (m, 4 H), 2.68–2.78 (m, 2 H), 3.05–3.16 (m, 1 H), 4.11 (q, J = 7.2 Hz, 2 H), 5.17 (br s, 1 H), 7.17–7.41 (m, 5 H).

13C NMR (75 MHz, CDCl₃): δ = 14.1, 20.4, 23.8, 30.5, 36.3, 41.8, 47.9, 59.2, 60.4, 126.8, 127.5, 128.8, 137.2, 171.6, 194.7.

EI-MS: m/z (%) = 379 (M⁺, 7), 57 (100).

N-2-Butyroxy-7-methylcycloheptylidine-tert-butan sulfonylamine (8)

Mp 115–116 °C; Rf = 0.31 (PE–EtOAc, 10:1).

IR (neat): 1734, 1625, 1301, 1122 cm⁻¹.

1H NMR (300 MHz, CDCl₃): δ = 1.27 (t, J = 7.2 Hz, 3 H), 1.51 (s, 9 H), 1.57–1.72 (m, 2 H), 1.81–2.22 (m, 4 H), 2.68–2.78 (m, 2 H), 3.05–3.16 (m, 1 H), 4.11 (q, J = 7.2 Hz, 2 H), 5.17 (br s, 1 H), 7.17–7.41 (m, 5 H).

13C NMR (75 MHz, CDCl₃): δ = 14.1, 20.4, 23.8, 30.5, 36.3, 41.8, 47.9, 59.2, 60.4, 126.8, 127.5, 128.8, 137.2, 171.6, 194.7.

EI-MS: m/z (%) = 379 (M⁺, 10), 259 (100).

Anal. Calc'd for C₆H₁₂N₃O₅S: C, 63.30; H, 7.70; N, 3.69. Found: C, 63.36; H, 7.65; N, 3.69.

Acknowledgment

The project was generously supported by Natural Science Foundation of China (Grant Nos. 20572002, 20521202, 20225205, and 20390050) and the Ministry of Education of China.

References


(4) Very recently Aggarwal and co-workers reported a rare case in which 1,2-\textsuperscript{C}–\textsuperscript{C} bond migration occurs preferentially over 1,2-\textsuperscript{C}–\textsuperscript{H} migration, see: Vitale, M.; Lecourt, T.; Sheldon, C. G.; Aggarwal, V. K. J. Am. Chem. Soc. 2006, 128, 2524.


