RING CLEAVAGE REACTION OF HETEROCYCLIC KETONES
BASED ON CROSSED ALDOL CONDENSATION

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Abstract- Ring cleavage reaction based on crossed aldol condensation using heterocyclic ketones such as 4-piperidone and nortropinone derivatives with benzaldehyde under acetalization conditions (BF3·Et2O/ethylene glycol) has been achieved.

We previously reported a new type of ring transformation based on tandem aldol condensation and ring cleavage using a combination of Lewis acid and 1,2-diol. This reaction has been found to be widely applicable to not only the intramolecular system but also the intermolecular system.1,2 Furthermore, we have also developed an asymmetric version of this reaction in both the above systems.3 So far, this reaction has been restricted to carbocyclic ketones as a substrate. In this report, we describe the first application of this reaction to heterocyclic ketones of σ-symmetry in the intermolecular system.

STUDY OF RING CLEAVAGE OF CARBOCYCLIC KETONES INTO HETEROCYCLES

As an example of ring transformation based on intramolecular aldol condensation, the transformation of cyclohexanones with 3-oxobutyl substituent (1a) into products (2a) could be depicted as in Scheme 1 (X = CH2).1a If X in compound (1) was a heteroatom such as in compounds (1b: X = O) and (1c: X = NAc), the same reaction was expected to afford heterocyclic products (2b) and (2c), respectively. Based on the above assumption, reaction of compounds (1b-e) was performed under the usual conditions (BF3·Et2O (5 equiv.), ethylene glycol (7 equiv.) in CH2Cl2 at room temperature). However, these reactions resulted in the formation of the corresponding monoacetals (10-20%) as a mixture of positional isomers and bisacetals (3b-type) in 40-55% yields, and the expected heterocyclic products could not be detected at all.
These results were rationalized by considering the stereoelectronic effect of the substrates. For compound 1a, an axial orientation of C4-substituent (B) was required for initial aldol condensation, but chelation of BF3 to ether oxygen might shift the equilibrium between A and B to A having an equatorial orientation of the C4-substituent (Scheme 2). These considerations brought us to study the ring cleavage reaction of heterocyclic ketones based on intramolecular aldol condensation with benzaldehyde.

\[ \text{Scheme 1} \]

\[ \begin{align*}
\text{BF}_3\cdot\text{Et}_2\text{O} \\
\text{CH}_2\text{Cl}_2
\end{align*} \]

\[ \begin{array}{c}
\text{1a-c} \\
\text{2a: } X = \text{CH}_2 : 78\% \\
\text{2b: } X = \text{O} : 0\% \\
\text{2c: } X = \text{NAc} : 0\%
\end{array} \]

\[ \text{Scheme 2} \]

RING CLEAVAGE REACTION OF HETEROCYCLIC KETONES

N-Substituted 4-piperidones (4) and N-substituted nortropinones (8) were designed as a substrate because the stereoelectronic effect as above mentioned could be neglected in the case of the reaction based on intermolecular aldol condensation. Furthermore, an electron-withdrawing substituent on the nitrogen atom in 4 and 8 might act to prevent a coordination of Lewis acid to the nitrogen atom, that is to say, the situation might become similar to the carbocyclic system. Based on the above assumption, at first, substrates (4a-c) were subjected to ring cleavage reaction with benzaldehyde (1.3 equiv.) under the conditions of using BF3-Et2O (3 equiv.) and ethylene glycol (2 equiv.) in CH2Cl2 at room temperature. Results are summarized in Table 1. In all the cases, the desired products (5a-c) were obtained in 22-50% yields, and the trifluoroacetamide (4b) showed the best yield of 5b (50%, entry 2). It was found that this reaction was highly affected by the substituent on the nitrogen atom. In the case of using compound (4: R = CH2Ph) as a substrate, the ring-cleaved product (5: R = CH2Ph) was not obtained at all.
Table 1. Ring Cleavage Reaction of 4-Piperidones.

\[
\begin{align*}
4 + CH_2(CHO)_{1.3} eq & \xrightarrow{BF_3\cdot Et_2O, (CH_2OH)_2, CH_2Cl_2} 5 \\
R & T ime(h) & Y ielding(\%) \\
1 & 4a & 92 & 5a & 22 & 6a & 44 & 7a & 29 \\
2 & 4b & 42 & 5b & 50 & 6b & 10 & 7b & 16 \\
3 & 4c & 48 & 5c & 15 & 6c & 12 & 7c & 5
\end{align*}
\]

In all Entries in Table 1, the corresponding 6a-c and 7a-c were afforded in 10-44 and 5-29% yields, respectively. Yield of 6a in entry 2 was 44%, and reaction under the same conditions without ethylene glycol gave no ring-cleaved product but 6a in 40% yield. These results suggest that formation of 6 might be competitive with that of 5. The structure of 5a-c was determined by spectroscopic analyses. Reaction of 7b with benzaldehyde in the presence of BF3-Et2O in CH2Cl2 without ethylene glycol also gave ring-cleaved 5b in 46% yield.

Next, N-substituted nortropinones (8a-c), prepared by reported procedure, were submitted to the same reaction conditions, and the results are summarized in Scheme 3. Among them, compound (8c) gave the best yield of ring-cleaved (9c: 67%), and other two substrates (8a,b) did not afford satisfactory results (9a: 16%; 9b: 24%). In latter two cases a small amount of the dienones (6-type) were obtained. These results showed that the effective protecting group on the nitrogen atom was not same as the case of 4-piperidone derivatives. The structure of 5a-c and 9a-c was confirmed by spectroscopic analyses and
conversion into the corresponding methyl esters by treatment with K$_2$CO$_3$/MeOH in 85-93% yields. The stereochemistry of the double bond in 5 and 9 was determined to be E based on the coupling constants between the olefinic protons (J=16 Hz) in $^1$H nmr spectra, and relative stereochemistry between C2- and C5-substituents in 9 was assumed to be cis, retaining the stereochemistry of the substrate.

**Scheme 3**

\[
\begin{array}{c}
\text{8a-c} \\
\text{BF$_3$-Et$_2$O} \\
\text{(CH$_2$OH)$_2$} \\
\end{array}
\]

\[
\begin{array}{c}
\text{+} \\
\text{CHO} \\
\text{Ph} \\
\text{9a : R= Me} \\
\text{9b : R= COCF$_3$} \\
\text{9c : R= COOCH$_2$CCl$_3$} \\
\text{16%} \\
\text{24%} \\
\text{67%} \\
\end{array}
\]

**Scheme 4**

\[
\begin{array}{c}
\text{8} \\
\text{BF$_3$-Et$_2$O} \\
\text{(CH$_2$OH)$_2$} \\
\end{array}
\]

\[
\begin{array}{c}
\text{C} \\
\text{D} \\
\text{9} \\
\end{array}
\]

Reaction mechanisms, tentatively proposed as shown in Scheme 4, include three steps: 1. formation of enol ether (C); 2. acetal formation and subsequent aldol condensation to form D; 3. Grob's fragmentation into ring-cleaved product (9). This reaction might provide a new route for preparation of dialkylamides (5-type) and monocyclic amides (9-type), respectively. In particular, the diastereoselective construction of $\alpha,\alpha'$-cis-disubstituted pyrrolidine derivatives might be useful for synthetic study of related compounds. This one-step conversion is formally considered to be equivalent to a four-step sequence (i. Baeyer-Villiger reaction of cyclic ketone to lactone; ii. solvolysis of lactone; iii. oxidation of alcohol to aldehyde; iv. Wittig reaction into a benzylidene derivative).
**EXPERIMENTAL**

Infrared (ir) spectra were measured on a JASCO A-202 spectrophotometer, and $^1$H and $^{13}$C nmr spectra were measured on a JEOL JNM-GX-270 or JEOL JNM-FX-100 spectrometer using CDCl$_3$ as a solvent.

Mass spectra (ms) were taken on a JEOL JMS-D-300 spectrometer. For column chromatography, silica gel (Merck, Kieselgel 60, 70-230 mesh) was used. The $^1$H nmr spectroscopic data of 5 and 9 showed those of the major conformational isomer based on amide structure.

**General procedure of ring-cleaved reaction using 4-piperidone derivatives as a substrate.**

To a solution of benzaldehyde (413 mg, 3.9 mmol) in CH$_2$Cl$_2$ (8 ml) at 0°C were subsequently added BF$_3$-Et$_2$O (1.1 ml, 9.0 mmol), 4-piperidones (4) (3.0 mmol) in CH$_2$Cl$_2$ (4 ml), and ethylene glycol (372 mg, 6.0 mmol) in CH$_2$Cl$_2$ (3 ml). The whole was stirred at room temperature for 40-72 h. Reaction mixture was diluted with 5% aqueous NaHCO$_3$ (40 ml) and extracted with CH$_2$Cl$_2$ (40 ml x 2). The combined extracts were washed with brine and dried over MgSO$_4$. After removal of solvent in vacuo, oily residue was purified by silica gel column chromatography. Elution with 10-15% AcOEt-hexane gave dienone (6) as a pale yellow oil, and that with 20-25% AcOEt-hexane afforded acetal (7). Further elution with 50-60% AcOEt-hexane provided desired ring-cleaved product (5) as a pale yellow oil.

**2-Hydroxyethyl (E)-4-Acetyl-4-aza-7-phenyl-6-heptenoate (5a).** 22% yield. Ir (neat, cm$^{-1}$): 3400, 1730, 1630, 1480, 1450, 1250, 1195, 1090. $^1$H-Nmr (δ, ppm): 2.13 (3H, s), 2.63 (2H, t, $\delta$=6.6 Hz), 3.47-3.81 (5H, m), 4.12 (2H, d, $J$=5.6 Hz), 4.21 (2H, m), 6.13 (1H, dt, $J$=15.8, 5.6 Hz), 6.47 (1H, d, $J$=15.8 Hz), 7.25-7.39 (5H, m). Ms (m/z): 291 (M$^+$), 248, 230, 200, 132.

**2-Hydroxyethyl (E)-4-Aza-4-trifluoroacetyl-7-phenyl-6-heptenoate (5b).** 50% yield. Ir (neat, cm$^{-1}$): 3450, 1735, 1690, 1450, 1200, 1160, 1085. $^1$H-Nmr (δ, ppm): 2.72 (2H, t, $J$=6.6 Hz), 3.72 (2H, t, $J$=6.6 Hz), 3.75-3.85 (3H, m), 4.18-4.28 (4H, m), 6.08 (1H, dt, $J$=16.2, 6.3 Hz), 6.60 (1H, d, $J$=16.2 Hz), 7.23-7.47 (5H, m). Ms (m/z): 345 (M$^+$), 255, 248, 144, 117.

**2-Hydroxyethyl (E)-4-Aza-4-(2,2,2-trichloroethoxycarbonyl)-7-phenyl-6-heptenoate (5c)** 15% yield. Ir (neat, cm$^{-1}$): 3450, 1720 (br), 1465, 1420, 1220, 1120. $^1$H-Nmr (δ, ppm): 2.68 (2H, t, $J$=6.6 Hz), 3.63-3.83 (5H, m), 4.14 (2H, d, $J$=6.0 Hz), 4.22 (2H, m), 6.19 (1H, dt, $J$=16.2, 6.0 Hz), 6.55 (1H, d, $J$=16.2 Hz), 7.25-7.38 (5H, m). FDms (m/z): 425 (M$^+$), 399, 390, 213.

**N-Acetyl-3,5-bisbenzyliden-4-piperidone (6a).** 44% yield. Ir (neat, cm$^{-1}$): 1650, 1600, 1450, 1375, 1250, 1175. $^1$H-Nmr (δ, ppm): 1.92 (3H, s), 4.70 (2H, s), 4.93 (2H, s), 7.37-7.48 (10H, m), 7.83 (1H, s), 7.89 (1H, s). Ms (m/z): 317 (M$^+$), 274, 258, 156.
3,5-Bisbenzyliden-N-trifluoroacetyl-4-piperidone (6b). 10% yield. Ir (neat, cm\(^{-1}\)): 1700, 1675, 1615, 1445, 1275, 1195, 1150. \(^1\)H-Nmr (\(\delta, \text{ppm}\)): 4.86 (2H, s), 4.97 (2H, s), 7.34-7.50 (10H, m), 7.91 (1H, s), 7.95 (1H, s). Ms (m/z): 371 (M\(^+\)), 258, 195, 149.

3,5-Bisbenzyliden-N-(2,2,2-trichloroethoxycarbonyl-4-piperidone (6c). 12% yield. Ir (neat, cm\(^{-1}\)): 1705, 1655, 1600, 1420, 1260. \(^1\)H-Nmr (\(\delta, \text{ppm}\)): 4.84 (2H, s), 4.87 (4H, s), 7.34-7.44 (10H, m), 7.88 (2H, s). FDMs (m/z): 449 (M\(^+\)), 329.

N-Trifluoroacetylnortropinone (8b). To a solution of nortropinone\(^4\) (500 mg, 4.0 mmol) and pyridine (1 ml) in CH\(_2\)Cl\(_2\) (8 ml) at 0\(^\circ\)C was added bifluoroacetic anhydride (1.1 ml, 8.0 mmol). The whole was stirred at room temperature for 24 h. Usual work-up and purification by silica gel column chromatography (eluent: 20-30% AcOEt in hexane) afforded 8b (433 mg, 49%) as a colorless oil. Ir (CHCl\(_3\), cm\(^{-1}\)): 1750, 1720, 1485, 1365, 1275, 1220, 1195, 1165. \(^1\)H-Nmr (\(\delta, \text{ppm}\)): 1.85 (2H, m), 2.21 (2H, m), 2.50 (2H, m), 2.74 (2H, m), 4.71 (1H, br s), 5.00 (1H, br s). \(^1^3\)C-Nmr (CDCl\(_3\)) \(\delta\): 27.2 (t), 29.8 (t), 48.8 (t), 49.7 (t), 52.7 (d), 54.4 (d), 114.2 (s), 118.5 (s), 205.4 (s). Ms (m/z): 221 (M\(^+\)), 164, 110, 82, 58.

**General procedure of ring-cleaved reaction using nortropinone derivatives as a substrate.**

Reaction was performed by a similar manner to that aforementioned using substrate (8) (3.0 mmol), benzaldehyde (413 mg, 3.9 mmol), BF\(_3\)-Et\(_2\)O (1.1 ml, 9.0 mmol) and ethylene glycol (744 mg, 12 mmol) in CH\(_2\)Cl\(_2\) (15 ml). The whole was stirred at room temperature for 24-92 h. Reaction mixture was diluted with 5% aqueous NaHCO\(_3\) (40 ml) and extracted with CH\(_2\)Cl\(_2\) (40 ml x 2). The combined extracts were washed with brine and dried over MgSO\(_4\). After removal of solvent in vacuo, oily residue was purified by silica gel column chromatography. Elution with 30-50% AcOEt-hexane gave desired ring-cleaved product (9) as a pale yellow oil.

2-Hydroxyethyl [(2S,5RS)-(E)-N-Methyl-5-styrylpiperidin-2-yl]acetate (9a). 16% yield. Ir (neat, cm\(^{-1}\)): 3400, 1730, 1500, 1450, 1175, 1075. \(^1\)H-Nmr (\(\delta, \text{ppm}\)): 1.64-1.98 (4H, m), 2.28 (3H, s), 2.58-2.65 (3H, m), 2.76-2.85 (2H, m), 3.77 (2H, m), 4.10 (1H, ddd, J=4.3, 5.6, 11.5 Hz), 4.47 (1H, ddd, J=1.7, 5.5, 11.5 Hz), 6.10 (1H, dd, J=8.6, 15.8 Hz), 6.49 (1H, d, J=15.8 Hz), 7.19-7.41 (5H, m). \(^1^3\)C-Nmr (CDCl\(_3\)) \(\delta\): 28.4 (t), 29.8 (t), 38.3 (t), 38.5 (q), 60.6 (t), 63.6 (d), 65.8 (t), 70.9 (d), 126.4 (d), 127.5 (d), 128.5 (d), 131.3 (d), 132.5 (d), 136.8 (s), 171.8 (s). Ms (m/z): 289 (M\(^+\)), 252, 244, 186, 82. HRMs m/z: 289.1685 (M\(^+\), calcd for C\(_{17}\)H\(_{23}\)N\(_3\)O\(_3\) 289.1678).
2-Hydroxyethyl [(2SR,5RS)-(E)-N-Trifluoroacetyl-5-styrylpiperidin-2-yl]acetate (9b). 24% yield. \( \text{Ir (neat, cm}^{-1}$): 3400, 1735, 1680, 1450, 1215, 1155. \( ^1\text{H-Nmr (}\delta\text{, ppm)}: 1.48-1.81 (4H, m), 2.50-2.71 (2H, m), 3.68 (1H, m), 3.83 (2H, m), 4.05-4.30 (3H, m), 6.24 (1H, dd, J=7.2, 15.8 Hz), 6.64 (1H, d, J=15.8 Hz), 7.25-7.48 (5H, m). FABms (m/z): 372 (M$^+\,$1), 354, 310, 250, 197. HRms m/z: 371.1352 (M$^+$, calcd for C$_{18}$H$_{20}$NO$_4$F$_3$ 371.1344).

2-Hydroxyethyl [(2SR,5RS)-(E)-N-(2,2,2-Trichloroethoxycarbonyl)-5-styrylpiperidin-2-yl]acetate (9c). 67% yield. \( \text{Ir (neat, cm}^{-1}$): 3450, 1740-1700 (br), 1410, 1125, 1060. \( ^1\text{H-Nmr (}\delta\text{, ppm)}: 1.90 (2H, m), 2.22 (2H, m), 2.50 (1H, m), 2.99 (1H, m), 3.83 (2H, m), 4.23 (2H, m), 4.60-4.80 (3H, m), 6.11 (1H, dd, J=6.6, 15.8 Hz), 6.56 (1H, d, J=15.8 Hz), 7.20-7.38 (5H, m). FDms (m/z): 449 (M$^+$), 362, 249, 183.

Methyl [(2SR,5RS)-(E)-N-(2,2,2-Trichloroethoxycarbonyl)-5-styrylpiperidin-2-yl]-acetate. To a solution of 9c (270 mg, 0.60 mmol) in MeOH (3 ml) was added K$_2$CO$_3$ (28 mg, 0.2 mmol), and the whole was stirred for 6 h at room temperature. The reaction mixture was diluted with brine (5 ml) and extracted with CH$_2$Cl$_2$ (10 ml x 2). The combined extracts were dried over Na$_2$SO$_4$. After removal of solvent in vacuo, oily residue was purified by silica gel column chromatography. Elution with 15% AcOEt-hexane gave the corresponding methyl ester (195 mg, 79%) as a pale yellow oil. \( \text{Ir (neat, cm}^{-1}$): 1740-1700 (br), 1410, 1345, 1195, 1130. \( ^1\text{H-Nmr (}\delta\text{, ppm)}: 1.88 (2H, m), 2.22 (2H, m), 2.48 (1H, m), 3.17 (1H, m), 3.68 (3H, s), 4.40 (1H, m), 4.64 (1H, m), 4.73 (2H, br s), 6.11 (1H, dd, J=6.6, 15.8 Hz), 6.54 (1H, d, J=15.8 Hz), 7.20-7.36 (5H, m). FDms (m/z): 419 (M$^+$), 331, 318. HRms m/z: 419.0453 (M$^+$, calcd for C$_{18}$H$_{20}$NO$_4$Cl$_4$ 419.0458).

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