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 (BF_3·Et_2O/ethylene glycol) has been achieved.

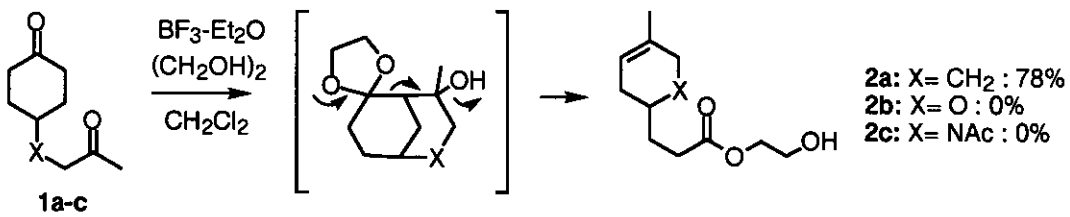
We previously reported a new type of ring transformation based on tandem aldol condensation and ring cleavage using a combination of Lewis acid and 1,2-diol. This reaction has been found to be widely applicable to not only the intramolecular system but also the intermolecular system.[1, 2] Furthermore, 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

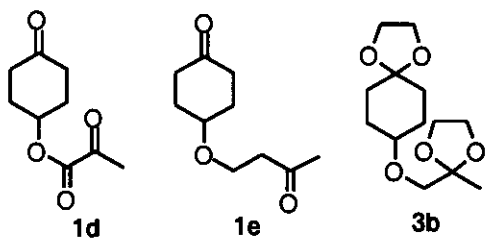
As an example of ring transformation based on intramolecular aldol condensation, the transformation of cyclohexanones with 3-oxobutyl substituent (**1a**) into products (**2a**) could be depicted as in Scheme 1 (X = CH_2).[1a] If X in compound (**1**) was a heteroatom such as in compounds (**1b**: X = 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 (BF_3-Et_2O (5 equiv.), ethylene glycol (7 equiv.) in CH_2Cl_2 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 BF_3 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.

Scheme 1

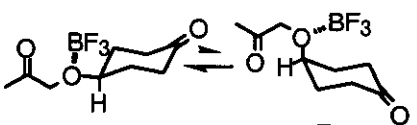


1a-c



1d **1e** **3b**

Scheme 2

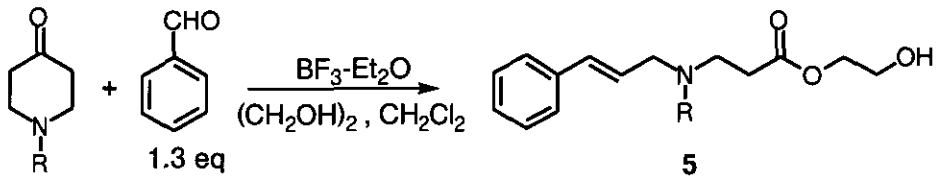


A **B**

RING CLEAVAGE REACTION OF HETEROCYCLIC KETONES

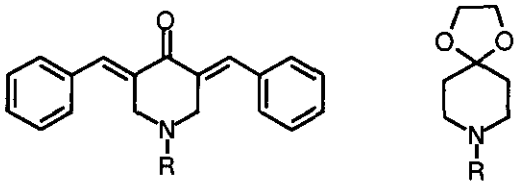
N-Substituted 4-piperidones (**4**) and N-substituted nortropinones (**8**) were designed as a substrate because the stereoelectronic effect as above mentioned could be neglected in the case of the reaction based on intermolecular aldol condensation. Furthermore, an electron-withdrawing substituent on 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.[1a] 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 BF_3-Et_2O (3 equiv.) and ethylene glycol (2 equiv.) in CH_2Cl_2 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 = CH_2Ph) as a substrate, the ring-cleaved product (**5**: R = CH_2Ph) was not obtained at all.

Table 1. Ring Cleavage Reaction of 4-Piperidones.



4 5

Entry		R	Time(h)		Yield (%)			
1	**4a**	Ac	92	**5a**	22	**6a** 44	**7a**	29
2	**4b**	$COCF_3$	42	**5b**	50	**6b** 10	**7b**	16
3	**4c**	$COOCH_2Cl_3$	48	**5c**	15	**6c** 12	**7c**	5



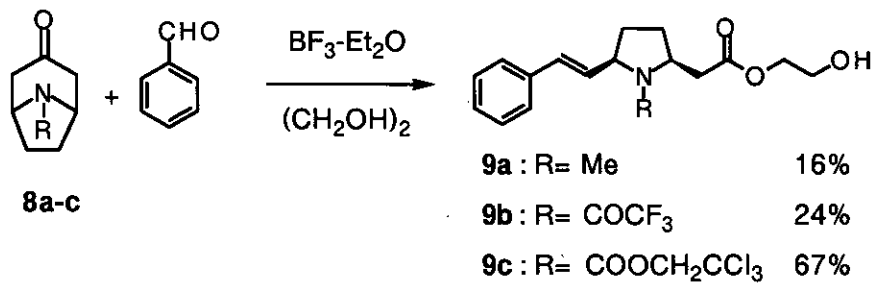
6 7

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 BF_3-Et_2O in CH_2Cl_2 without ethylene glycol also gave ring-cleaved **5b** in 46% yield.

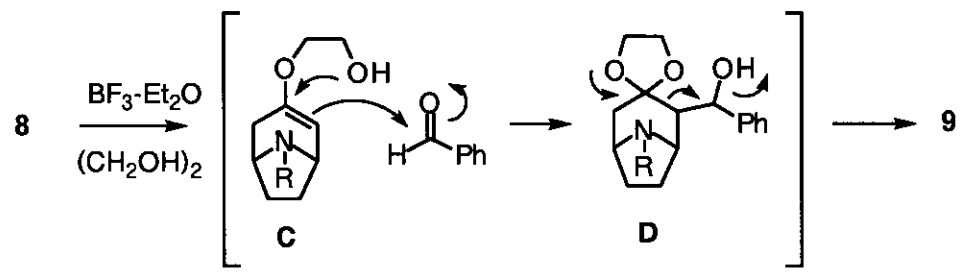
Next, N-substituted nortropinones (**8a-c**), prepared by reported procedure,[4] were submitted to the same reaction conditions, and the results are summarized in Scheme 3. Among them, compound (**8c**) gave the best yield of ring-cleaved (**9c**: 67%), and other two substrates (**8a,b**) did not afford 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_2CO_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 ^1H 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



Scheme 4



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 α,α'-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_2Cl_2 (8 ml) at 0°C were subsequently added BF_3-Et_2O (1.1 ml, 9.0 mmol), 4-piperidones (**4**) (3.0 mmol) in CH_2Cl_2 (4 ml), and ethylene glycol (372 mg, 6.0 mmol) in CH_2Cl_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_2Cl_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, J=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 (δ, 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 (δ, 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_2Cl_2 (8 ml) at 0°C was added trifluoroacetic 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 (δ, 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). ^{13}C-Nmr ($CDCl_3$) δ: 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_2O (1.1 ml, 9.0 mmol) and ethylene glycol (744 mg, 12 mmol) in CH_2Cl_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_2Cl_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 [(2SR,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 (δ, 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). ^{13}C-Nmr ($CDCl_3$) δ: 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 $C_{17}H_{23}NO_3$ 289.1678).

2-Hydroxyethyl [(2SR,5RS)-(E)-N-Trifluoroacetyl-5-styrylpiperidin-2-yl]acetate (9b). 24% yield. Ir (neat, cm^{-1}): 3400, 1735, 1680, 1450, 1215, 1155. ^{1}H-Nmr (δ, ppm): 1.48-1.81 (4H, m), 2.50-2.71 (2H, m), 3.20-3.38 (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 $C_{18}H_{20}NO_4F_3$ 371.1344).

2-Hydroxyethyl [(2SR,5RS)-(E)-N-(2,2,2-Trichloroethoxycarbonyl)-5-styrylpiperidin-2-yl]acetate (9c). 67% yield. Ir (neat, cm^{-1}): 3450, 1740-1700 (br), 1410, 1125, 1060. ^{1}H-Nmr (δ, 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_2CO_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_2Cl_2 (10 ml x 2). The combined extracts were dried over Na_2SO_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. Ir (neat, cm^{-1}): 1740-1700 (br), 1410, 1345, 1195, 1130. ^{1}H-Nmr (δ, 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 $C_{18}H_{20}NO_4Cl_3$ 419.0458).

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