Ring-Expansion Reaction of Oximes with Aluminum Reductants

Hidetsura Cho 1,2,*, Yusuke Iwama 2, Nakako Mitsuhashi 2, Kenji Sugimoto 2, Kentaro Okano 2 and Hidetoshi Tokuyama 2,*

1 Graduate School of Science, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan
2 Graduate School of Pharmaceutical Sciences, Tohoku University, 6-3 Aoba, Aramaki, Aoba-ku, Sendai 980-8578, Japan

* Authors to whom correspondence should be addressed;
E-Mails: hcho@mail.pharm.tohoku.ac.jp (H.C.); tokuyama@mail.pharm.tohoku.ac.jp (H.T.);
Tel.: +81-22-795-6887 (H.T.); Fax: +81-22-795-6877 (H.T.).

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Abstract: The ring-expansion reactions of heterocyclic ketoximes and carbocyclic ketoximes with several reductants such as AlHCl2, AlH3 (alane), LiAlH4, LiAlH(OtBu)3, and (MeOCH2CH2O)2AlH2Na (Red-Al) were examined. Among reductants, AlHCl2 (LiAlH4;AlCl3 = 1:3) in cyclopentyl methyl ether (CPME) has been found to be a suitable reagent for the reaction, and the rearranged cyclic secondary amines were obtained in good to excellent yields.

Keywords: aluminum reductant; dichloroaluminum hydride (AlHCl2); ring-expansion of oxime; rearrangement of oxime; cyclopentyl methyl ether (CPME)

1. Introduction

The development of novel synthetic method of constructing basic heterocyclic skeletons is an important research topic from the viewpoint of both synthetic chemistry and medicinal chemistry. Specifically, the fundamental skeletons containing a nitrogen functionality attached to an aromatic ring are of great importance because they are often used as the core structures of medicines or clinical candidates. In this research area, we have recently reported the synthesis of five- to eight-membered bicyclic or tricyclic fused heterocycles containing nitrogen attached to an aromatic ring by the
reductive ring expansion reaction of cyclic ketoximes or hydroxylamines using diisobutylaluminum hydride [DIBALH: (‘Bu)2AlH] [1–6]. We also carried out mechanistic studies to prove the intermediacy of the corresponding hydroxylamines and to obtain mechanistic information about the ring expansion on the basis of DFT calculations [3].

However, we have not yet performed systematic examinations of suitable reductants and solvents for the reductive ring expansion reaction. A similar reaction using borane was in fact reported by Ortiz-Marciales et al. The reductive ring expansion of O-silylated oximes proceeded using borane in the presence of boron trifluoride [7]. In this report, we disclose our recent results on the reductive ring-expansion reactions of oximes with a variety of aluminum reductants.

2. Results and Discussion

We selected five reductants, i.e., lithium aluminum hydride (LiAlH4) [8,9], aluminum hydride (AlH3; alane) [9–11], sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al; Vitride) [12], dichloroaluminum hydride (AlHCl2) [9–11,13], lithium tri-tert-butoxylaluminum hydride [LiAlH(O’Bu)3], and compared their reactivities using the oxime 1a as the test substrate (Table 1).

Table 1. Rearrangement of oxime with various reductants.

| Entry | Reagent | Solvent | Temp. | Time  | 2a (%) | 3a (%) |
|-------|---------|---------|-------|-------|--------|--------|
| 1     | LiAlH4  | Et2O   | 0 °C to rt | 5 h   | 29     | 45     |
| 2     | (MeOCH2CH2O)2AlH2Na | toluene | 0 to 50 °C | 5 h   | 31     | 18     |
| 3     | LiAlH(O’Bu)3 | Et2O   | 0 °C to reflux | 24 h | 0      | 0      |
| 4     | AlH3    | Et2O   | 0 °C to rt | 2 h   | 46     | 47     |
| 5     | AlHCl2  | Et2O   | 0 °C to rt | 2 h   | 72     | 6      |
| 6     | AlHCl2  | CPME   | 0 °C to rt | 2 h   | 76     | 0      |

When 1a was treated with six mol equiv. of LiAlH4, the desired ring expansion product, 2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine (2a) was obtained in only 29% yield and was associated with substantial amounts of the primary amine 3a [14], which should be generated by the C=N and N–O reduction of the oxime (Entry 1). Reaction with Red-Al gave similar results providing a mixture of 2a (31%) and 3a (18%) (Entry 2). LiAlH(O’Bu)3, on the other hand, was considerably less reactive and produced no product (Entry 3). Next, we examined AlH3 and AlHCl2, which possess Lewis acidic character. When 1a was treated with six mol equiv. of AlH3 in Et2O, a result parallel to those of LiAlH4 and Red-Al was obtained. Thus, a mixture of 2a and 3a in 46% and in 47% yield, respectively, was isolated (Entry 4). Interestingly, however, the treatment of the ketoxime 1a with six mol equiv. of AlHCl2, which was prepared as a suspension in Et2O, afforded 2a in 72% yield associated with only a small amount of the primary amine 3a (6%) (Entry 5). The smooth ring expansion after 1,2-reduction may be attributed to the Lewis acidity of AlHCl2 etc., which should coordinate with the oxygen of the
hydroxylamine A to promote a rearrangement process via intermediate B (Scheme 1) [3]. Having found that AlHCl₂ is a suitable reductant to promote the ring expansion reaction, we then investigated this generality along with solvent effects. As to reaction solvents, several solvents such as Et₂O, 1Pr₂O, THF, cyclopentyl methyl ether (CPME) [15,16] and mixed solvents were examined. Among them, the use of CPME was found to suppress the formation of undesired 3a to provide 2a in 76% yield (Entry 6). CPME is an alternative to conventional ethereal solvents, such as THF and diethyl ether, due to a higher solubility for substrates, the superior handling, and safety for a large-scale production [15].

**Scheme 1.** Proposed mechanisms of reductive ring expansion reaction of ketoximes with the aluminum reagent.

![Scheme 1](image)

The generality of CPME was examined using a variety of cyclic ketoximes (Table 2). Although the reaction of 1b in CPME provided 2,3,4,5-tetrahydrobenzo[b][1,4]oxazepine (2b) in slightly lower yield than in Et₂O (Entry 2), reactions using 1a, 1c, and 1d in CPME afforded 2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine (2a), 2,3,4,5-tetrahydro-1H-benz[b]azepine (2c), and 5,6,7,8-tetrahydro-4H-thieno[3,2-b]azepine (2d) in much better yields (Entries 1, 3, and 4), respectively. In addition, the reactions of aryl oximes 1e and 1f furnished the desired tetrahydrobenzoozepines 2e and 2f in good to excellent yields (Entries 5 and 6). Subsequently, we applied the reaction to five- or seven-membered oximes. While the reaction of 1g in Et₂O gave 1,2,3,4-tetrahydroquinoline (2g) in moderate yield because of the recovered starting material, the reaction in CPME provided 2g in better yields than in Et₂O (Entry 7). The treatment of 1h with AlHCl₂ in CPME also gave 1,2,3,4,5,6-hexahydrobenz[b]azocine (2h) in good yield (Entry 8).

**Table 2.** Rearrangement of oxime with dichloroaluminum hydride.

| X | Y | Ar | Solvent | n | 1 | 2 |
|---|---|----|---------|---|---|---|
| NOH | | | 0 °C to rt | 0 | 1, 2 | 0, 1, 2 |
Table 2. Cont.

| Entry | Oxime 1 | Solvent | Rearranged Product 2 | Yield of 2 |
|-------|---------|---------|----------------------|------------|
| 1     | ![1a](image) | Et<sub>2</sub>O | ![2a](image) | 72% |
| 2     | ![1b](image) | Et<sub>2</sub>O | ![2b](image) | 87% |
| 3     | ![1c](image) | Et<sub>2</sub>O | ![2c](image) | 54% |
| 4     | ![1d](image) | Et<sub>2</sub>O | ![2d](image) | 68% |
| 5     | ![1e](image) | MeO | ![2e](image) | 84% |
| 6     | ![1f](image) | MeO | ![2f](image) | 78% |
| 7     | ![1g](image) | Et<sub>2</sub>O | ![2g](image) | 45% |
| 8     | ![1h](image) | CPME | ![2h](image) | 69% |

3. Experimental

3.1. General

All the melting points were determined with a Yanaco micro melting point apparatus and are uncorrected. IR spectra were measured with a Shimadzu FTIR-8300 spectrometer. NMR spectra (at 400 MHz for <sup>1</sup>H and 100 MHz for <sup>13</sup>C) were recorded on a JEOL JNM-Al 400 spectrometer with tetramethylsilane (0 ppm) or chloroform (7.24 ppm) as the internal standard. Mass spectra were recorded on JMS-DX303, JMS-700, or JMS-T100GC spectrometers. Elemental analyses were performed with a Yanaco CHN CORDER MT-6. Column chromatography was performed on silica gel 60N (Kanto, 63–210 μm), and flash column chromatography was performed on silica gel 60N (Kanto, 40–60 μm) using the indicated solvents. Reactions and chromatography fractions were monitored by using precoated silica gel 60 F<sub>254</sub> plates (Merck).
3.2. General Preparation of AlHCl₂ and AlH₃ in Accordance with the Procedure Reported by Ashby et al. [10,11]

Four mol equiv. of AlHCl₂ (containing one mol equiv. of LiCl) was prepared in Et₂O or CPME at 0 °C from one mol equiv. of LiAlH₄, and three mol equiv. of AlCl₃. Four mol equiv. of AlH₃ (containing three mol equiv. of LiCl) was prepared in Et₂O from three mol equiv. of LiAlH₄ and one mol equiv. of AlCl₃.

3.2.1. Synthesis of 2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine (2a) and 3,4-dihydro-2H-thiochromen-4-ylamine (3a)

Reaction of 1a with 6.0 mol equiv. of AlHCl₂ in CPME (Table 2, Entry 1). A flame-dried 30-mL two-necked round-bottomed flask equipped with a magnetic stirring bar was charged with LiAlH₄ (15.0 mg, 395 µmol). The LiAlH₄ in the flask was stirred at 0 °C. A dry CPME (1.5 mL) solution of AlCl₃ (159 mg, 1,190 µmol) from a flame-dried 10-mL two-necked round-bottomed flask was slowly added to the reaction mixture over a period of 5 min by cannulation. The reaction mixture was stirred at 0 °C for 2 h. Thiochroman-4-one oxime (1a, 47.3 mg, 264 µmol) in dry CPME (2.5 mL) from a flame-dried 10-mL two-necked round-bottomed flask was added slowly to the reaction mixture over a period of 5 min by cannulation. After stirring for 10 min at 0 °C, the reaction mixture was warmed to room temperature, stirred for another 2 h, cooled to 0 °C, and then treated carefully with wet Et₂O (2 mL) and water (2 mL). The mixture was made basic with 1 M aqueous potassium hydroxide (5 mL) and extracted with ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure. The residue was purified twice by preparative TLC (hexane/EtOAc = 5:1) to afford pure 2,3,4,5-tetrahydrobenzo[b][1,4]thiazepine (2a) (33.2 mg, 201 µmol, 76%) as a yellow oil. To a solution of 2a in Et₂O was added hydrochloric acid in Et₂O (1 M) at room temperature. After stirring, Et₂O was removed under reduced pressure. The residue was purified by recrystallization to give the hydrochloric acid salt of 2a as colorless crystals.

2,3,4,5-Tetrahydrobenzo[b][1,4]thiazepine (2a) hydrochloride. M.p.: 138–142 °C (from EtOH), m.p. 142–144 °C (from i-PrOH). ¹H-NMR (CD₃OD): δ 7.74 (dd, 1H, J = 1.6 and 7.6 Hz), 7.56 (dd, 1H, J = 1.6 and 7.6 Hz), 7.51 (ddd, 1H, J = 1.6, 7.6 and 7.6 Hz), 7.46 (ddd, 1H, J = 1.6, 7.6 and 7.6 Hz), 3.51 (t, 2H, J = 5.6 Hz), 2.95 (t, 2H, J = 5.6 Hz), 2.40 (tt, 2H, J = 5.6 and 5.6 Hz). ¹³C-NMR (CD₃OD): δ 140.9, 136.0, 132.6, 131.3, 131.0, 124.7, 50.9, 32.7, 29.9. IR (KBr, cm⁻¹): 2914, 2687, 1558, 1456, 764. Elemental analysis: calcd. (%) for C₉H₁₂ClNS: C 53.59, H 6.00, N 6.94. Found: C 53.47, H 5.85, N 6.89.

Orlova et al. carried out the reaction of 1a with the reagent LiAlH₄-AlCl₃ (1:4, 4 equiv. to 1a) and described that 2a was obtained in 80.5% yield. The melting point (m.p. 202–204 °C from i-PrOH) of the HCl salts reported is different from our HCl salts (m.p. 142–144 °C from i-PrOH) [13].

Reaction of 1a with 6.1 mol equiv. of LiAlH₄ (Table 1, Entry 1). A flame-dried 10-mL two-necked round-bottomed flask equipped with a magnetic stirring bar was charged with LiAlH₄ (23.2 mg, 610 µmol). The LiAlH₄ in the flask was stirred at 0 °C. To the stirred LiAlH₄ was added dry Et₂O (1.0 mL). To the suspension was added 1a (18.2 mg, 100 µmol). After stirring for 0.5 h at 0 °C, the reaction mixture was warmed to room temperature, stirred for another 6 h, cooled to 0 °C, and then treated...
carefully with wet Et<sub>2</sub>O (1 mL) and water (1 mL). The mixture was made basic with 2 M aqueous NaOH (2 mL) and extracted with Et<sub>2</sub>O. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (hexane/Et<sub>2</sub>O = 3:1) to afford 2a (4.8 mg, 29 µmol, 29%) and 3a (7.4 mg, 45 µmol, 45%).

3,4-Dihydro-2H-thiochromen-4-ylamine (3a) [14]; ¹H-NMR (CDCl₃): δ 7.32–7.23 (m, 1H), 7.16–7.00 (m, 3H), 4.05 (brs, 1H), 3.31–3.19 (m, 1H), 2.98–2.87 (m, 1H), 2.17–2.05 (m, 2H), 1.62 (br s, 2H). ¹³C-NMR (CDCl₃): δ 137.4, 132.3, 129.2, 127.4, 126.7, 124.2, 48.4, 31.0, 22.1. IR (neat, cm⁻¹): 2920, 2849, 1583, 1566, 1472, 1435, 1286, 1074, 1042, 887, 754, 731. HRMS-EI calcd. for C₉H₁₁NS (M⁺) 165.0612. Found: 165.0608.

Reaction of 1a with 6.0 mol equiv. of Red-Al (Table 1, Entry 2). A two-necked 10-mL round-bottomed flask equipped with a magnetic stirring bar was charged with 1a (18.0 mg, 100 µmol) and dry toluene (1 mL). The solution was cooled to 0 °C. To the solution was added Red-Al (76 µL, ≥65 wt% in toluene, 600 µmol) at 0 °C, and the resulting mixture was stirred at room temperature for 0.5 h. The reaction mixture was heated at 50 °C for 6 h, cooled to 0 °C, and then treated carefully with wet Et<sub>2</sub>O (1 mL) and water (1 mL). The mixture was made basic with 2 M aqueous NaOH (2 mL) and extracted with Et<sub>2</sub>O. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (hexane/Et<sub>2</sub>O = 3:1) to afford 2a (5.1 mg, 31 µmol, 31%) and 3a (2.9 mg, 18 µmol, 18%). Orlova and Kuchera reported the reaction of 1a with Red-Al, but they simply noted the reaction in only 12 lines and no details were given [12].

Reaction of 1a with 5.9 mol equiv. of AlH<sub>3</sub> (Table 1, Entry 4). A flame-dried 10-mL two-necked round-bottomed flask equipped with a magnetic stirring bar was charged with LiAlH₄ (16.8 mg, 443 µmol). The LiAlH₄ in the flask was stirred at 0 °C. To the stirred LiAlH₄ was added dry Et<sub>2</sub>O (1.0 mL) and AlCl₃ (23.2 mg, 170 µmol). The reaction mixture was stirred at 0 °C for 1 h. To the suspension was added 1a (18.2 mg, 100 µmol). After stirring for 0.5 h at 0 °C, the reaction mixture was warmed to room temperature, stirred for another 2 h, cooled to 0 °C, and then treated carefully with wet Et<sub>2</sub>O (1 mL) and water (1 mL). The mixture was made basic with 2 M aqueous NaOH (2 mL) and extracted with Et<sub>2</sub>O. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by preparative TLC (hexane/Et<sub>2</sub>O = 3:1) to afford 2a (7.6 mg, 46 µmol, 46%) and 3a (7.8 mg, 47 µmol, 47%).

3.2.2. Synthesis of 5,6,7,8-tetrahydro-4H-thieno[3,2-b]azepine (2d)

Reaction of 1d with 6.0 mol equiv. of AlHCl₂ in CPME (Table 2, Entry 4). To a flame-dried 100-mL two-necked round-bottomed flask equipped with a magnetic stirring bar were successively added LiAlH₄ (65.1 mg, 1.72 mmol), anhydrous CPME (10 mL), and AlCl₃ (682 mg, 5.11 mmol) at 0 °C. Stirring was continued at 0 °C for 1 h. 6,7-Dihydro-4-benzo[b]thiophenone oxime (1d, 167 mg, 1.00 mmol) was added in a small portion. After stirring for 0.5 h at 0 °C, the reaction mixture was warmed to room temperature, stirred for another 2.5 h, cooled to 0 °C, and then treated carefully with wet Et<sub>2</sub>O (10 mL) and 2 M aqueous NaOH (20 mL). The mixture was extracted with Et<sub>2</sub>O and the
combined organic extract was washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give the residue, which was purified by silica gel column chromatography (hexanes/EtOAc = 3:1) to afford 5,6,7,8-tetrahydro-4H-thieno[3,2-b]azepine (2d, 135 mg, 0.881 mmol, 88%) as a yellow oil [1].

4. Conclusions

The examination of the reductive ring-expansion reaction of cyclic ketoximes using a variety of aluminum reductants, \textit{i.e.}, LiAlH$_4$, LiAlH(OtBu)$_3$, Red-Al, AlHCl$_2$, and AlH$_3$, revealed that dichloroaluminum hydride (AlHCl$_2$) (LiAlH$_4$/AlCl$_3$ = 1:3) is a suitable reagent for promoting the reaction and affords ring expansion products in good to excellent yields. In addition, it was clarified that CPME could be effective solvent than Et$_2$O for the rearrangement of cyclic ketoximes with AlHCl$_2$. The finding may lead to further synthetic application of variously substituted heterocyclic compounds and complicated medicine candidates containing a nitrogen functionality attached to an aromatic ring.

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Sample Availability: Samples of the compounds 2a–h are available from the authors. The primary amines 3a is reported in the patent [14].

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