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**REGIOSPECIFIC SYNTHESIS OF UNSUBSTITUTED BASIC
SKELETONS OF HETEROCYCLES CONTAINING NITROGEN
NEIGHBORING AN AROMATIC RING BY THE REDUCTIVE RING
EXPANSION REACTION USING DIISOBUTYLALUMINUM HYDRIDE**

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Hidetoshi Tokuyama^{*b}**

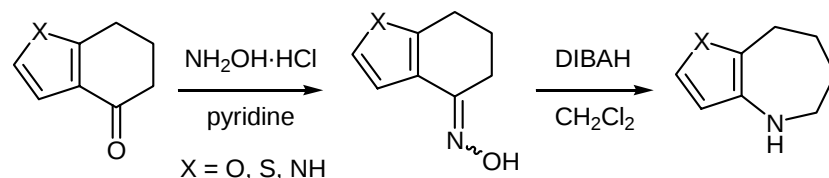
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Abstract – A systematic investigation of reductive ring expansion reaction of oximes with diisobutylaluminum hydride (DIBAH) was performed. The reaction regiospecifically provided a variety of unsubstituted bicyclic heterocycles **3a-3g** or tricyclic heterocycles **3h, 3j-3l** that contained nitrogen attached to an aromatic ring.

INTRODUCTION

Development of synthetic methods for unsubstituted basic skeletons of heterocycles is important from the viewpoint of both synthetic chemistry and medicinal chemistry. In particular, synthesis of bicyclic or tricyclic fused-heterocycles containing nitrogen attached to an aromatic ring (including benzazepine, benzoxazine, benzoxazepine, benzthiazine, and benzthiazepine) is crucial, since these often form the core structures of medicines or clinical candidates. However, there are only few synthetic procedures available to construct heterocycles containing nitrogen attached to an aromatic ring. While Beckmann rearrangement or Schmidt rearrangement of bicyclic aryl ketones is a possible approach to obtaining these compounds, such reactions generally produce two isomeric lactam derivatives.¹ On the other hand, structural simplicity means that construction of unsubstituted basic skeletons is relatively difficult and usually requires lengthy procedures when conventional methods are employed, such as lactamization and

reduction.² Cho and co-workers devised a method for the construction of heterocyclic fused-azepines by ring expansion of oxime derivatives with diisobutylaluminum hydride (DIBAH) during the course of investigating arginine vasopressin antagonists (Scheme 1).^{3,4}



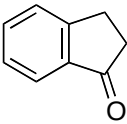
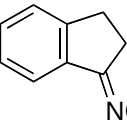
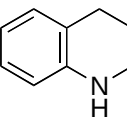
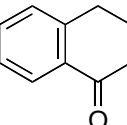
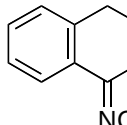
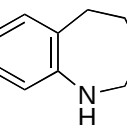
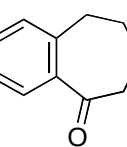
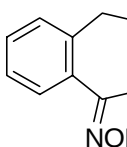
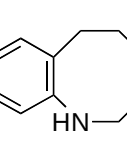
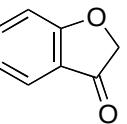
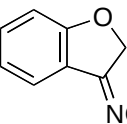
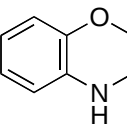
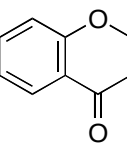
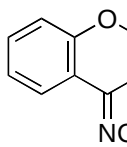
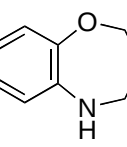
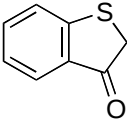
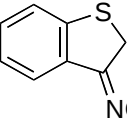
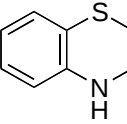
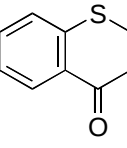
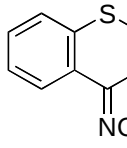
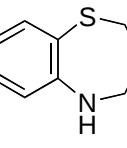
Scheme 1

Namely, it was found that the regiospecific ring expansion reaction of oximes with DIBAH gave the corresponding heterocyclic fused-azepines such as 5,6,7,8-tetrahydro-4*H*-thieno[3,2-*b*]azepine, 5,6,7,8-tetrahydro-4*H*-furo[3,2-*b*]azepine, and 5,6,7,8-tetrahydro-4*H*-pyrro[3,2-*b*]azepine as the sole product. Yamamoto and Maruoka reported that the rearrangement of aliphatic hydroxylamine carbonates by trialkylaluminum compounds and the reduction of oximes and oxime sulfonates with DIBAH gave the corresponding simple amines.⁵ After Cho's preliminary report, Torisawa⁶ and Willand⁷ more recently applied the ring expansion reaction with DIBAH to the synthesis of heterocyclic compounds. On the other hand, Ortiz-Marciales⁸ reported the synthesis of similar heterocycles by rearrangement of *O*-silylated oximes via reduction with boran in the presence of boron trifluoride. Similarly, Naito studied ring expansion for several azepines by reactions of *N*-alkoxy(arylmethyl)amines to *N*-alkyl arylamines with an organolithium or a magnesium reagent.⁹ While several applications have been reported, there have been no investigations about its general applicability. Here we describe a systematic investigation of using the reductive ring expansion reaction with DIBAH for regiospecific synthesis of unsubstituted basic skeletons of bicyclic or tricyclic heterocycles.

RESULTS AND DISCUSSION

A series of aryl ketones **1a–1l**, which are commercially available or known in the literature,¹⁰ were converted to the corresponding oxime derivatives **2a–2l**¹¹ by treatment with two to four equivalents of hydroxylamine hydrochloride in pyridine (Table 1 and Table 2). Without separation, the *E*, *Z* mixture of oximes was reacted with six equivalents of a hexane solution of DIBAH at 0 °C to r.t. Then the reaction mixture was treated with NaF to give the corresponding bicyclic or tricyclic secondary amine compounds (Table 1 and Table 2) at good to excellent yields. Reaction of a series of oximes **2a**, **2b**, or **2c**, derived from five-, six-, or seven-membered carbocyclic ketones, resulted in the six-, seven-, or eight-membered cyclic secondary amines 1,2,3,4-tetrahydroquinoline **3a**, 2,3,4,5-tetrahydro-1*H*-benz[*b*]azepine **3b**,⁸ and 1,2,3,4,5,6-hexahydrobenz[*b*]azocine **3c**,¹² respectively (Table 1; entries 1-3). Similarly, oximes **2d**, **2e**, **2f**, or **2g** prepared from five- or six-membered oxygen- or sulfur-containing cyclic-ketones **1d**, **1e**, **1f**, and **1g**

Table 1. Ring Expansion Reaction of Bicyclic Oximes with DIBAH

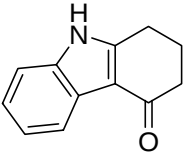
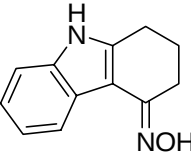
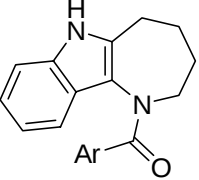
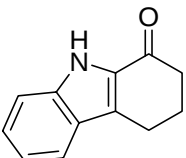
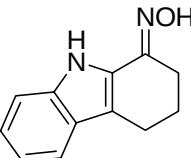
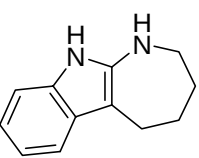
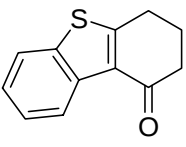
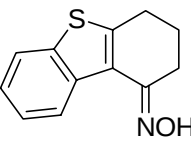
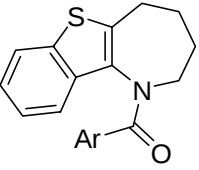
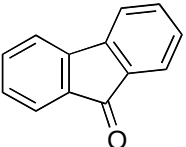
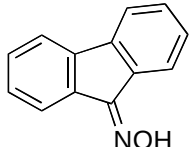
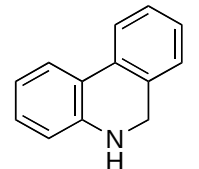
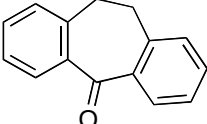
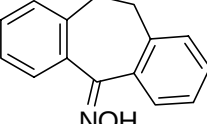
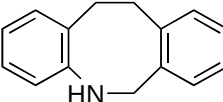
Entry	Ketone 1a-1g	Oxime 2a-2g (% yield) ^a	Aromatic amine 3a-3g (% yield) ^b
1	 1a	 2a (85)	 3a (92)
2	 1b	 2b (87)	 3b (80)
3	 1c	 2c (90)	 3c (73)
4	 1d	 2d (69)	 3d (80)
5	 1e	 2e (80)	 3e (87)
6	 1f	 2f (64)	 3f (60)
7	 1g	 2g (96)	 3g (71)

^aThe reactions were carried out with ketone (1 eq) and hydroxyamine hydrochloride (2 eq) in pyridine at room temperature for 1-3 h.^bThe reactions were carried out with oxime (1 eq) and DIBAH (6-9 eq) in CH₂Cl₂ at room temperature for 2-5 h.

were converted to six- or seven-membered cyclic secondary amine derivatives, including 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine **3d**,¹³ 2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepine **3e**,⁸ 3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine **3f**,¹⁴ and 2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine **3g**,^{14, 15} respectively (Table 1; entries 4-7).

Significantly, the procedure was applicable to performing the ring expansion reaction of oxime **2h**¹¹ which was prepared from 1,2,3,4-tetrahydrocarbazol-4-one **1h**, leading to the tricyclic compound 1,2,3,4,5,6-hexahydroazepino[3,2-*b*]indole **3h**.

Table 2. Ring Expansion Reaction of Tricyclic Oximes with DIBAH

Entry	Ketone 1h-1l	Oxime 2h-2l (% yield) ^a	Aromatic amine 3h-3l, 4, 5 (% yield) ^b
1	 1h	 2h (91)	 3h (not isolated) 4 (63) ^c Ar = <i>p</i> -nitrophenyl
2	 1i	 2i (99)	 3i (0)
3	 1j	 2j (77)	 3j (not isolated) 5 (21) ^c Ar = <i>p</i> -nitrophenyl
4	 1k	 2k (99)	 3k (69)
5	 1l	 2l (54) ^d	 3l (60)

^aThe reactions were carried out with ketone (1 eq) and hydroxyamine hydrochloride (2 eq) in pyridine at room temperature for 1-3 h.

^bThe reactions were carried out with oxime (1 eq) and DIBAH (6-9 eq) in CH₂Cl₂ at room temperature for 2-5 h.

^cThe yields were based on oximes. ^dThe reactions were carried out with ketone (1 eq) and hydroxyamine hydrochloride (4 eq) in pyridine under reflux for 11 h.

Since the product **3h** was unstable, its yield was determined after benzylation with *p*-nitrobenzoyl chloride and Et₃N in dichloromethane to afford **4** (Table 2; entry 1). The NMR spectrum of **4** exhibited only one proton at a lower field (δ 5.11 ppm), apart from the other aliphatic protons. Therefore, the structure of this tricyclic compound **4** was unambiguously determined by X-ray crystallographic analysis (Figure 1).¹⁶ This also confirmed the regiochemistry of the ring expansion reaction. Thus, the ORTEP drawing of compound **4** in Figure 1 shows that the product **3h** had a nitrogen atom attached to an aromatic ring, indicating that aryl migration occurred regiospecifically to produce the tricyclic compound. Despite successful conversion from indole derivative **1h** to **3h**, reaction of oxime **2i** derived from 2,3,4,9-tetrahydrocarbazol-1-one **1i** gave a complex mixture under the same reaction conditions and the desired tricyclic compound **3i** was not detected.

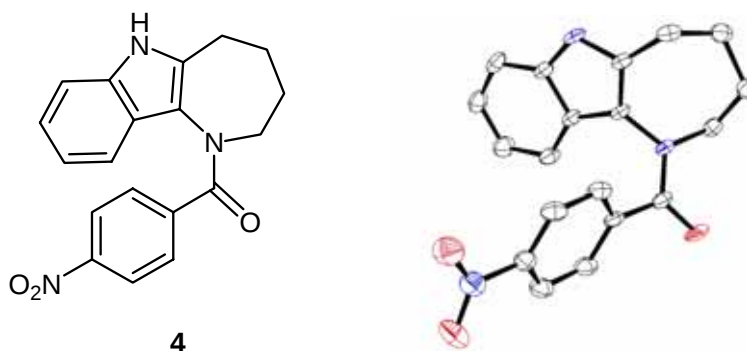


Figure 1 ORTEP drawing of the molecular structure of compound **4** with thermal ellipsoids at 50 % probability levels. Hydrogen atoms are omitted for clarity.

Similarly, we tried to synthesize the other tricyclic heterocycle, 2,3,4,5-tetrahydro-1*H*-benzothieno[3,2-*b*]azepine **3j** from the corresponding ketone **1j** which was obtained by the new synthetic methods (Scheme 2). As the compound **3j** was also unstable, benzylation was carried out as mentioned above to afford compound **5**, which was observed as a mixture (6.6:1) of rotamers in ¹H NMR and ¹³C NMR spectra. Next, the possibility of rearrangement on the oximes of the tricyclic ketones; 9-fluorenone **1k** and dibenzosuberone **1l** was examined. Preparation of oxime **2l** from **1l** proceeded in pyridine under reflux for 11 h, and rearrangement from **2k** to 5,6-dihydrophenanthridine **3k**¹⁷ or from **2l** to 5,6,11,12-tetrahydrodibenz[*b, f*]azocine **3l** needed longer reaction time (3 h or 4 h), respectively.

The mechanism of the ring expansion reaction using DIBAH has been briefly described in previous studies.³ We speculate that the reaction is initiated by reduction of the C-N double bond of oximes and subsequent aromatic ring-assisted N-O bond cleavage, followed by ring expansion to furnish the ring expansion product with nitrogen attached to the aromatic ring. Further studies on the detailed

mechanisms are currently under way and will be reported in due course.

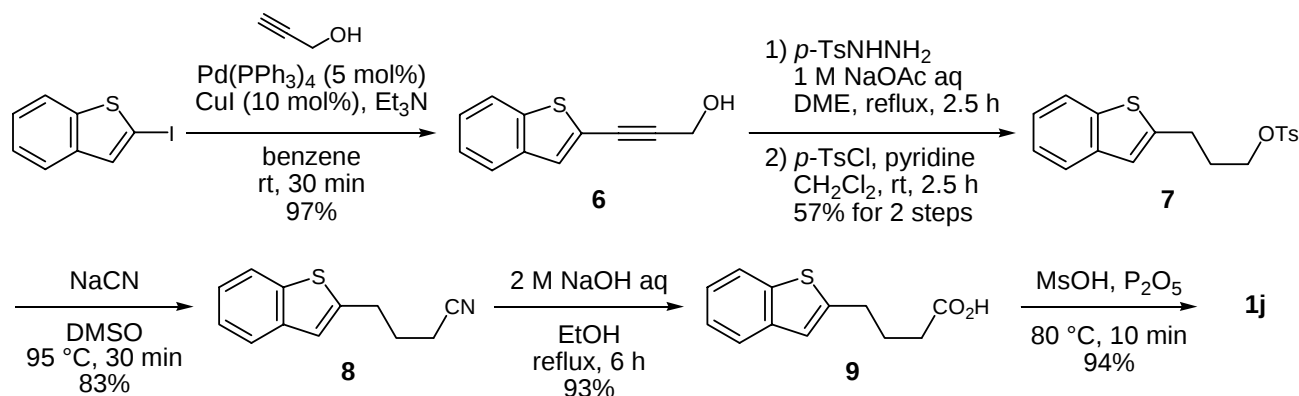
In conclusion, we carried out a systematic investigation of the reductive ring expansion reaction of oximes with DIBAH. It was demonstrated that this procedure was general and useful for constructing a variety of bicyclic or tricyclic heterocycles containing nitrogen attached to an aromatic ring from the corresponding aryl ketones. Reactions using a series of substrates revealed that this method is not only applicable to preparation of the core structures (such as 1,2,3,4-tetrahydroisoquinoline, 2,3,4,5-tetrahydro-1*H*-benz[*b*]azepine, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine, 2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepine, 3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine and 2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine derivatives) of medicines or clinical candidates, but can also be used for the synthesis of 1,2,3,4,5,6-hexahydrobenz[*b*]azocine, 5,6,11,12-tetrahydrodibenz[*b, f*]azocine, 2,3,4,5-tetrahydro-1*H*-benzothieno[3,2-*b*]azepine, 1,2,3,4,5,6-hexahydroazepino[3,2-*b*]indole, and 5,6-dihydrophenanthridine derivatives which have potential as the core structures of new drugs. Furthermore, this procedure should be applicable to other bicyclic or tricyclic basic skeletons containing a heteroaryl ring instead of a benzene ring. This method might be practically useful since it has been possible to employ DIBAH on an industrial scale.¹⁸ Due to its versatility, this synthetic procedure may find widespread use in the fields of medicinal chemistry and process chemistry for creation of novel drugs as well as for synthesis of the related natural products.

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10. The starting materials **1a**, **1b**, **1c**, **1e**, **1g**, **1k** and **1l** are commercially available. Compounds **1d**, **1f**, and **1h** were prepared according to the procedures in the literatures. For **1d**, see: A. Inoue, K. Kitagawa, H. Shinokubo, and K. Oshima, *J. Org. Chem.*, 2001, **66**, 4333. For **1f**, see: C. Mukherjee, S. Kamila, and A. De, *Tetrahedron*, 2003, **59**, 4767. For **1h**, see: X. Li and R. Vince, *Bioorg. Med. Chem.*, 2006, **14**, 2942. For cyclization from the carboxylic acid to **1i** or **1j**, see: H. Cho and S. Matsuki, *Heterocycles*, 1996, **43**, 127. For new synthesis of **1j**, see: **Scheme 2** shown below. (As for the starting material, 2-iodobenzo[*b*]thiophene, consult ref. 19.)



Scheme 2

11. The spectral data of oximes **2a**, **2b**, **2c**, **2d**, **2e**, **2k** are identical with those reported previously. For **2a** and **2b**, see: H. Zhao, C. P. Vandenbossche, S. G. Koenig, S. P. Singh, and R. P. Bakale, *Org. Lett.*, 2008, **10**, 505. For **2c**, see: P. A. Bonvallet, E. M. Todd, Y. S. Kim, and R. J. McMahon, *J. Org. Chem.*, 2002, **67**, 9031. For **2d** and **2e**, see: D. L. J. Clive, M. P. Pham, and R. Subedi, *J. Am. Chem. Soc.*, 2007, **129**, 2713. For **2h**, see: S.-I. Bascop, J.-Y. Laronze, and J. Sapi, *Monat. Chem.*, 1999, **130**, 1159. For **2k**, see: N. Jain, A. Kumar, and S. M. S. Chanhan, *Tetrahedron Lett.*, 2005, **46**, 2599.
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15. General Procedure for the ring expansion reaction using DIBAH: Synthesis of 2,3,4,5-Tetrahydrobenzo[*b*][1,4]thiazepine (**3g**): To a stirred solution of 1-thiochroman-4-one **1g** (4.40 g, 26.8 mmol) in pyridine (50.0 mL) was added hydroxylamine hydrochloride (3.76 g, 54.1 mmol) at rt. After stirring for 1.5 h, pyridine was removed *in vacuo*. The residue was diluted with water and extracted with EtOAc. The aqueous layer was extracted with EtOAc and the combined organic extracts were washed with brine, dried over MgSO₄, and evaporated under reduced pressure to give the crude

material. Chromatography on a silica gel column (EtOAc:*n*-hexane = 1:3) resulted in oxime **2g** (4.61 g, 96%). To a stirred solution of **2g** (1.01 g, 5.63 mmol) in CH₂Cl₂ (56.0 mL) was added DIBAH (33.0 mL, 33.7 mmol, 1.02 M in *n*-hexane) over 10 min at 0–5 °C (internal temperature) under Ar. Stirring was continued for 5 min at 0 °C and for 2 h at rt. NaF powder (6.76 g, 161 mmol) and water (2.2 mL) were added at 0 °C and the resulting mixture was stirred for 30 min at the same temperature. Then the reaction mixture was filtered through a pad of Celite. The filter cake was washed with EtOAc and the combined organic solutions were evaporated to give the crude product. Purification by chromatography on a silica gel column (Et₂O:*n*-hexane = 1:3) yielded 2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine **3g** (662 mg, 71%). (¹H NMR data was identified with that reported in ref 14. Although 3 mol eq. of DIBAH is theoretically sufficient in this method, we often employed 6–9 mol eq. of the reagent to finish each reaction.)

16. *Crystal data* for **4** C₁₉H₁₇N₃O₃: MW = 335.36, monoclinic, *a* = 8.481(2), *b* = 21.573(6), *c* = 18.718(5) Å, β = 99.133(3)°, *V* = 3381.2(16) Å³, *T* = 173 K, space group *P*2₁/*c* (no. 14), *Z* = 8, μ(MoKα) = 0.911 cm^{−1}, *D*_{calc} = 1.317 g/cm³. A total of 49590 reflections were measured, of which 7695 unique (*R*_{int} = 0.051) reflections were used for analysis. The structure was refined to a goodness of fit (GOF) of 0.96 and the final residuals were *R* = 0.064 and *wR* = 0.084. Crystallographic data of **4** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-700651. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB1 1EZ, UK (fax:+44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk).
17. J. Barluenga, F. J. Fañanas, R. Sanz, and Y. Fernández, *Chem. Eur. J.*, 2002, **8**, 2034.
18. For an example to use DIBAH in the process chemistry, see: L. A. Hobson, W. A. Nugent, S. R. Anderson, S. S. Deshmukh, J. J. Haley III, P. Liu, N. A. Magnus, P. Sheeran, J. P. Sherbine, B. R. P. Stone, and J. Zhu, *Org. Process Res. Develop.*, 2007, **11**, 985. In the case of cyclohexanone oxime, the large-scale production using DIBAH is also progressing in a chemical corporation.
19. Y. Nicolas, P. Blanchard, E. Levillain, M. Allain, N. Mercier, and J. Roncali, *Org. Lett.*, 2004, **6**, 273.