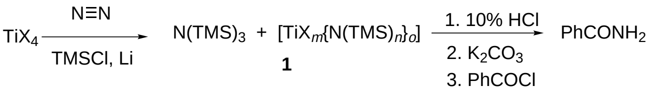
Fixation of Atmospheric Nitrogen: Synthesis of Heterocycles with Atmospheric Nitrogen as the Nitrogen Source**

Miwako Mori,* Katsutoshi Hori, Masaya Akashi, Masanori Hori, Yoshihiro Sato, and Mayumi Nishida

Since nitrogen fixation was first described by Vol'pin, Shur, et al.[1b, c] and van Tamelen et al.[1d, e] in the early 1960s there have been reports of molecular nitrogen fixation by various transition metals.[1] It is well known that nitrogenase catalyzes the reduction of atmospheric nitrogen to NH_3, fixation of atmospheric nitrogen in the laboratory remains quite challenging.[1d, e] Here we report the first example of the fixation of atmospheric nitrogen by TiX_4-Li-TMSCl[2] and the synthesis of heterocycles with atmospheric nitrogen as the nitrogen source (TMS = trimethylsilyl).

To examine whether atmospheric nitrogen can be fixed in titanium–nitrogen complexes of the type **1**,[2] we first attempted to prepare $PhCONH_2$ as a product of nitrogen fixation with benzoyl chloride. A solution of $TiCl_4$ (1.0 equiv) and TMSCl (10.0 equiv) in THF was stirred in the presence of Li (10.0 equiv, porous) under dry air at room temperature for 24 h. The solution turned black with a green tinge. After hydrolysis the solution was made basic with K_2CO_3. To this was added a solution of PhCOCl in benzene, and the mixture was stirred overnight. After the usual workup, we were pleased to identify $PhCONH_2$ in 88% yield. Various titanium complexes such as $[Cp_2TiCl_2]$ and Ti(O*i*Pr)$_4$ were applicable to this reaction, and $TiCl_4$ also gave good results (Table 1).



$$TiX_4 \xrightarrow[\text{TMSCl, Li}]{N\equiv N} N(TMS)_3 + \underset{\mathbf{1}}{[TiX_m\{N(TMS)_n\}_o]} \xrightarrow[\text{2. } K_2CO_3 \text{ 3. PhCOCl}]{\text{1. 10\% HCl}} PhCONH_2$$

This means that atmospheric nitrogen can be fixed in the form of titanium–nitrogen complexes **1**. We next tried to synthesize N-heterocycles with dry air or molecular nitrogen as the nitrogen source using a TiX_4-Li-TMSCl system.[2] To a solution of cyclohexadione derivative **2a** and CsF in THF was added a solution of **1** in THF prepared under dry air from $TiCl_4$, Li, and TMSCl. The resulting mixture was heated at reflux overnight. After the usual workup indole derivative **3a** was obtained in 56% yield (Table 2, entry 1). When molecular nitrogen was used instead of air, **3a** was obtained in 86% yield.[2b] Similar treatment of diketone **2b** led to pyrrole derivative **3b** in moderate yield (entry 2). Michael addition of **1** to **2c** followed by condensation with the associated keto group proceeded smoothly at room temperature to give the tetrahydroindole derivative **3c** in good yield (entry 3). Lactams **3d**[3] and **3e** were obtained in a similar manner from the activated esters **2d** and **2e** (entries 4 and 5), respectively, which also contain keto groups and were prepared from the corresponding carboxylic acids by treatment with $ClPO(OEt)_2$. Interestingly, use of dry air as the nitrogen source gave nearly the same results as with molecular nitrogen.

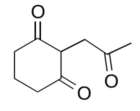
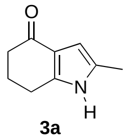
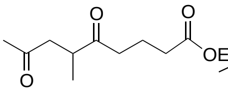
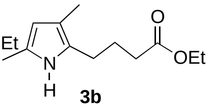
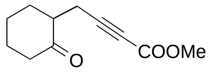
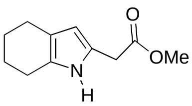
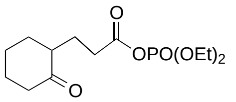
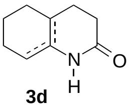
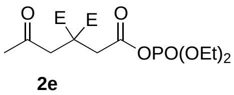
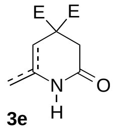
We next investigated whether $TiCl_4$ could act as a catalyst.[2] To a solution of **1**—prepared under dry air from $TiCl_4$ (1 equiv), TMSCl (50 equiv), and Li (50 equiv)—in THF was added a solution of **2a** (10 equiv) and CsF (25 equiv) in THF. The mixture was heated at reflux for 24 h. After hydrolysis of the crude product indole derivative **3a** was isolated in 220% yield based on $TiCl_4$.[4] This means that nitrogen can be fixed catalytically from dry air in the form of $N(TMS)_3$, which acts as a ligand for titanium.

Table 1. Yields [%] of benzamide.[a]

TiX_4	N_2 (pure)	Air
$TiCl_4$	90	88
Ti(O*i*Pr)$_4$	91	80

[a] Yields are based on the titanium compound.

Table 2. Synthesis of heterocycles with fixed nitrogen.[a]

Entry	Substrate	Product	TiX_4	Yield [%][b] (N_2 Source)
1	 **2a**	 **3a**	$TiCl_4$ $TiCl_4$	86 (N_2) 56 (air)
2	 **2b**	 **3b**	$TiCl_4$ $TiCl_4$	51 (N_2) 37 (air)
3	 **2c**	 **3c**	$TiCl_4$ Ti(O*i*Pr)$_4$ Ti(O*i*Pr)$_4$	90 (N_2) 82 (N_2[c]) 72 (air[c])
4	 **2d**	 **3d**	Ti(O*i*Pr)$_4$ Ti(O*i*Pr)$_4$	58 (N_2) 60 (air)
5	 **2e** E=COO*t*Bu	 **3e**	Ti(O*i*Pr)$_4$ Ti(O*i*Pr)$_4$	51 (N_2) 50 (air)

[a] Complex **1** was prepared from TiX_4 (1.25 equiv), Li (12.5 equiv), and TMSCl (12.5 equiv) in THF under pure nitrogen or dry air at room temperature over 24 h. The reaction with **1** was conducted in the presence of CsF (5 equiv) in THF under reflux (24 h). [b] The yields are based on the substrate. [c] The reaction was carried out at room temperature (24 h).

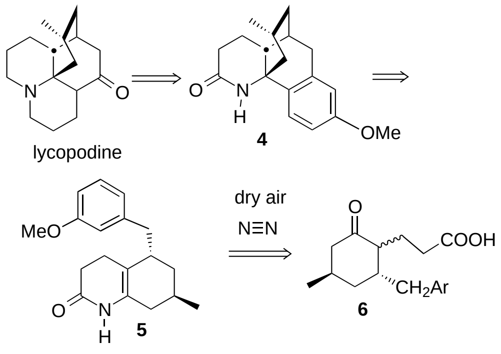
---

[*] Prof. Dr. M. Mori, K. Hori, M. Akashi, M. Hori, Y. Sato, M. Nishida
Faculty of Pharmaceutical Sciences
Hokkaido University
Sapporo 060 (Japan)
Fax: (+81) 11-721-6045
E-mail: mori@pharm.hokudai.ac.jp

[**] We thank the Hokkaido Foundation for the Promotion of Scientific and Industrial Technology for their support of this work. Supporting information for this contribution is available on the www under www/wiley-vch.de/home/angewandte.

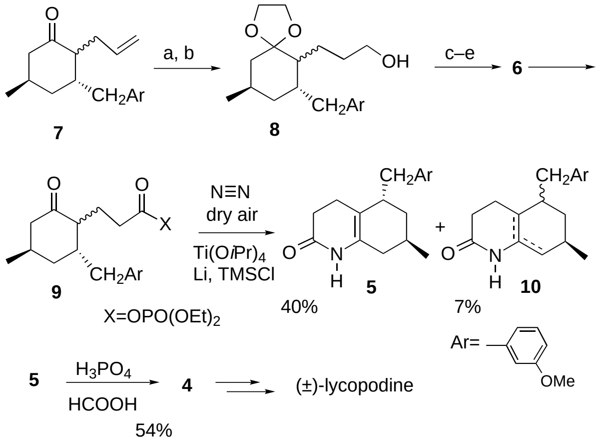
1433-7851/98/3705-0636 $ 17.50+.50/0

We then attempted to prepare the key intermediate in the synthesis of (±)-lycopodine[5] with dry air as the nitrogen source (Scheme 1). The total synthesis of (±)-lycopodine was achieved by Stork and co-workers[6] starting with the tetracycle **4**, which was obtained from lactam **5**. It was our intent to generate **5** from carboxylic acid **6** with dry air as the nitrogen source.



Scheme 1. Retrosynthesis of lycopodine.

Ketalization of **7**, which was easily prepared from 5-methyl-2-cyclohexenone,[7] followed by hydroboration and subsequent treatment with H_2O_2 in aqueous NaOH led to compound **8**, which was transformed into carboxylic acid **6** by oxidation and removal of the protecting group (Scheme 2).



Scheme 2. Synthesis of the lycopodine precursors **4** and **5**. a) $\mathrm{TMSOCH_2CH_2OTMS}$, TMSOTf, 88%; b) $\mathrm{(Sia)_2BH}$, then H_2O_2, NaOH, 98%; c) PCC; d) TsOH, acetone/H_2O; e) $\mathrm{NaClO_2}$, $\mathrm{KH_2PO_4}$, 2-methyl-2-butene, 67% based on **8**. Tf = Trifluoromethanesulfonate, Sia = 1,2-dimethylpropyl, PCC = pyridinium chlorochromate, Ts = 4-toluenesulfonyl.

A solution of **9**, derived from **6** and $\mathrm{ClPO(OEt)_2}$, in THF together with **1**—prepared from Ti(O*i*Pr)$_4$, Li, and TMSCl under dry air—was heated at reflux for 36 h; lactam **5** was then isolated in 40% yield along with a mixture of the stereoisomeric compounds **10**[8] in 7% yield. The melting point of **5** was in complete agreement with that reported in the literature.[6a, b] Conversion of **5** into **4** proceeded smoothly according to the procedure of Stork et al.

Thus, a formal total synthesis of (±)-lycopodine has been achieved with the aid of complexes of type **1** prepared from dry air; fixation of atmospheric nitrogen for the synthesis of heterocyclic compounds is clearly feasible. Notable characteristics of this procedure are the following: 1) the reaction is simple (a THF solution of $\mathrm{TiCl_4}$ or Ti(O*i*Pr)$_4$ and TMSCl in the presence of Li need only be stirred under dry air at room temperature), 2) $\mathrm{TiCl_4}$ acts as a catalyst, and 3) nitrogen fixed from dry air can be introduced directly into organic compounds to produce useful heterocyclic compounds.

Received: October 8, 1997 [Z11020IE]
German version: *Angew. Chem.* **1998**, *110*, 659–661

Keywords: heterocycles · lycopodine · nitrogen fixation · titanium

---

[1] a) M. Hidai, Y. Mizobe, *Chem. Rev.* **1995**, *95*, 1115; b) M. E. Vol'pin, V. B. Shur, *Dokl. Akad. Nauk SSSR*, **1964**, *156*, 1102; c) M. E. Vol'pin, M. A. Ilatovskaya, L. V. Kosyakova, V. B. Shur, *J. Chem. Soc. Chem. Commun.* **1968**, 1074; d) E. E. van Tamelen, D. Seeley, S. Schneller, H. Rudler, W. Cretney, *J. Am. Chem. Soc.* **1970**, *92*, 5251; e) E. E. van Tamelen, *Acc. Chem. Res.* **1970**, *3*, 361; f) A. Yamamoto, M. Ookawa, S. Ikeda, *J. Chem. Soc. Chem. Commun.* **1969**, 841; g) K. Shiina, *J. Am. Chem. Soc.* **1972**, *94*, 9266; h) M. Mori, Y. Uozumi, M. Shibasaki, *Tetrahedron Lett.* **1987**, *28*, 6187; i) Y. Uozumi, N. Kawasaki, E. Mori, M. Mori, M. Shibasaki, *J. Am. Chem. Soc.* **1989**, *111*, 3725; j) Y. Uozumi, M. Mori, M. Shibasaki, *J. Chem. Soc. Chem. Commun.* **1991**, 81.

[2] a) M. Kawaguchi, S. Hamaoka, M. Mori, *Tetrahedron Lett.* **1993**, *34*, 6907; b) M. Mori, M. Kawaguchi, M. Hori, S. Hamaoka, *Heterocycles* **1994**, *39*, 729; c) M. Hori, M. Mori, *J. Org. Chem.* **1995**, *60*, 1480.

[3] D. Elad, D. Ginsburg, *J. Chem. Soc.* **1953**, 4137.

[4] When the same reaction was carried out under nitrogen gas, the indole derivative **3a** was isolated in 273% yield.

[5] a) K. Wiesner, *Fortschr. Chem. Org. Naturst.* **1962**, *20*, 271; b) D. B. MacLean, *Alkaloids (NY)* **1968**, *10*, 305.

[6] Total synthesis of (±)-lycopodine: a) G. Stork, R. A. Kretchmer, R. H. Schlessinger, *J. Am. Chem. Soc.* **1968**, *90*, 1647; b) G. Stork, *Pure Appl. Chem.* **1968**, *36*, 383; c) C. H. Heathcock, E. F. Kleinman, E. S. Binkley, *J. Am. Chem. Soc.* **1982**, *104*, 1054; d) C. H. Heathcock, E. F. Kleinman, *Tetrahedron Lett.* **1979**, 4125; e) C. H. Heathcock, E. F. Kleinman, E. S. Binkley, *J. Am. Chem. Soc.* **1978**, *100*, 8036; f) E. Wenkert, C. A. Broka, *J. Chem. Soc. Chem. Commun.* **1984**, 714; g) W. A. Ayer, W. R. Bowman, T. C. Joseph, P. Smith, *J. Am. Chem. Soc.* **1968**, *90*, 1648; h) D. Schuman, H. J. Muller, A. Nauman, *Liebigs Ann. Chem.* **1982**, 1700; i) S. W. Kim, Y. Bando, Z. I. Horii, *Tetrahedron Lett.* **1978**, 2293; j) T. Momose, S. Uchida, T. Imanishi, S. Kim, N. Takahashi, Z. I. Horii, *Heterocycles* **1977**, *6*, 1105; k) G. A. Kraus, Y. S. Hon, *ibid.* **1987**, *25*, 377; l) G. A. Karus, Y. S. Hon, *J. Am. Chem. Soc.* **1985**, *105*, 4341.

[7] W. Oppolzer, X. Petrzilka, *Helv. Chim. Acta* **1978**, *61*, 2755.

[8] The mixture consists of a pure constitutional isomer of **5** together with *cis*-**5** and the corresponding constitutional isomer. When *trans*-3-(3-methoxybenzyl)-5-methylcyclohexanone was synthesized by the reaction of 5-methyl-2-cyclohexenone with 3-methoxybenzylmagnesium chloride in the presence of CuI, a small amount of the *cis* isomer was obtained: A. Padwa, M. A. Brodney, J. P. Marino, Jr., S. M. Sheehan, *J. Org. Chem.* **1997**, *62*, 78.