

Communications

Synthesis of Heterocycles Utilizing N_2 -TiCl₄-Li-TMSCl

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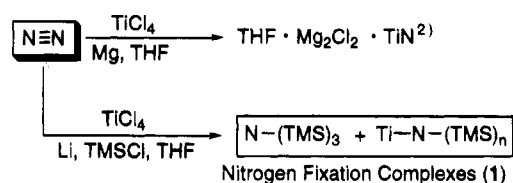
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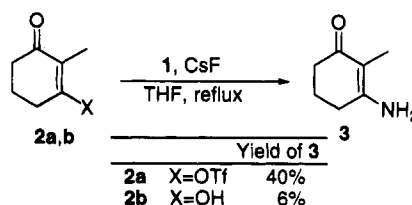
The incorporation of molecular nitrogen into organic compounds is a challenging process in synthetic organic chemistry. We have reported the successful syntheses of heterocycles¹ that incorporated nitrogen with a N_2 -TiCl₄-Mg system.² The nitrogenation process was extended to a catalytic reaction based on TiCl₄, using excess Li and TMSCl.³ We now wish to report the synthesis of heterocycles from molecular nitrogen and di- or tricarbonyl compounds with a TiCl₄-Li-TMSCl system (Scheme 1).

A THF solution of TiCl₄ (1.25 equiv), Li (12.5 equiv), and TMSCl (12.5 equiv)⁴ was stirred under nitrogen at room temperature for 24 h to produce nitrogen fixation complexes 1. To the resultant black solution was added β -keto enol triflate **2a** (1 equiv), and the solution was refluxed for 24 h under argon. Hydrolysis of the reaction mixture afforded enaminone **3** in 35% yield (Scheme 2). The addition of CsF with substrate to the THF solution of **1** improved the yield of **3** (40% yield). The main component of nitrogen fixation complexes **1** was thought to be $N(TMS)_3$.⁵ To determine whether enaminone **3** is formed from **2a** and $N(TMS)_3$ in the presence of CsF, a THF solution of **2a** and $N(TMS)_3$ was refluxed in the presence of CsF. No nitrogen-containing product was obtained. In the nitrogenation reaction using TiCl₄-Li-TMSCl, the titanium nitrogen complex in **1** might act as a Lewis acid to activate the carbonyl group of **2a**. For this reaction, OTf is the most suitable leaving group since others provide lower product yields [X = OMe (29%), OMs (11%), OAc (8%), OCOOMe (10%), OCOOPh (4%), Cl (0%), and OH (6%)]. Thus, we obtained enaminone **3** from **2a** and nitrogen fixation complexes **1**, prepared from molecular nitrogen, TiCl₄, Li, and TMSCl, in a one-pot reaction.

Scheme 1



Scheme 2



Scheme 3

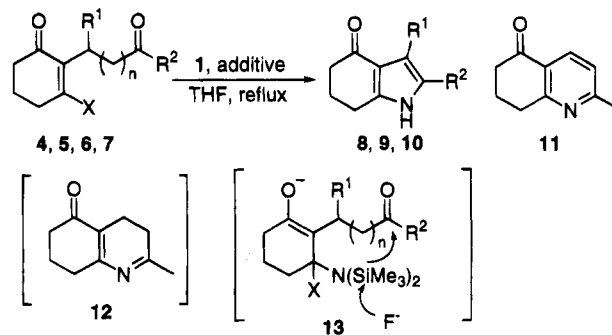


Table 1. Reaction of Nitrogen Fixation Complexes with 4-7

run	SM	n	R ¹	R ²	X	additive	product	yield (%)
1	4a	0	H	Me	OTf	CsF	8	51
2	5a	0	Me	Me	OTf	CsF	9	46
3	4b	0	H	Me	OH	none	8	71
4	4b	0	H	Me	OH	CsF	8	86
5	5b	0	Me	Me	OH	CsF	9	86
6	6b	0	H	Ph	OH	CsF	10	34 (57) ^a
7	7	1	H	Me	OH	CsF	11	32

^a 2 equiv of nitrogen fixation complexes were used.

This reaction was extended to an intramolecular cyclization format for the synthesis of heterocycles. When a THF solution of β -keto enol triflate **4a** (1 equiv), which has a keto carbonyl group in the tether, and nitrogen fixation complexes **1** [prepared from molecular nitrogen, TiCl₄ (1.25 equiv), Li (12.5 equiv), and TMSCl (12.5 equiv)] was refluxed in the presence of CsF for 24 h, indole derivative **8** was produced in 51% yield (Scheme 3 and Table 1, run 1). In a similar manner, compound **5a** afforded indole derivative **9** in 46% yield (run 2). The reaction of 1,3-diketone derivative (X = OH) **4b** with complexes **1** also gave compound **8** in 71% yield. The addition of CsF (6.25 equiv) improved the yield of **8** to 86% (run 4). Indole derivatives **9** and **10** were obtained from 1,3-diketone derivatives **5b** and **6b** in 86% and 34% yields, respectively. In the reaction of **6b** with **1**, the use of 2 equiv of nitrogen fixation complexes **1** improved the yield of desired product **10** (57%). The reaction was further applied to the synthesis of quinoline derivatives. The reaction of 1,3-diketone derivative **7** with complex **1** gave quinoline derivative **11** in 32% yield (run 7). In this

(1) Mori, M.; Uozumi, Y.; Shibasaki, M. *Tetrahedron Lett.* **1987**, *28*, 6187. Uozumi, Y.; Kawasaki, N.; Mori, E.; Mori, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1989**, *111*, 3725. Mori, M.; Uozumi, Y.; Shibasaki, M. *J. Organomet. Chem.* **1990**, *395*, 255. Uozumi, Y.; Mori, E.; Mori, M.; Shibasaki, M. *J. Organomet. Chem.* **1990**, *399*, 93. Uozumi, Y.; Mori, M.; Shibasaki, M. *J. Chem. Soc., Chem. Commun.* **1991**, 81. Mori, M.; Uozumi, Y.; Shibasaki, M. *Heterocycles* **1992**, *33*, 819.

(2) Yamamoto, A.; Ookawa, M.; Ikeda, S. *J. Chem. Soc., Chem. Commun.* **1969**, 841. Yamamoto, A.; Go, S.; Ookawa, M.; Takahashi, M.; Ikeda, S.; Keii, T. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3110.

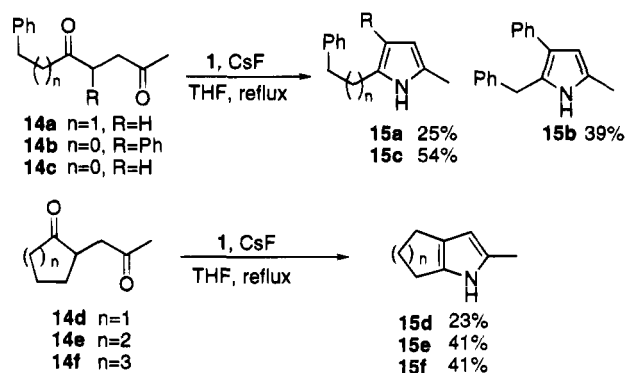
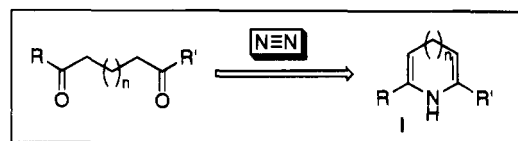
(3) Kawaguchi, M.; Hamaoka, S.; Mori, M. *Tetrahedron Lett.* **1993**, *34*, 6907. Mori, M.; Kawaguchi, M.; Hori, M.; Hamaoka, S. *Heterocycles* **1994**, *37*, 729.

(4) The use of 1,2-bis(chlorodimethylsilyl)ethane or dichlorodimethylsilane instead of TMSCl was unsuccessful for the incorporation of molecular nitrogen.

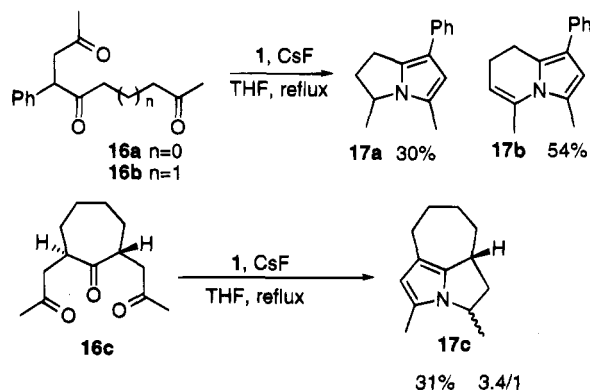
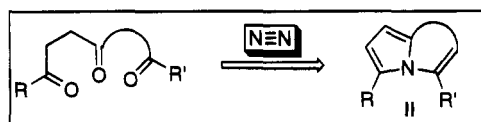
(5) Shiina⁶ reported that the reductive silylation of molecular nitrogen using various metal complexes afforded tris(trimethylsilyl)amine. He reported that a 0.8 equivolar amount of $N(TMS)_3$ was produced in the catalytic system based on TiCl₄. However, 250% of benzamide (based on TiCl₄) was obtained by the reaction of nitrogen fixation complexes which were prepared in a similar manner with benzoyl chloride.³ It means that other nitrogen sources were produced for this reaction. Thus, we called the reaction mixture as nitrogen fixation complexes **1**.

(6) Shiina, K. *J. Am. Chem. Soc.* **1972**, *94*, 9266.

Scheme 4



Scheme 5



case, the thin layer chromatography spot pertaining to the reaction mixture gave way to the product spot during the workup. Possibly, air oxidation of initial product **12** occurred to give **11**. In the intramolecular cyclization, a hydroxyl group is superior to triflate as the leaving group, although the reaction of **2b** with **1** afforded **3** in only 6% yield. Presumably, the intermediate for this reaction is **13** and the silylamide reacts immediately with the keto carbonyl group in the tether to give the cyclized product.

Subsequently, the incorporation of molecular nitrogen into a keto carbonyl group was examined, as shown in Scheme 4. When a THF solution of compound **14a** and complexes **1** was refluxed for 24 h, pyrrole derivative **15a** was obtained in 25% yield. Similar treatment of **14b** and **14c** gave **15b** and **15c** in 39% and 54% yields, respectively. The bicyclic pyrroles **15d**, **15e**, and **15f** were prepared from **14d**, **14e**, and **14f**, respectively, in good yields. The method was applied to the synthesis of pyrrolizine and indolizine derivatives **II** as shown in Scheme 5. Thus, compounds **17a** and **17b** were obtained from 2,5,8-triketone **16a** and 2,6,9-triketone **16b** in 30% and 54% yields, respectively, in a similar manner. The former product **17a** was obtained as the reduced form of enamine **II**. Tricyclic compound **17c** was obtained from cyclic triketone **16c** as an inseparable mixture of two isomers differing in methyl group configuration in 31% yield (3.4/1).⁷

We also tried to synthesize heterocycles by employing a catalytic nitrogenation reaction based on $TiCl_4$. A THF solution of $TiCl_4$ (1 equiv) and $TMSCl$ (50 equiv) was stirred in the presence of Li (50 equiv)⁸ under nitrogen at room temperature for 24 h. Then, a mixture of **4b** (10 equiv) and CsF (50 equiv) was added to the solution of nitrogen fixation complexes **1**, and the mixture was refluxed for 24 h. After the usual workup, desired indole

Table 2. Titanium-Catalyzed Nitrogenation

run	SM	product	yield ^a (%)
1	4b	8	273
2	5b	9	369
3	6b	10	208
4	14b	15b	247
5	14c	15c	354
6	14d	15d	57
7	14e	15e	350
8	14f	15f	335

^a Based on $TiCl_4$.

derivative **8** was obtained in 273% yield based on $TiCl_4$ (Table 2, run 1).⁹ In a similar manner, indole derivatives **9** and **10** were obtained in 369% and 208% yields based on $TiCl_4$, respectively (runs 2 and 3). Interestingly, pyrrole derivatives **15b**, **15c**, **15e**, and **15f** were also obtained in high yields, based on $TiCl_4$ (runs 4–8).

The remarkable characteristics of this reaction are as follows: The synthesis of heterocycles, such as indole, quinoline, pyrrole, pyrrolizine, and indolizine derivatives, from molecular nitrogen can be realized using a N_2 (1 atm)– $TiCl_4$ – Li – $TMSCl$ system in a one-pot reaction. That is, a THF solution of substrate and nitrogen fixation complexes **1** is refluxed in the presence of CsF for 24 h. If an excess amount of Li and $TMSCl$ is used, the catalytic cycle is established based on $TiCl_4$. Continuing studies on the synthesis of nitrogen heterocycles from molecular nitrogen are in progress.

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Supplementary Material Available: Experimental procedures and compound characterization data (10 pages).

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(7) From the GC/MS, each product shows m/z 189 (M^+), and the ratio of two isomers was determined by 1H NMR.

(8) In order to obtain 1 equiv of $N(TMS)_3$, at least 5 equiv of Li and 3 equiv of $TMSCl$ were required for 1 equiv of $TiCl_4$.

(9) In a similar manner, enamino **3** was obtained in 189% yield based on $TiCl_4$.