Synthesis of Tetrahydroindole Derivatives Using Titanium-Nitrogen Complexes Derived from Molecular Nitrogen

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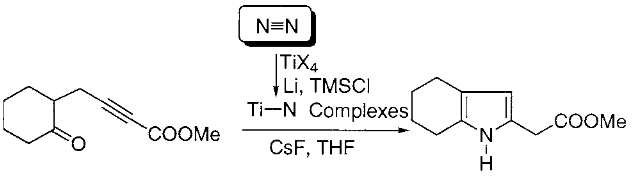
Synthesis of tetrahydroindole derivatives was realized from keto-alkyne using titanium-nitrogen complexes generated from $Ti(OiPr)_4$, Li, and TMSCl. In this reaction, the electron-withdrawing group on the alkyne gave a good yield, and keto-alkynes having an aromatic ring on the alkyne also gave tetrahydroindole derivatives in good to moderate yields.

Nitrogen fixation is very attractive process, and we recently reported nitrogen fixation using $TiCl_4$ or $Ti(OiPr)_4$, Li and TMSCl.[1] Our procedure is very simple: a THF solution of TiX_4 and TMSCl in the presence of Li was stirred under nitrogen (1 atm) at room temperature for 12-24 h. Using this nitrogen-fixation complexes, we demonstrated the synthesis of various heterocyclic compounds.[2] Moreover, we succeeded in atmospheric nitrogen fixation using this method under dry air instead of nitrogen gas. The reaction of **1a** with titanium-nitrogen complexes prepared from dry air gave tetrahydroindole derivative **2a** in 64% yield. Surprisingly, use of nitrogen gas instead of dry air gave **2a** in 90% yield based on **1a**. The reaction proceeded smoothly at room temperature using $Ti(OiPr)_4$ instead of $TiCl_4$.[3]

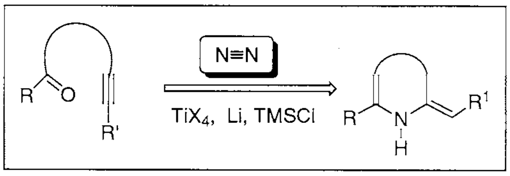


1a **2a**

molecular nitrogen	reflux	$TiCl_4$	90%
molecular nitrogen	rt	$Ti(OiPr)_4$	82%
dry air	rt	$Ti(OiPr)_4$	64%

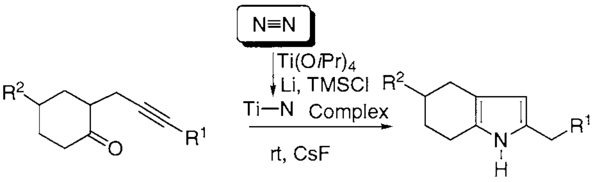
Scheme 1.

We now want to report the synthesis of tetrahydroindole derivatives from keto-alkynes using nitrogen gas as the nitrogen source according to our plan for the synthesis of heterocycles as shown in Scheme 2.



Scheme 2. Plan for Synthesis of Heterocycles from Keto-alkyne Using Titanium-Nitrtogen Complexes.

When to a THF solution of titanium-nitrogen complexes, prepared from $Ti(OiPr)_4$ (1.25 equiv.), Li (12.5 equiv.), and TMSCl (20 equiv.) under nitrogen (1 atm) at room temperature for 24 h, was added **1b** and then the solution was stirred at room temperature for 50 min, we obtained tetrahydroindole derivative **2b** in 62% yield (Table 1, run 2). The first stage of this reaction would be the reaction of the keto-carbonyl group with titanium-nitrogen complexes, and then Michael-type addition of the resultant keto-imine to α,β-unsaturated ester occurs to give **2a**. Thus, we examined the keto-alkyne **1** having an amide- or keto-carbonyl group on the alkyne. The results are shown in Table 1. In each case, the desired product **2** was obtained in moderate yield. However, the keto-alkyne having a methyl group on the alkyne did not give a good result, and only a trace amount of **2e** was produced.[4]



1 **2**

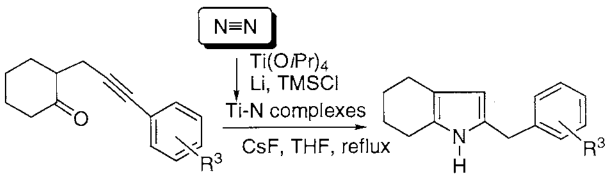
Scheme 3.

Table 1. Reaction of **1** with titanium-nitrogen complexes

Run	R^1	R^2		Time/ h		Yield/ %
1	COOMe	H	**1a**	0.8	**2a**	82
2	COOMe	OAc	**1b**	0.8	**2b**	62
3	$CONEt_2$	H	**1c**	24	**2c**	45
4	COMe	H	**1d**	1.8	**2d**	35
5[a]	Me	H	**1e**	20	**2e**	3[b]

All reactions were carried out at room temperature in THF.
[a] The THF solution was refluxed. [b] The starting material was recovered in 45% yield.

Subsequently, we examined the synthesis of tetrahydroindole derivatives **4** from keto-alkyne **3** having a phenyl group on the alkyne. In this reaction, Michael addition of keto-imine can not be expected



3 **4**

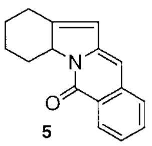
Scheme 4.

When a THF solution of **3a** and titanium-nitrogen complexes was stirred at room temperature, the desired tetrahydroindole derivative was not formed. Thus, various attempts were made to obtain tetrahydroindole derivative. When the solution of **3a** and titanium-nitrogen complexes was stirred at room temperature for 50 min and then refluxed for 20 h, the desired product **4a** was obtained in 35% yield along with the starting material **3a** (21% yield, Table 2. run 1).[5] The reaction of various keto-alkynes with titanium-nitrogen complexes were examined, and the results are shown in Table 2. Although the yields from keto-alkynes having an electron-withdrawing group on the aromatic ring increased (runs, 3, 4, and 5), the keto-alkyne **3f** having a nitro group on the aromatic ring did not give the desired product, and the starting material **3f** decomposed (run 6). It was interesting that the alkyne **3g** having ester at the ortho-position of the aromatic ring gave **4g** in 35% yield along with tetracyclic compound **5**, although the yield was low. Usually, the reaction of a hydroxy or amino group with alkyne in a tether proceeds in the presence of transition metals such as palladium or samarium complex.[6] However, in this reaction, nitrogen was incorporated between the carbonyl carbon and alkyne carbon without a transition metal complex.

Table 2. Reaction of **3** with titanium-nitrogen complexes

Run	R^3		Time/ h		Yield/ %	3/ %
1	H	**3a**	20	**4a**	35	21
2	*p*-CH_3	**3b**	20	**4b**	32	31
3	*p*-COOMe	**3c**	20	**4c**	42	30
4	*p*-CN	**3d**	5	**4d**	45	21
5	*p*-CF_3	**3e**	20	**4e**	49	14
6	*p*-NO_2	**3f**	12	**4f**	0	8
7	*o*-COOMe	**3g**	20[a]	**4g**	35[b]	19

All reactions were carried out upon heating in THF. [a] Reaction temp.; 40 °C. [b] Compound **5** was obtained in 3% yield.



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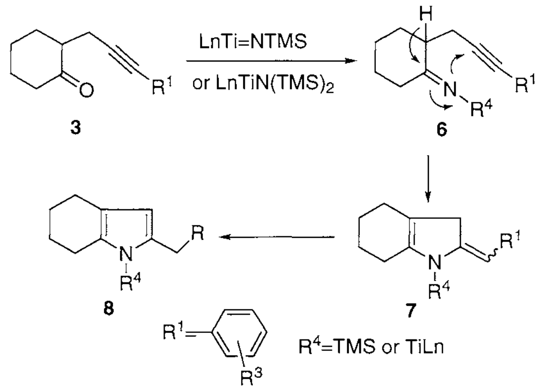
Recently, Arcadi reported a very interesting reaction of keto-alkyne with primary amine or NH_3 to produce enamine.[7] The reaction was carried out in a sealed tube in MeOH at 120 °C.



Scheme 5. Possible Reaction Course.

Our reaction would proceed by the reaction of titanium-nitrogen complexes with carbonyl group to form imine **6**, and then it attacks the alkyne part because the electron-withdrawing group on the aromatic ring accelerated the reaction. Titanium complex may act as Lewis acid.

In conclusion, we could synthesize various tetrahydroindole derivatives from keto-alkynes using titanium-nitrogen complexes prepared from molecular nitrogen, $\mathrm{Ti(O}i\mathrm{Pr)_4}$, Li, and TMSCl. The electron-withdrawing group on the alkyne or that on the aromatic ring as a substituent on the alkyne accelerates the reaction rate. The reaction procedure is very simple and the reaction conditions are mild. Thus, various heterocycles could be synthesized using titanium-nitrogen complexes.

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5 When the solution was refluxed without stirring at room temperature, the yield of the desired product **4** decreased.

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