# PREPARATION OF CYCLIC AMINES BY THE TITANOCENE(II)-PROMOTED CYCLIZATION OF THIOACETALS HAVING A CARBON-CARBON DOUBLE BOND†

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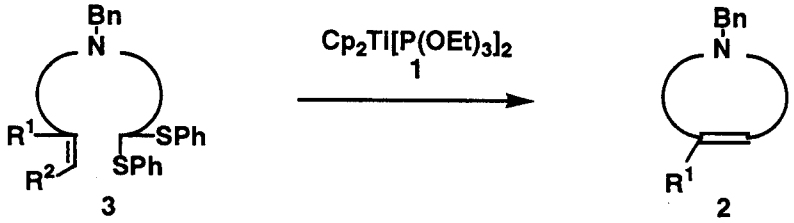
*Abstract*-Nitrogen-containing unsaturated heterocycles were obtained in good yields by the titanocene(II)-promoted ring-closing metathesis of the amines possessing an olefin and a diphenyl thioacetal moieties.

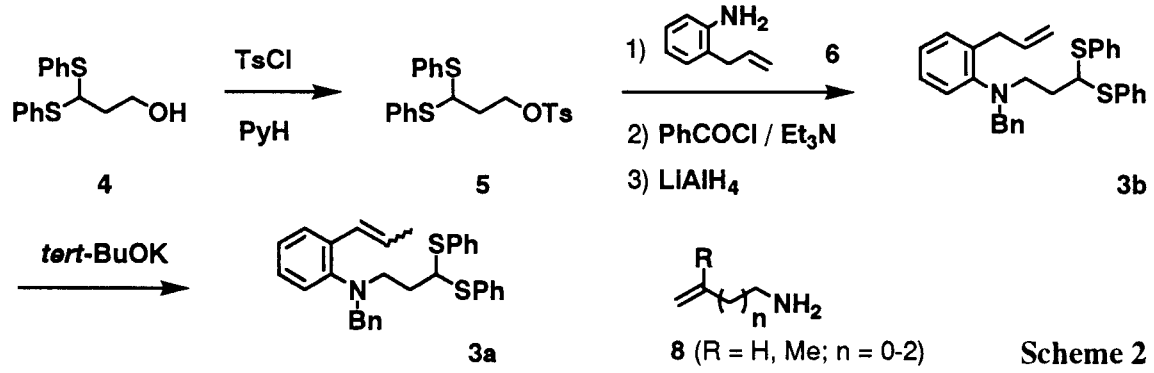
Recently much attention has been paid to ring-closing metathesis (RCM) as a tool for the construction of various carbocyclic compounds,[1] and this methodology has been applied to the synthesis of a variety of heterocyclic compounds. For example, nitrogen,[2] sulfur,[3] and oxygen[4] containing medium rings were prepared from the corresponding tertiary amines, sulfides, or ethers possessing two olefin moieties by the use of ruthenium- or molybdenum-carbene complex as a catalyst. The similar preparation of cyclic enol ethers using methylidene-titanocene prepared from Tebbe or Petasis reagent was also reported.[5]
Recently we found that titanium-carbene complexes or their equivalents were produced by the desulfurization of thioacetals with the low-valent titanium $Cp_2Ti[P(OEt)_3]_2$ (**1**). These titanium species are highly reactive toward various organic molecules having a multiple bond.[6] We also showed that the RCM takes place to produce cycloalkenes and cyclic ethers when thioacetals having a carbon-carbon double bond are treated with the low-valent titanium (**1**).[7] These results prompted us to study the synthesis of unsaturated nitrogen heterocycles (**2**) by the RCM using the thioacetals (**3**) (Scheme 1).




**Scheme 1**

We first examined the formation of cyclic amines fused with a benzene ring, which would be conformationally more favorable process than of monocyclic compounds. The starting unsaturated amines having a thioacetal moiety (**3a** and **b**) were prepared from 3,3-bis(phenylthio)-1-propanol (**4**)[8] as shown in Scheme 2. The treatment of tosylate (**5**), prepared from **4** and TsCl (1.1 equiv, pyridine, 0 °C, overnight), with 2-allylaniline (**6**) (4 equiv, EtOH, reflux, 8 h) followed by benzoylation (PhCOCl / 1.1 equiv, $Et_3N$ / 1.5 equiv, $Et_2O$, 0 °C to rt, overnight) and the reduction of the resulting amide ($LiAlH_4$ / 2 equiv, $Et_2O$, 0 °C to rt, overnight) produced the thioacetal (**3b**) in 74% overall yield. The conjugation of double bond of **3b** under the basic conditions (*tert*-BuOK / 1 equiv, DMSO, rt, 45 min) afforded **3a** ($E : Z = 95 : 5$) in 85% yield. As would be expected, the treatment of **3a** and **b** with 4 equiv of the low-valent titanium reagent (**1**) in THF at rt and then at the reflux temperature afforded the seven- and eight-membered cyclic amines (**2a** and **b**) in

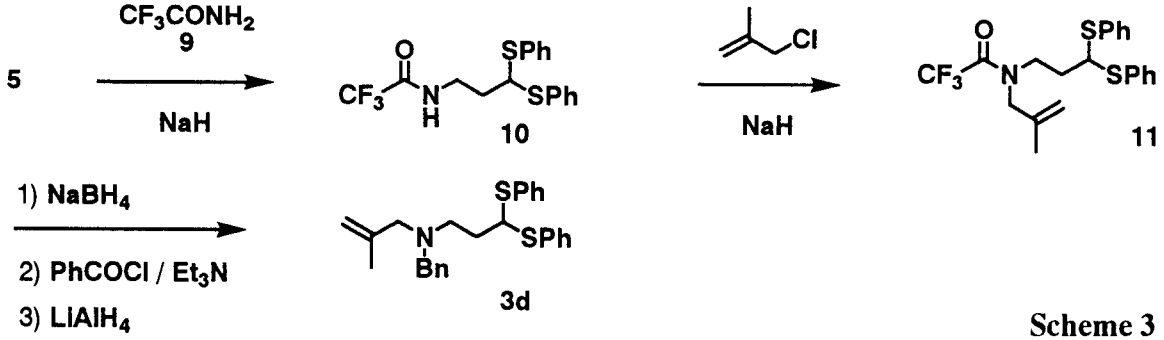
† Dedicated to Prof. Teruaki Mukaiyama on the occasion of his 73rd birthday.




Scheme 2

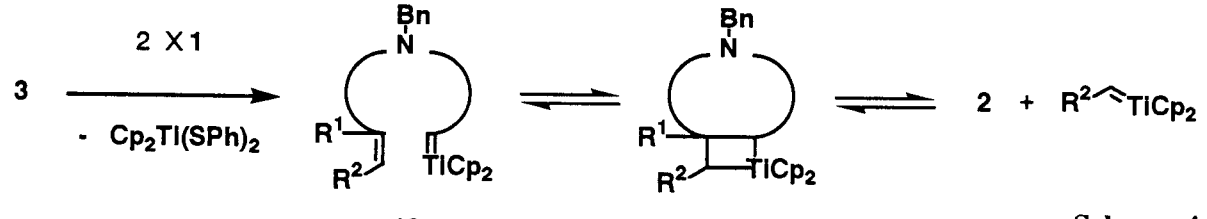
good yields, respectively (Entries 1 and 2). In the case of allylbenzene derivatives (**3b**), the conjugation of double bond of **2b** partially proceeded to produce a mixture of **2b** and its isomer (**7**).

Next the preparation of monocyclic amines was examined. The starting unsaturated amines (**3c**, **e**, **f**, and **g**) were prepared from the alcohol (**4**) similarly to the preparation of **3b**. The reaction of unsaturated primary amine (**8**) with the tosylate (**5**) followed by the benzoylation and reduction gave the unsaturated amines in good overall yields (**3c**; 73%, **3e**; 77%, **3f**; 73%, **3g**; 75%). The thioacetal (**3d**) was separately synthesized *via* the stepwise alkylation of 2,2,2-trifluoroacetamide (**9**) according to the procedure reported by Harland and Hodge[9] (Scheme 3). The reaction of **5** with **9** (1.1 equiv, NaH / 1 equiv, DMF, 80 °C, 3 h) gave the amide (**10**) (63%) which was then treated with methallyl chloride (1.2 equiv, NaH / 1 equiv, 80 °C, 4 h) to produce allylic amide (**11**) (70%). The reductive removal of trifluoroacetyl group ($NaBH_4$ / 8 equiv, EtOH, rt, 2.5 h) and the usual benzylation described above afforded **3d** (81%, 3 steps).



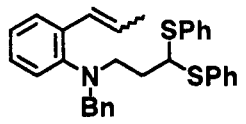
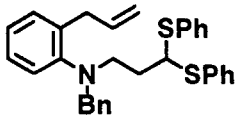
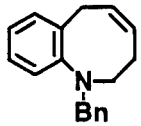
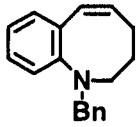
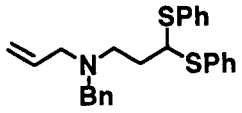
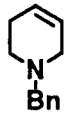
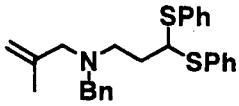
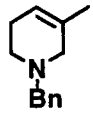
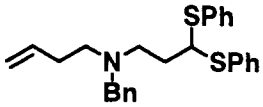
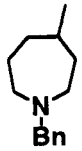
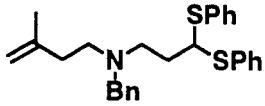
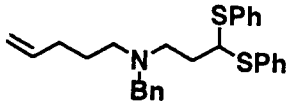
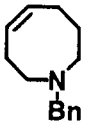

Scheme 3

Although the treatment of **3c** with the low-valent titanium reagent (**1**) afforded the six-membered amine (**2c**) in moderate yield (Entry 3), the presence of a methyl group in an allylic system favored the formation of the RCM product (Entry 4). On the other hand, the cyclic amines (**2e** and **f**) were produced in good yields irrespective of the substituent on the double bond (Entries 5 and 6). The formation of perhydroazepine (**12**) indicates that the compositions of the equilibrium mixture formed from the carbene complex (**13**) is dependent on the ring size and substituent on the double bond because it is reasonable to assume that **12** is produced by the protonation of titanacyclobutane intermediate (**14**) (Scheme 4). In the case of the formation of eight-membered ring, the slow addition of **3g** to a THF solution of **1** increased the yield of cyclic amine (**2g**) (see Entries 7 and 8).




Scheme 4

**Table 1.** Preparation of cyclic amines (**2**).[a]

| Entry | Thioacetal (**3**) | Titanocene(II) (**1**) (equiv) | Concentration (M) | Product[b] (Yield / %) |
|---|---|---|---|---|
| 1[c] |  **3a** ($E:Z = 95:5$) | 4 | 0.03 |  **2a** (77) |
| 2[d] |  **3b** | 4 | 0.015 |  **2b**  **7** (51; **2b** : **7** = 80 : 20)[e] |
| 3 |  **3c** | 3 | 0.03 |  **2c** (35) |
| 4 |  **3d** | 3 | 0.03 |  **2d** (61) |
| 5 |  **3e** | 4 | 0.03 |  **2e** (62)  **12** (15) |
| 6 |  **3f** | 4 | 0.03 |  **2f** (71) |
| 7 |  **3g** | 3 | 0.03 |  **2g** (65) |
| 8[f] | **3g** | 4 | 0.03 | **2g** (73) |

a) All reactions were performed with a similar procedure as described in the text, unless otherwise noted. b) The spectral data were consistent with the postulated structures. c) After stirring at rt for 2 h, the reaction mixture was refluxed for 2 h. d) After stirring at rt for 4 h, the reaction mixture was refluxed for 3 h. e) The NMR spectrum contained some unidentified signals. f) The thioacetal (**3g**) was added dropwise over 3 h.

The typical reaction procedure is as follows: To a THF (6.7 mL) solution of **1**, prepared from titanocene dichloride (498 mg, 2 mmol), magnesium turnings (54 mg, 2.2 mmol), molecular sieves 4 A (200 mg), and triethyl phosphite (0.69 mL, 4 mmol),[7] was added a THF (10 mL) solution of **3f** (217 mg, 0.5 mmol) at rt. The reaction mixture was stirred for 2 h at the same temperature and then refluxed for 1 h. After cooling, the reaction was quenched by addition of 1M NaOH and the insoluble materials were filtered off through Celite and washed with ether. The organic phase was separated and dried ($K_2CO_3$). After removal of solvent, the residue was purified by PTLC (silica gel, hexane : AcOEt = 4 : 1) to yield **2f** (71 mg, 71%) as an oil.

In conclusion, it should be noted that the titanocene(II)-mediated cyclization of unsaturated amines having a thioacetal moiety provides a useful method for the preparation of various types of unsaturated cyclic amines.

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