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Titanocene(II)-promoted reductive alkylation of anilides with thioacetals

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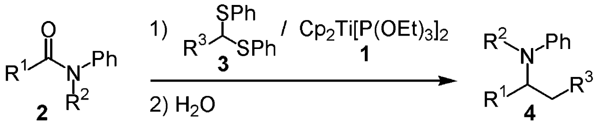
Abstract—Titanocene(II)-promoted reaction of anilides with thioacetals followed by treatment with a small amount of water gave reductive alkylation products, anilines with a secondary alkyl group.

In the course of study on the carbonyl olefination utilizing a thioacetal–titanocene(II) system,[1] we observed the unusual formation of pyrrolidines when *N*-[3,3-bis(phenylthio)propyl]anilides were treated with titanocene(II) $Cp_2Ti[P(OEt)_3]_2$ **1**.[2] We were intrigued with the reduction of carbon–carbon double bond of enamine involved in the above transformation, and further investigated the titanocene(II)-promoted carbonyl olefination of amides with thioacetals. Here, we report a convenient method for the reductive alkylation of anilides **2** using a titanocene(II) **1**–thioacetal **3** system (Scheme 1). The method consists of the carbonyl olefination of **2** and reduction of the resulting enamines, giving alkylated anilines **4**.



Scheme 1.

We initially made a detailed study of the titanocene(II)-promoted intramolecular reaction of 5,5-bis(phenylthio)pentanilides **5** and found that the reaction gave two types of products depending on the work-up conditions. Reaction of 5,5-bis(phenylthio)-1-phenylpentanilide **5a** with the titanocene(II) species **1** under reflux in THF for 1 h and an alkaline work-up produced the trisubstituted enamine **6a** in high yield (Table 1, entry 1). The highly substituted enamine **6b** was also obtained by the reaction of α-substituted anilide **5b** (entry 2). When the β-substituted anilide **5c** was treated with the titanocene(II) reagent **1**, the cyclopentanone **7** was isolated (entry 3). It is reasonable to assume that the highly substituted enamine **6** is produced by the isomerization of the enamine **8** initially formed by the intramolecular carbonyl olefination of the intermediary titanium carbene complex **9** (Scheme 2). The disubstituted enamine, formed from **5c**, would be rather susceptible to hydrolysis hence the cyclopentanone **7** was obtained.

Contrary to these results, cyclopentylamines **10** were obtained when the reaction mixture was treated with a small amount of water (entries 4–8). The yield of **10** is dependent on the position of the substituent of the amide **5**. Although the reactions of α-substituted amides **5a** and **5b** gave the cyclic amines **10** in moderate yields (entries 4 and 5), the amines **10** were obtained in good yields when α-unsubstituted amides **5c**–**e** were subjected to the reaction (entries 6–8). Since the enamines **6** are produced by the reaction of the anilides **5** with **1** followed by the alkaline aqueous work-up, it is reasonable to assume that the amines **10** are produced by reduction of the enamines **6** or **8**.[3]

The typical experimental procedure for the preparation of cyclopentylamines is as follows: finely powdered molecular sieves 4 A (120 mg), magnesium turnings (35 mg, 1.4 mmol) and Cp_2TiCl_2 (299 mg, 1.2 mmol)

Keywords: Anilides; Carbonyl olefination; Reduction; Anilines; Titanocene(II); Thioacetals.

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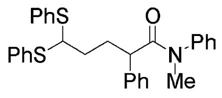
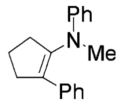
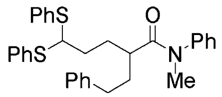
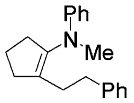
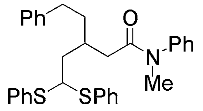
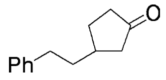
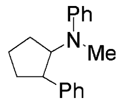
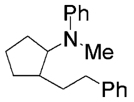
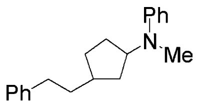
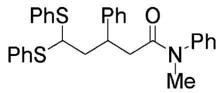
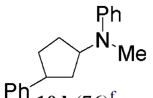
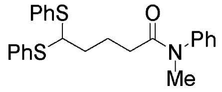
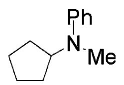
Table 1. Titanocene(II)-promoted intramolecular reaction of 5,5-bis(phenylthio)pentanilides **5**[a]

Entry	Anilide **5**	Product (yield/%)
1[b]	 **5a**	 **6a** (89)[c]
2[b]	 **5b**	 **6b** (75)[c]
3[b]	 **5c**	 **7** (54)
4	**5a**	 **10a** (20)[d]
5	**5b**	 **10b** (49)[e]
6	**5c**	 **10c** (71)[f,g]
7	 **5d**	 **10d** (76)[f]
8	 **5e**	 **10e** (72)

[a] All the reactions were performed with a similar procedure as described in the text, unless otherwise noted.

[b] Without treatment with water before quenching.

[c] Isolated by column chromatography on aluminia (eluted with 1% triethylamine in hexane).

[d] Only the *cis*-isomer was produced. Compound **3a** was obtained in 46% yield.

[e] *cis*:*trans* = 81:19.

[f] Obtained as a mixture of stereoisomers.

[g] Compound **4** was obtained in 13% yield.

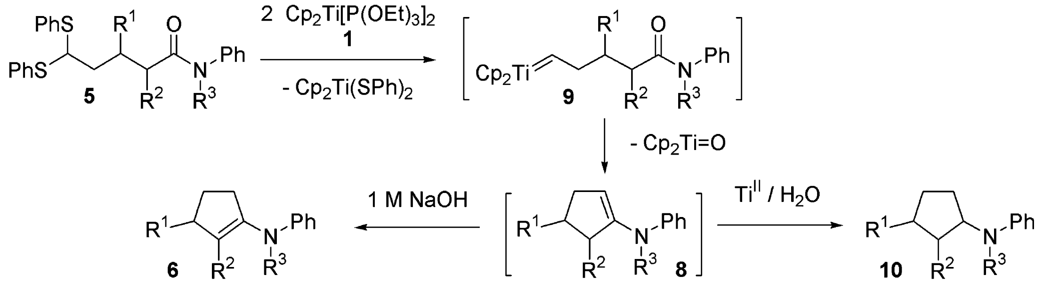
were placed in a flask and dried by heating with a heat gun under reduced pressure (2–3 mmHg). After cooling, THF (3.6 mL) and $P(OEt)_3$ (0.41 mL, 2.4 mmol) were added successively with stirring at 25 °C under argon, and the reaction mixture was stirred for 3 h. A THF (6 mL) solution of **5b** (154 mg, 0.3 mmol) was added dropwise to the mixture over 20 min, and the mixture was refluxed for 1 h. After cooling to 25 °C, water (0.3 mL) was added to the reaction mixture, which was stirred for 30 min. The reaction was quenched by addition of 1 M NaOH. The insoluble materials were filtered off through Celite and washed with ether. The organic materials were extracted with ether and dried over Na_2SO_4. After removal of the solvent, the residue was purified by PTLC (silica gel, hexane–AcOEt = 9:1) to give **10b** (41 mg, 49%).

To investigate the mechanism for the reduction of the double bond, the reaction mixture of **5b** with **1** was treated with D_2O (1 mL/1 mmol of **5b**) at 25 °C for 1 h. The formation of the 1,2-dideuteriocyclopentylamine **11**, in which lesser extent of deuterium incorporation was observed at the position β to the amino group in the major isomer (Scheme 3), suggests that the reduction proceeds via the β-aminoalkyltitanium species **12** (Scheme 4). Two pathways for the formation of such species would be plausible: partial deuteration of a titanacyclopropane intermediate **13** generated by the reaction of the enamine **6b** with a titanocene(II) species and deuteriotitanation of **6b** with a titanium deuteride **14**. Considering that the conditions of aqueous work-up determines, which product is formed, the latter pathway seems to be likely. Similar reduction of enamines with metal hydrides has been well documented[4] and Brown and co-workers reported that the hydroboration of enamines with borane–methyl sulfide complex proceeds regioselectively to produce β-amino alkylboranes.[4f]

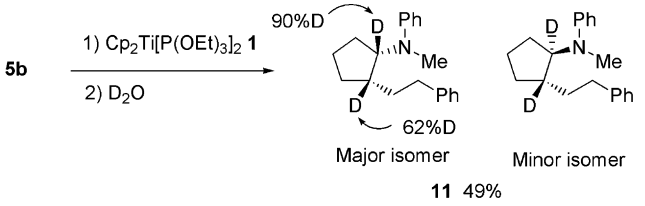
On the basis of the above consideration, we expected that acyclic amines would be produced by the reductive alkylation of anilides using a thioacetal–titanocene(II) system (Scheme 1). After the carbonyl olefination of anilide **2** with thioacetal **3** and the titanocene(II) reagent **1** at 30 °C or under reflux in THF, the reaction mixture was treated with water to produce acyclic amine **4**. Using different thioacetals, a variety of anilines bearing a secondary alkyl group were obtained in good overall yields (Table 2).

Various Wittig-like olefinations of amides using titanium based reagents, such as the Tebbe and related reagents,[5] dialkyltitanocenes,[6] and *gem*-dihalides–Zn(Pb)–$TiCl_4$,[7] have been developed. Although preparation of 1-benzyl-2-methylpyrrolidine by methylenation of 1-benzyl-2-pyrrolidinone with dimethyltitanocene and subsequent reduction of the crude enamine with CF_3CO_2H–$NaBH_4$ was reported,[7b] no one-pot procedure for the carbonyl olefination of amide and reduction of the resulting enamine has ever been reported. Therefore, since thioacetals are readily prepared from various starting materials, the present one-pot procedure using the same reagent for both the processes is a facile and convenient way for the preparation of amines.

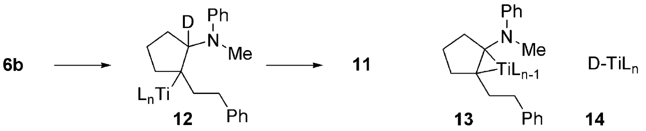
In summary, we have developed a one-pot procedure for the reductive alkylation of anilides by the combination of titanocene(II)-promoted carbonyl olefination of



Scheme 2.



Scheme 3.



Scheme 4.

amides and reduction of the resulting enamines. Further study on the reduction of carbon–carbon double bonds with low-valent titanium reagents is currently underway.

Acknowledgements

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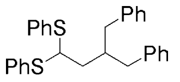
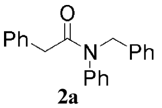
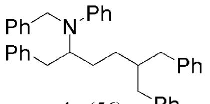
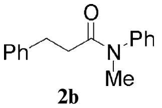
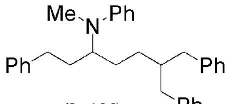
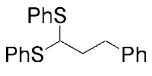
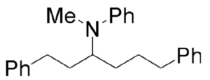
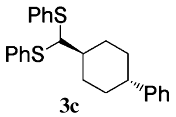
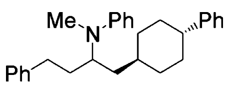
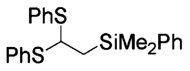
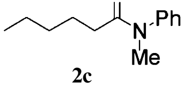
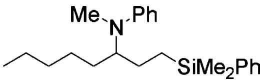
References and notes

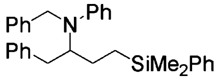
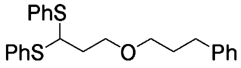
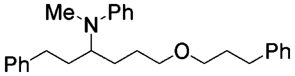
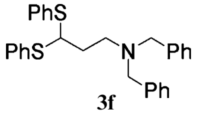
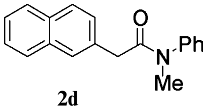
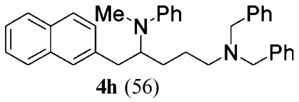
1. (a) Horikawa, Y.; Watanabe, M.; Fujiwara, T.; Takeda, T. *J. Am. Chem. Soc.* **1997**, *119*, 1127; (b) Takeda, T.;

Table 2. Preparation of acyclic amines **10**[a]

Entry	Thioacetal **3**	Anilide **2**	Temp/°C	Acyclic amine **4** (yield/%)
1	 **3a**	 **2a**	30	 **4a** (56)
2	**3a**	 **2b**	30	 **4b** (66)
3	 **3b**	**2b**	30	 **4c** (52)
4	 **3c**	**2b**	Reflux	 **4d** (55)
5	 **3d**	 **2c**	Reflux	 **4e** (54)

(*continued on next page*)

Table 2 (*continued*)

Entry	Thioacetal **3**	Anilide **2**	Temp/°C	Acyclic amine **4** (yield/%)
6	**3d**	**2a**	Reflux	 **4f** (51)
7	 **3e**	**2b**	Reflux	 **4g** (54)
8	 **3f**	 **2d**	Reflux	 **4h** (56)

[a] All the reactions were performed with a similar procedure as described in Ref. 8.

Watanabe, M.; Nozaki, N.; Fujiwara, T. *Chem. Lett.* **1998**, 115; (c) Rahim, M. A.; Taguchi, H.; Watanabe, M.; Fujiwara, T.; Takeda, T. *Tetrahedron Lett.* **1998**, *39*, 2153; (d) Takeda, T.; Watanabe, M.; Rahim, M. A.; Fujiwara, T. *Tetrahedron Lett.* **1998**, *39*, 3753; (e) Fujiwara, T.; Iwasaki, N.; Takeda, T. *Chem. Lett.* **1998**, 741; (f) Rahim, M. A.; Fujiwara, T.; Takeda, T. *Tetrahedron* **2000**, *56*, 763; (g) Takeda, T.; Takagi, Y.; Saeki, N.; Fujiwara, T. *Tetrahedron Lett.* **2000**, *41*, 8377; (h) Rahim, M. A.; Sasaki, H.; Saito, J.; Fujiwara, T.; Takeda, T. *Chem. Commun.* **2001**, 625.

2. Takeda, T.; Saito, J.; Tsubouchi, A. *Tetrahedron Lett.* **2003**, *44*, 5571.
3. The treatment of enamine **6b** with a mixture of titanocene(II) reagent **1** (2 equiv) and water (1 mL/1 mmol of **6b**) at 25 °C for 30 min produced the amine **10b** in 61% yield. It is of interest that **10b** was obtained in better yield (74%) when a THF solution of **1** was refluxed for 15 min before use. This fact implies that a certain low-valent titanium species other than the titanocene(II) species **1** also acts as a reducing agent in the one-pot reaction.
4. For examples (a) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897; (b) Bach, R. D.; Mitra, D. K. *J. Chem. Soc., Chem. Commun.* **1971**, 143 3; (c) Barieux, J. J.; Gore, J. *Tetrahedron* **1972**, *28*, 1537; (d) Mitsudo, T.; Watanabe, Y.; Tanaka, M.; Atsuta, S.; Yamamoto, K.; Takegami, Y. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1506; (e) Kim, S.; Oh, C. H.; Ko, J. S.; Ahn, K. H.; Kim, Y. J. *J. Org. Chem.* **1985**, *50*, 1927; (f) Goralski, C. T.; Singaram, B.; Brown, H. C. *J. Org. Chem.* **1987**, *52*, 4014; (g) Periasamy, M.; Devasagayaraj, A.; Satyanarayana, N.; Narayana, C. *Synth. Commun.* **1989**, *19*, 565; (h) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.
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7. Takai, K.; Fujimura, O.; Kataoka, Y.; Utimoto, K. *Tetrahedron Lett.* **1989**, *30*, 211.
8. The experimental procedure for the preparation of **4b** is as follows: after the treatment of **3a** (198 mg, 0.45 mmol) with the titanocene(II) reagent **1**, prepared from magnesium turnings (39 mg, 1.6 mmol), Cp_2TiCl_2 (336 mg, 1.4 mmol), molecular sieves 4 A (135 mg), and $P(OEt)_3$ (0.46 mL, 2.7 mmol), at 25 °C for 15 min, a THF (0.9 mL) solution of **2b** (72 mg, 0.3 mmol) was added to the reaction mixture, which was stirred for 3 h at 30 °C. After addition of water (0.3 mL), the mixture was further stirred for 30 min at 25 °C. The usual work-up and purification by PTLC (silica gel, hexane–AcOEt = 95:5) gave **4b** (88 mg, 66%).