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Formation of pyrrolidines by the titanocene(II)-promoted intramolecular reaction of *N*-[3,3-bis(phenylthio)propyl]anilides

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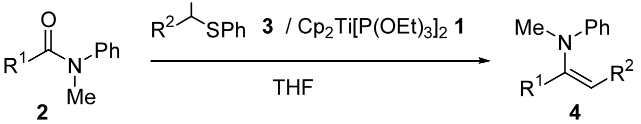
Abstract—The reaction of anilides with the titanium carbene complexes generated by the desulfurization of thioacetals with the titanocene(II) species $Cp_2Ti[P(OEt)_3]_2$ produced the corresponding enamines. Unusual formation of pyrrolidines was observed when *N*-[3,3-bis(phenylthio)propyl]anilides were treated with the titanocene(II) reagent.

Although the Wittig and related reactions of phosphorous carbanions are versatile methods for the transformation of carbonyl compounds into olefins, their use for olefination of carboxamides is largely restricted. Only the amides possessing an electron-withdrawing trifluoromethyl group or conformationally rigid amides in which amide resonance is disrupted are olefinated by these reactions.[1] Such transformation is successfully achieved using nucleophilic metal carbene complexes.[2] Among them titanium-based reagents,[3] such as the Tebbe and related reagents,[4] dialkyltitanocenes,[5] and *gem*-dihalides–Zn–$TiCl_4$,[6] have been developed for the Wittig-like olefination of amides.

We have studied a new carbonyl olefination utilizing a thioacetal–titanocene(II) system.[7] The active species of the system is assumed to be a titanium carbene complex and it transforms a variety of carbonyl compounds to the corresponding olefins. As part of this study, we investigated the carbonyl olefination of amides and, in this communication, we wish to report the unusual formation of pyrrolidine derivatives by the titanocene(II)-promoted intramolecular reaction of *N*-[3,3-bis(phenylthio)propyl]anilides.

Initially the titanocene(II) **1**-promoted intermolecular reaction of the benzanilide **2a** with several thioacetals **3** was investigated and it was found that the corresponding enamines **4** were produced in good yields with excellent stereoselectivity (Scheme 1, Table 1). All the products were obtained as single stereoisomers, and NOE experiment of **4c** indicated that its configuration is *Z*.[8] In the case of the *N*-methyl-3-phenylpropanilide **2b**, the enamines were easily hydrolyzed during work-up, so that the products were isolated as ketones **5** after acid hydrolysis (Entries 5 and 6).

The typical experimental procedure is as follows: finely powdered molecular sieves 4 A (225 mg), magnesium turnings (66 mg, 2.7 mmol) and Cp_2TiCl_2 (560 mg, 2.25 mmol) were placed in a flask and dried by heating with a heat gun under reduced pressure (2–3 mmHg). After cooling, THF (4 ml) and $P(OEt)_3$ (0.77 ml, 4.5 mmol) were added successively with stirring at room temperature under argon, and the reaction mixture was stirred for 3 h. A THF (1 ml) solution of the thioacetal **3a** (252 mg, 0.75 mmol) was added to the mixture and stirring was continued for 10 min at the same temperature. A THF (1.5 ml) solution of the anilide **2a** (106 mg, 0.5 mmol) was added dropwise over 10 min and the reaction mixture was refluxed for 3 h. After cooling to room temperature, the reaction was quenched by addition of 1 M NaOH. The insoluble materials were filtered off through Celite and washed with ether. The layers were separated, and the aqueous layer was extracted with ether. The combined organic extracts



Scheme 1. Titanocene(II)-promoted reaction of thioacetals with anilides.

Keywords: carbonyl olefination; cyclization; enamines; pyrrolidines; titanocene(II).

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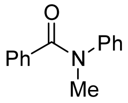
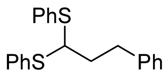
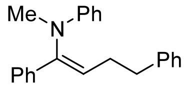
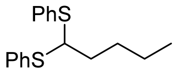
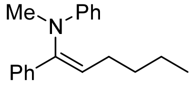
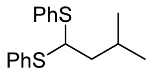
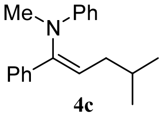
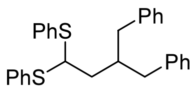
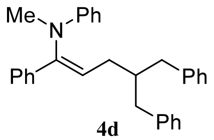
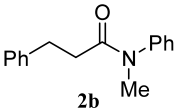
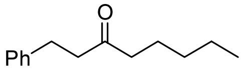
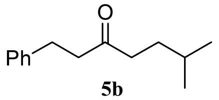
Table 1. Intermolecular carbonyl olefination of anilides **2**

Entry	Anilide **2**	Thioacetal **3**	Product	Yield (%)
1	 **2a**	 **3a**	 **4a**	66
2	**2a**	 **3b**	 **4b**	70
3	**2a**	 **3c**	 **4c**	76
4	**2a**	 **3d**	 **4d**	74
5	 **2b**	**3b**	 **5a**	54[a]
6	**2b**	**3c**	 **5b**	56[a]

[a] Isolated after treatment of the crude product with 1 M HCl-methanol.

were washed with 1 M NaOH and dried over K_2CO_3. After removal of the solvent, the residue was chromatographed over alumina gel (deactivated with 5% of H_2O; eluted with 1% triethylamine in hexane) to afford 105 mg (66%) of **4a**.

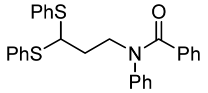
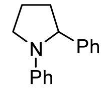
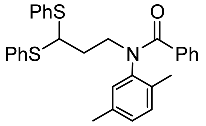
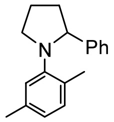
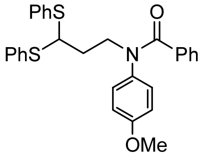
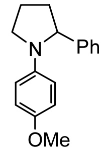
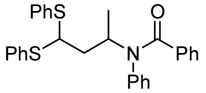
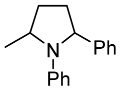
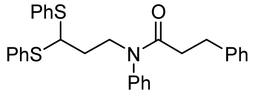
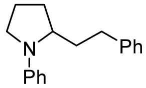
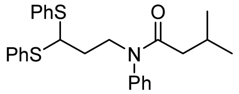
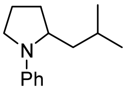
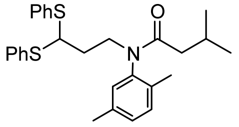
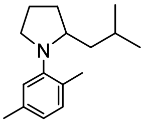
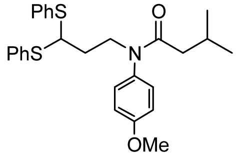
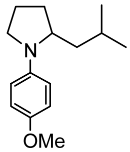
The intramolecular carbonyl olefination of amides is one of the most attractive routes for the construction of nitrogen heterocycles. The Wittig and related reactions are employed only for the formation of aromatic rings such as indoles and the unsaturated cyclic compounds in which the formed double bond is stabilized with π-conjugation with a carbonyl group or an aromatic ring.[1] The intramolecular Peterson[9] and McMurry[10] reactions are also employed for the preparation of indoles and pyrroles. We then tried the preparation of 5-membered unsaturated nitrogen heterocycles by the intramolecular carbonyl olefination of *N*-[3,3-bis(phenylthio)propyl]anilides **6**.

Contrary to our expectation, the pyrrolidine derivatives **7** were obtained when the anilides **6** were treated with the titanocene(II) reagent **1** at 30°C under high dilution conditions (0.03 M) for 3–6 h followed by the treatment with a small amount of water (1 ml/mmol of **6**) for 1 h (Table 2).[11] In general 2-phenyl substituted pyrrolidines **7a**–**d** were obtained in better yields than 2-alkyl substituted ones **7e**–**h**. When **7e**–**h** were formed, the tendency that the use of a large excess amount of **1** decreased their yields was observed (see Entries 6–9).

In order to elucidate the pathway for the formation of the pyrrolidine **7**, the reaction of **6a** with the titanocene(II) reagent **1** was quenched with D_2O and the *vic*-dideuterated **7a** (77% deuterium incorporation) was isolated in 83% yield. Its NMR spectrum indicated that the product was a 3:1 mixture of stereoisomers.

Two different pathways for the formation of **7** should be considered (Scheme 2). One might assume that the reduction of the intramolecular carbonyl olefination product **8** with another equivalent of titanocene(II) affords the pyrrolidine **7** via the titanacyclopropane **9**. Alternative pathway for this process would be the one which involves the further reaction of the oxatitanacyclobutane intermediate **10** with **1** to produce the five-membered dimetallacycle **11**, the hydrolysis of which affords the pyrrolidine **7**. It is unclear at present which pathway is operating in the present reaction.

Table 2. Titanocene(II) **1**-promoted intramolecular reaction of the anilide **6**

Entry	Anilide **6**		$Cp_2Ti[P(OEt)_3]_2$ **1** (equiv)	Time (h)	Pyrrolidine **7**		Yield (%)
1		**6a**	3	5		**7a**	76
2	**6a**		4	5	**7a**		82
3		**6b**	4	3		**7b**	85
4		**6c**	4	3		**7c**	85
5		**6d**	4	5		**7d**	80[a]
6		**6e**	3	6		**7e**	70
7	**6e**		4	6	**7e**		63
8		**6f**	3	6		**7f**	76
9	**6f**		4	6	**7f**		69
10		**6g**	3	6		**7g**	61
11		**6h**	3	6		**7h**	53

[a] The ratio of isomers = 78 : 22.

In conclusion, we established a new route to five-membered nitrogen heterocycles. Since the starting materials **6** are readily available by the acylation of *N*-[3,3-bis(phenylthio)propyl]anilines, this reaction provides a practical way for the synthesis of various 2-substituted pyrrolidines.

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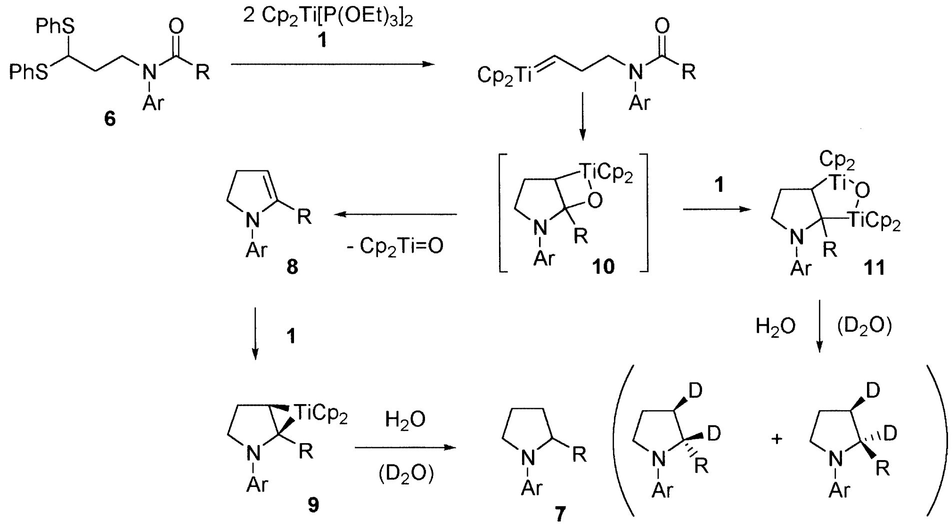

Scheme 2. Plausible pathway for the formation of pyrrolidines by titanocene(II)-promoted intramolecular reaction of *N*-[3,3-bis(phenylthio)propyl]anilides.

from the Ministry of Education, Culture, Sports, Science and Technology, Japan. This work was carried out under the 21st Century COE program of "Future Nano-materials" in Tokyo University of Agriculture & Technology.

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8. Compound **4c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (d, $J=6.7$ Hz, 6H), 1.68–1.76 (m, 1H), 1.95 (dd, $J=7.0$, 7.0 Hz, 2H), 3.09 (s, 3H), 6.01 (t, $J=7.0$ Hz, 1H), 6.65–6.76 (m, 3H), 7.16–7.36 (m, 7H). When the allylic proton at 1.95 ppm was irradiated, NOE was observed on the signal of the proton at the *ortho*-position of the aniline moiety near 6.70 ppm.
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11. The reactions were carried out in a manner similar to the intermolecular carbonyl olefination. In a typical procedure, a THF (10 ml) solution of the anilide **6a** (228 mg, 0.50 mmol) was added over 20 min at 30°C to a THF (6 ml) solution of the titanocene(II) reagent **1**, prepared from Cp_2TiCl_2 (2.0 mmol) and Mg (2.4 mmol) in the presence of $P(OEt)_3$ (4.0 mmol), and the mixture was stirred for 5 h. After addition of water (0.5 ml), the mixture was stirred for additional 1 h and the reaction was quenched by addition of 1 M NaOH. The usual work-up gaive the crude product, which was purified by silica gel PTLC (hexane:ethyl acetate = 9:1) to afford 92 mg of **7a** in 82% yield.