Low-Valent Titanium-Induced Reductive Coupling of Amino Ketones

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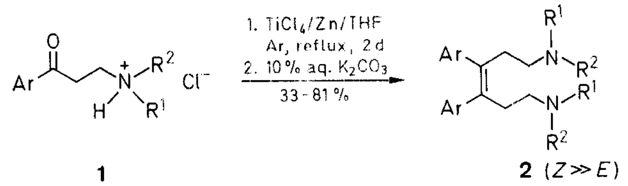
The reaction of amino ketones with titanium tetrachloride/zinc powder has been studied in tetrahydrofuran and 1,4-dioxane under an argon atmosphere. Symmetrical 1,8-diaminoalkenes **2** were obtained from the corresponding Mannich base hydrochlorides **1** via the intermolecular reductive coupling, and azacycloalkenes **4** were prepared from diketoamines **3** via the intramolecular reductive coupling under similar conditions.

Recently, low-valent titanium reagents have been shown to be the most useful reagent for the synthesis of olefins from carbonyl compounds.[1] Low-valent titanium reagent can be made in several ways, but it is more convenient to prepare it from titanium tetrachloride with zinc powder. Aldehydes and ketones were reductively coupled to form the corresponding pinacols and/or olefins by the low-valent titanium reagent.[1] The products depended on the reaction conditions, generally, pinacols were formed at lower temperature, and olefins were produced at higher temperature.[2] But until now the reaction of titanium tetrachloride/zinc powder reagent with amino ketones has not been reported. We have now studied this reaction, and report herein our results on the reaction of Mannich bases with titanium tetrachloride/zinc powder. Symmetrical 1,8-diaminoalkenes **2**, predominantly with *Z*-configuration,[3] were obtained from hydrochloride of the Mannich bases **1** via intermolecular reductive coupling at reflux temperature of tetrahy-



1 **2** ($Z \gg E$)

1, 2	Ar	R^1	R^2
a	Ph	CH_3	CH_3
b	Ph	$(CH_2)_5$	
c	4-BrC_6H_4	$(CH_2)_5$	
d	4-BrC_6H_4	CH_3	CH_3
e	4-$CH_3C_6H_4$	CH_3	CH_3
f	4-$CH_3C_6H_4$	$(CH_2)_5$	
g	4-$CH_3OC_6H_4$	$(CH_2)_5$	
h	Ph	$CH_2CH_2OCH_2CH_2$	

drofuran or 1,4-dioxane by titanium tetrachloride/zinc powder. But at room temperature, we obtained only the corresponding pinacols, which were also formed using aqueous titanium trichloride in basic media.[4]

On the other hand, we obtained azacycloalkenes **4** from β-diketoamines **3** (n = 2) as well as from some analogous α-derivatives **3** (n = 1) via the intramolecular reductive coupling in dilute tetrahydrofuran solution.

Table 1. Diaminoalkenes **2** Prepared

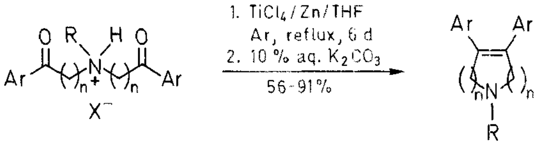
Product	Yield[a] (%)	mp (°C)[b] (solvent)	Molecular Formula[c]	IR (KBr)[d] ν(cm^{-1})	^{1}H-NMR (CDCl$_3$/TMS)[e] δ	MS (70 eV)[f] m/z (M$^+$)
2a	71	322–324 (EtOH)	$C_{22}H_{30}N_2 \cdot 2HCl$ (322.4)	3400, 2500, 1600, 1500, 1450, 960, 780, 700	2.85 (s, 12H, CH$_3$); 3.09 (s, 8H, CH$_2$); 7.15 (s, 10H$_{arom}$)	322
2b	81	81–84 (EtOH/H$_2$O)	$C_{28}H_{38}N_2$ (402.5)	3100, 2900, 1600, 1450, 1300, 1100, 760, 700	1.48–1.55 (m, 12H, ring CH$_2$); 2.22–2.38 (m, 12H, 2 × N(CH$_2$–)$_3$; 2.68–2.86 (m, 4H, 2 × =CCH$_2$); 6.87–7.04 (m, 10H$_{arom}$)	402
2c	51	80–83 (EtOH/H$_2$O)	$C_{28}H_{36}Br_2N_2$ (560.3)	2900, 2800, 1590, 1490, 1450, 1100, 820, 780	1.48 (m, 12H, ring CH$_2$); 2.29–2.34 (m, 12H, 2 × N(CH$_2$–)$_3$); 2.74 (m, 4H, 2 × =CCH$_2$); 6.73–7.24 (q, 8H$_{arom}$)	560
2d	45	123–126 (EtOH/H$_2$O)	$C_{22}H_{28}Br_2N_2$ (480.2)	2950, 2800, 1580, 1490, 1460, 1000, 820, 740	2.10–2.31 (m, 16H, CH$_3$ + NCH$_2$); 2.61 (m, 4H, 2 × =CCH$_2$); 6.74–7.25 (m, 8H$_{arom}$)	480
2e	38	294 (EtOH)	$C_{24}H_{34}N_2 \cdot 2HCl$ (350.5)	3400, 2600, 1600, 1510, 1460, 1250, 970, 810	2.15 (s, 6H, $\mathrm{ArC\underline{H}_3}$); 2.88 (s, 12H, NCH$_3$); 3.11 (s, 8H, CH$_2$); 6.98 (s, 8H$_{arom}$)	350
2f	66	296–298 (EtOH)	$C_{30}H_{42}N_2 \cdot 2HCl$ (430.6)	3400, 2900, 2700, 1600, 1500, 1450, 1080, 800	1.68–1.85 (m, 12H, ring CH$_2$); 2.19 (s, 6H, $\mathrm{ArC\underline{H}_3}$); 2.77–3.03 (m, 12H, 2 × N(CH$_2$–)$_3$); 3.43–3.56 (m, 4H, 2 × =CCH$_2$); 6.98 (s, 8H$_{arom}$)	430
2g	33	91–94 (PE)[g]	$C_{30}H_{42}N_2O_2$ (462.6)	2900, 2750, 1600, 1500, 1450, 1250, 800	1.48 (m, 12H, ring CH$_2$); 2.32–2.37 (m, 12H, 2 × N(CH$_2$–)$_3$); 2.64–2.82 (m, 4H, 2 × =CCH$_2$); 3.70 (s, 6H, OCH$_3$); 6.54–6.90 (m, 8H$_{arom}$)	462
2h	57	92–95 (PE)[g]	$C_{26}H_{34}N_2O_2$ (406.5)	3050, 2800, 1600, 1480, 1440, 1300, 1100, 750, 700	2.36–2.46 (m, 12H, 2 × N(CH$_2$–)$_3$); 2.68–2.85 (m, 4H, 2 × =CCH$_2$); 3.63–3.73 (t, 8H, 2 × CH$_2$OCH$_2$); 6.87–7.08 (m, 10H$_{arom}$)	406

[a] Yield of pure isolated product.
[b] Uncorrected, measured with a Yanaco MP-500 apparatus.
[c] Satisfactory microanalyses obtained: C ±0.30, H ±0.20, N ±0.30; except for **2c** (C −0.50) and **2b** (H +0.44).
[d] Recorded on Shimadzu IR-408 spectrophotometer.
[e] Recorded on JMN FX-90Q NMR spectrometer.
[f] Recorded on ZAB-HS spectrometer.
[g] PE = Petroleum ether (bp 60–90 °C).

Table 2. Azacycloalkanes **4** Prepared

Product	Yield[a]	mp (°C)[b] (EtOH)	Molecular Formula[c]	IR (KBr)[d] ν(cm^{-1})	^{1}H-NMR (CDCl$_3$/TMS)[e] δ	MS (70 eV)[f] m/z (M$^+$)
4a	90	83–84	$C_{23}H_{21}N$ (311.4)	3030, 2850, 1595, 1490, 1370, 880, 760, 740, 690	3.93 (m, 6H, CH$_2$); 7.10 (m, 15H$_{arom}$)	311
4b	91	121–122	$C_{23}H_{21}N$ (311.4)	3000, 2775, 1612, 1518, 1370, 750 683	2.26 (s, 3H, CH$_3$); 4.56 (s, 4H, CH$_2$); 7.20 (m, 14H$_{arom}$)	311
4c	63	103–104	$C_{19}H_{21}N$ (263.3)	3020, 2775, 1595, 1490, 1385, 760, 700	2.23 (s, 3H, CH$_3$); 2.83 (m, 8H, CH$_2$); 7.18 (s, 10H$_{arom}$)	263
4d	60	60–61	$C_{20}H_{23}N$ (277.4)	3050, 2800, 1600, 1390, 760, 700	1.10 (t, 3H, CH$_3$); 2.51 (q, 2H, CH$_2$); 2.70 (m, 8H, CH$_2$); 6.90 (s, 10H$_{arom}$)	277
4e	66	55–56	$C_{22}H_{27}N$ (305.4)	3050, 2850, 1590, 1490, 1370, 750, 694	1.02 (m, 3H, CH$_3$); 1.46 (m, 4H, CH$_2$); 2.8 (m, 10H, CH$_2$); 7.17 (m, 10H$_{arom}$)	305
4f	56	222–224	$C_{21}H_{25}N$[c] (291.4)	3000, 1700, 1625, 1610, 1560, 1510, 1360, 810, 780, 740, 705	2.23 (s, 3H, CH$_3$); 2.66–4.00 (m, 11H, CH$_2$, NCH$_3$); 6.78 (m, 8H$_{arom}$)	291

[a,b,d–f] Refers to a, b, d–f in Table 1.
[c] Satisfactory microanalyses obtained: C ±0.30, H ±0.20, N ±0.33; except for **4b** (H −0.41). Compound **4f** was isolated and analysed as the picrate.



3 4

3, 4	Ar	R	n	X
a	Ph	CH_2Ph	1	Br
b	Ph	$4\text{-}CH_3C_6H_4$	1	Br
c	Ph	CH_3	2	Cl
d	Ph	Et	2	Cl
e	Ph	*n*-Bu	2	Cl
f	$4\text{-}CH_3C_6H_4$	CH_3	2	Cl

From the synthetic point of view, it provides a convenient and useful method for the preparation of symmetrical 1,8-diaminoalkenes **2** and azacycloalkenes **4**. The results are summarized in Tables 1 and 2, respectively. All products obtained are new compounds and were characterized by elemental analyses, IR, ^{1}H-NMR, and mass spectra.

Symmetrical 1,8-Diaminoalkenes 2; General Procedure:

$TiCl_4$ (2.26 mL, 15 mmol) is added dropwise using a syringe to a stirred suspension of Zn powder (1.96 g, 30 mmol) in freshly distilled dry THF (60 mL) at room temperature under an argon atmosphere. After the completion of addition, the mixture is heated to reflux for 1 h. The suspension of the low-valent titanium reagent formed is cooled to 25 °C, and the Mannich base hydrochloride **1** (10 mmol) is added carefully. Reflux is continued with stirring for 2 days under an argon atmosphere, then most of the solvent is removed by vacuum, the residue is cooled, poured into 10% aq. K_2CO_3 (200 mL), and extracted with $CHCl_3$ (6 × 50 mL). The combined $CHCl_3$ extract is washed with water (3 × 20 mL), dried (Na_2SO_4), and the solvent is removed. The resulting crystalline material is recrystallized from EtOH or petroleum ether (Table 1).

Azacycloalkenes 4; General Procedure:

$TiCl_4$ (7.5 mL, 68 mmol) is added dropwise via a syringe to a stirred suspension of Zn powder (9.0 g, 138 mmol) in freshly distilled dry THF (180 mL) at room temperature under an argon atmosphere. When the addition is complete, the mixture is heated to reflux for 1 h. To the suspension of low-valent titanium reagent thus formed, diketoamine **3**[5] (12 mmol) is added carefully at room temperature. Reflux is continued with stirring for 6 days under an argon atmosphere, and then most of the THF is removed under reduced pressure. The residue is cooled, poured into 10% aq. K_2CO_3 (300 mL) and extracted with $CHCl_3$ (5 × 80 mL). The combined $CHCl_3$ extract is washed with water (3 × 20 mL), dried (Na_2SO_4), and the solvent is removed. The resulting crystalline material or oil is purified by recrystallization from EtOH or by column chromatography on silica gel (eluent: petroleum ether (bp 60-90 °C)/EtOH, 1 : 1), respectively (Table 2).

Financial support of this research from the National Natural Science Foundation of China is gratefully acknowledged.

Received: 4 July 1988; revised: 10 October 1988

(1) McMurry, J.E. *Acc. Chem. Res.* **1983**, *16*, 405.
(2) Mukaiyama, J., Sato, T., Hanna, J. *Chem. Lett.* **1973**, 1041.
(3) When compound **2g** is irradiated by UV light, the maximum absorption band of the UV spectrum is shifted to shorter wavelength, while for compounds **2a–f** and **2h** irradiation by UV light, shifted the maximum absorption bands to longer wavelengths.
(4) Unpublished work.
(5) **3a**: Mason, A.T., Winder, R. *J. Chem. Soc.* **1894**, 1360.
3b: Brown, F., Mann, F.G. *J. Chem. Soc.* **1948**, 859.
3c–f: Plati, J.T., Schmidt, R.A., Wenner, W. *J. Org. Chem.* **1949**, *14*, 873.