

# Low-Valent Titanium Induced Reductive Coupling of Nitriles with Nitro Compounds

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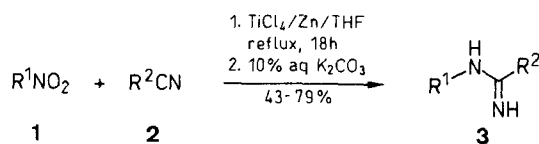
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The intermolecular and intramolecular coupling of a cyano group with a nitro group induced by a low-valent titanium reagent prepared from titanium tetrachloride and zinc powder was studied.

Low-valent titanium reagents have an exceedingly high ability in inducing reductive coupling of carbonyl compounds and is attracting increasing interest in organic synthesis. A large number of other functional groups can also be coupled.<sup>1</sup> However, little attention has been devoted to the intermolecular coupling of different functional groups, and these reactions have not been reported in the literature. In this paper, we describe the coupling of a cyano group with a nitro group induced by treatment with titanium tetrachloride/zinc.

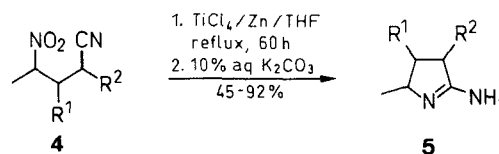
Nitro groups are known to be easily reduced by low-valent titanium.<sup>2</sup> A cyano group, however, is relatively more stable to a low-valent titanium reagent than a nitro group and could not be coupled unless the reaction mixture is refluxed for a long time.<sup>3,4</sup> We considered that the intermediate derived from a more active functional group by low-valent titanium treatment can perhaps attack the more stable functional group which does not react with low-valent titanium. Therefore, we have studied the behaviour of the cyano group and the nitro group when treated with titanium(IV) chloride and zinc in tetrahydrofuran at refluxing temperature.

As expected, amidines **3** were obtained by refluxing equimolar amounts of nitro compound **1** and nitrile **2** with titanium(IV) chloride and zinc in tetrahydrofuran. Products **3** are not derived from nitriles, and amines produced by the reduction of nitro compounds. Treating nitriles with amines under the same reaction conditions, no reaction took place. Aliphatic nitro compounds failed to react with nitriles to give similar amidines as products under the same conditions.



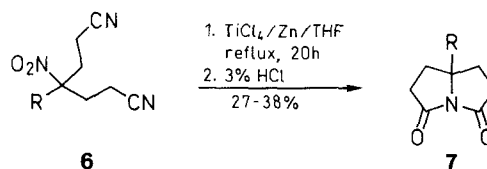
3	R <sup>1</sup>	R <sup>2</sup>	3	R <sup>1</sup>	R <sup>2</sup>
a	3-ClC <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	d	Ph	PhCH <sub>2</sub>
b	3-ClC <sub>6</sub> H <sub>4</sub>	PhCH <sub>2</sub>	e	3-ClC <sub>6</sub> H <sub>4</sub>	Ph
c	Ph	4-ClC <sub>6</sub> H <sub>4</sub> CH <sub>2</sub>	f	Ph	Ph

On the other hand, treatment with titanium(IV) chloride and zinc in dilute tetrahydrofuran of  $\gamma$ -nitronitriles **4** derived from  $\alpha,\beta$ -unsaturated nitriles and nitroethane gave the cyclic amidines **5**. Cyclic amidines may tautomerize, and exist in the amino form.<sup>7</sup>



4, 5	R <sup>1</sup>	R <sup>2</sup>
a	2-ClC <sub>6</sub> H <sub>4</sub>	Ph
b	4-ClC <sub>6</sub> H <sub>4</sub>	Ph
c	4-ClC <sub>6</sub> H <sub>4</sub>	4-ClC <sub>6</sub> H <sub>4</sub>

When 4-nitroheptanedinitriles **6** were subjected to the above procedure no product was formed. However, when the reaction mixture was quenched with dilute hydrochloric acid instead of 10% aqueous potassium carbonate, 3,5-dioxopyrrolizidines **7** were obtained. Compound **7a** has been identified as a potentially useful therapeutic agent for the treatment of cognitive disorders.<sup>8</sup> The successful reaction of **6** to give products **7** is of synthetic value because we are aware of no other direct one-step syntheses of these compounds.



6, 7	R
a	H
b	Me
c	Et

IR spectra were recorded on a Nicolet FT-5DX spectrophotometer, NMR spectra on JEOQ-PMX 60SI and JOEL JNMFX-90Q spectrometers and MS on a ZAB-HS spectrometer. Microanalyses were carried out on a Perkin-Elmer 240C instrument.

## Amidines 3: General Procedure:

TiCl<sub>4</sub> (3.3 mL, 30 mmol) was added dropwise using a syringe to a stirred suspension of Zn powder (3.90 g, 60 mmol) in freshly distilled dry THF (40 mL) at r.t. under an Ar atmosphere. After the completion of addition, the mixture was refluxed for 1 h. The suspension of the low-valent titanium reagent formed was cooled to r.t. and a solution of nitrile **1** (10 mmol) and nitro compound **2** (10 mmol) in THF (10 mL) was added carefully. Reflux was continued with stirring for 18 h under Ar atmosphere, most of the solvent was then removed under reduced pressure, the residue was cooled, poured into 10% K<sub>2</sub>CO<sub>3</sub> (300 mL), and extracted with CHCl<sub>3</sub> (3 × 150 mL). The combined extracts were washed with

**Table.** Amidines **3**, Cyclic Amidines **5** and 3,5-Dioxopyrrolizidines **7** Prepared

Product	Yield <sup>a</sup> (%)	mp (°C) (EtOH)	Molecular Formula <sup>b</sup> or Lit. mp (°C)	IR (KBr) $\nu$ (cm <sup>-1</sup> )	<sup>1</sup> H NMR (CDCl <sub>3</sub> /TMS) $\delta$ , <i>J</i> (Hz)	<sup>13</sup> C NMR (CDCl <sub>3</sub> /TMS) $\delta$	MS (70 eV) <i>m/z</i> (M <sup>+</sup> )
<b>3a</b>	70	145–147	C <sub>14</sub> H <sub>12</sub> Cl <sub>2</sub> N <sub>2</sub> (279.2)	3450, 3300, 3130, 1650, 1614, 850, 810, 780, 710	3.57 (s, 2H, CH <sub>2</sub> ), 4.55 (br, 2H, NH, C=NH), 6.57–7.57 (m, 8H <sub>arom</sub> )	–	278
<b>3b</b>	50	90–92	91–93 <sup>5</sup>	3450, 3293, 3160, 1638, 1611, 868, 788, 750, 695	3.55 (s, 2H, CH <sub>2</sub> ), 4.30 (br, 2H, NH, C=NH), 6.56–7.66 (m, 9H <sub>arom</sub> )	–	–
<b>3c</b>	53	154–156	153–154 <sup>5</sup>	3450, 3270, 3170, 1645, 1610, 800, 750, 690	3.43 (s, 2H, CH <sub>2</sub> ), 4.33 (br, 2H, NH, C=NH), 6.56–7.40 (m, 9H <sub>arom</sub> )	–	–
<b>3d</b>	43	135–137	139 <sup>6</sup>	3417, 3293, 3084, 1642, 1611, 761, 698	3.63 (s, 2H, CH <sub>2</sub> ), 4.47 (br, 2H, NH, C=NH), 6.53–7.66 (m, 9H <sub>arom</sub> )	–	–
<b>3e</b>	79	116–118	115–116 <sup>5</sup>	3495, 3300, 3130, 1640, 1614, 870, 780, 710	4.50 (br, 2H, NH, C=NH), 6.70–8.00 (m, 9H <sub>arom</sub> )	–	–
<b>3f</b>	51	110–112	111–112 <sup>6</sup>	3495, 3350, 3070, 1620, 750, 700	4.73 (br, 2H, NH, C=NH), 6.67–7.90 (m, 10H <sub>arom</sub> )	–	–
<b>5a</b>	92	182–185	C <sub>17</sub> H <sub>17</sub> ClN <sub>2</sub> (284.8)	3457, 3300–2500, 1660, 1370, 938, 879, 755, 703	1.31 (d, 3H, <i>J</i> = 6.1, CH <sub>3</sub> ), 3.60–4.23 (m, 3H), 4.70 (br, 2H), 7.27 (m, 9H <sub>arom</sub> )	165.4, 138.5, 138.4, 129.9, 129.3, 128.6, 128.2, 127.7, 127.5, 127.0, 68.3, 61.1, 59.0, 21.6	284
<b>5b</b>	63	149–151	C <sub>17</sub> H <sub>17</sub> ClN <sub>2</sub> (284.8)	3450, 3300–2500, 1660, 1370, 846, 748, 695	0.81 (d, 3H, <i>J</i> = 6.6, CH <sub>3</sub> ), 3.62–4.24 (m, 3H), 4.26–4.37 (br, 2H), 7.24 (m, 9H <sub>arom</sub> )	166.3, 138.6, 138.2, 132.3, 129.3, 129.1, 128.5, 128.2, 127.5, 64.1, 57.3, 55.6, 17.9	284
<b>5c</b>	45	148–150	C <sub>17</sub> H <sub>16</sub> Cl <sub>2</sub> N <sub>2</sub> (319.2)	3476, 3300–2500, 1655, 1376, 810	1.27 (d, 3H, <i>J</i> = 6.4, CH <sub>3</sub> ), 2.74–3.91 (m, 3H), 3.86–4.03 (br, 2H), 7.00–7.34 (m, 8H <sub>arom</sub> )	165.0, 138.5, 136.9, 133.6, 132.8, 129.7, 129.3, 128.9, 128.8, 127.9, 67.4, 63.8, 60.8, 21.1	318
<b>7a</b>	38	182–183	182–184 <sup>8</sup>	2992, 1775, 1690	4.41 (m, 1H, NCH), 2.60, 2.82 (m, 4H, 2CH <sub>2</sub> CO), 1.83–2.37 (m, 4H, 2CH <sub>2</sub> )	171.0, 59.9, 36.3, 28.7	–
<b>7b</b>	33	161–162	C <sub>8</sub> H <sub>11</sub> NO <sub>2</sub> (153.2)	2992, 1770, 1638, 1370	2.64–2.90 (m, 4H, 2CH <sub>2</sub> ), 1.97–2.26 (m, 4H, 2CH <sub>2</sub> ), 1.47 (s, CH <sub>3</sub> )	171.0, 66.3, 35.6, 35.1, 21.9	153
<b>7c</b>	27	98–101	C <sub>9</sub> H <sub>13</sub> NO <sub>2</sub> (167.2)	2972, 1788, 1690, 1370	2.60–2.92 (m, 4H, 2CH <sub>2</sub> ), 2.00–2.31 (m, 4H, 2CH <sub>2</sub> ), 1.80 (q, 2H, <i>J</i> = 7.0, CH <sub>2</sub> ), 1.02 (t, 3H, <i>J</i> = 7.0, CH <sub>3</sub> )	171.4, 69.2, 34.9, 32.7, 31.0, 8.8	167

<sup>a</sup> Yield of pure isolated product.<sup>b</sup> Satisfactory microanalyses obtained: C  $\pm$  0.39, H  $\pm$  0.33, N  $\pm$  0.33.

water (3  $\times$  40 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvent was removed to give the crude product, which was further purified by recrystallization from EtOH (Table).

#### Cyclic Amidines **5**: General Procedure:

A suspension of low-valent titanium reagent was prepared with same amount of reagents using the same procedure mentioned above. A solution of the appropriate  $\gamma$ -nitronitrile **4** (10 mmol) in THF (40 mL) was added carefully at r. t. to the suspension. The mixture was refluxed with stirring for 60 h under an Ar atmosphere, and most of the solvent was then removed under reduced pressure. The residue was cooled, poured into 10% K<sub>2</sub>CO<sub>3</sub> (300 mL), and extracted with CHCl<sub>3</sub> (4  $\times$  80 mL). The combined extracts were washed with water (3  $\times$  40 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvent was removed to give the crude product, which was further purified by column chromatography on silica gel [eluent: EtOH/petroleum ether (bp 60–90°C), 1 : 3] (Table).

#### 3,5-Dioxopyrrolizidines **7**: General Procedure:

A solution of the appropriate 4-nitroheptanedinitrile **6** (10 mmol) in THF (40 mL) was added carefully at r. t. to a suspension of low-valent titanium reagent prepared as mentioned above. The mixture was refluxed with stirring for 20 h under an Ar atmosphere, and most

of the solvent was then removed under reduced pressure. The residue was cooled, poured into 3% HCl (300 mL), and extracted with CHCl<sub>3</sub> (4  $\times$  80 mL). The combined extracts were washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvent was removed to give the crude product, which was further purified by column chromatography on silica gel [eluent: EtOAc/petroleum ether (bp 60–90°C), 1 : 5] (Table).

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- (1) McMurry, J. E. *Chem. Rev.* **1989**, 89, 1513.
- (2) George, J.; Chandrascharan, S. *Synthesis Commun.* **1983**, 13, 495.
- (3) Chen, W.-x.; Zhang, J.-h.; Hu, M.-y.; Wang, X.-c. *Synthesis* **1990**, 701.
- (4) Chen, J.-x.; Jiang, J.-p.; Chen, W.-x.; Kao, T.-y. *Heterocycles* **1991**, 32, 2339.
- (5) Wather, V. J. *Prakt. Chem.* **1908**, 485.
- (6) Bernthsen, A. *Liebigs Ann. Chem.* **1877**, 184, 321.
- (7) Sieveking, H. U.; Lütte, W. *Liebigs Ann. Chemie* **1977**, 189.
- (8) Butler, D. E. EP 48132, Warner-Lambert Co (1982); *Chem. Abstr.* **1982**, 96, 223312.