Titanium (III) Chloride for the Reduction of Heteroaromatic and Aromatic Nitro Compounds

MASANORI SOMEI, KEIKO KATO, and SATOMI INOUE

Faculty of Pharmaceutical Sciences, Kanazawa University

(Received February 18, 1980)

An improved procedure which avoids prolonged reaction at high temperature and handling under reduced pressure was found for the reduction of heteroaromatic and aromatic nitro compounds with aqueous titanium (III) chloride.

Keywords—titanium (III) chloride; reduction of nitro compounds; heteroaromatic nitro compounds; aromatic nitro compounds; amino quinoline; amino cinnoline

In the previous communication, we reported a one-step synthesis of 4-methylaminomethylindole from 2-methyl-5-nitroisoquinolinium iodide, utilizing aqueous titanium (III) chloride (TiCl$_3$). In the course of studies to extend the scope of the reaction, we observed that the reagent could reduce various heteroaromatic nitro compounds to amines.

The reaction was carried out simply by mixing aqueous TiCl$_3$ solution (16%) with a solution of nitro compounds in H$_2$O–AcOH (1:1, v/v) at room temperature under atmospheric pres-

<table>
<thead>
<tr>
<th>Nitro compound</th>
<th>Product, yield %</th>
<th>Nitro compound</th>
<th>Product, yield %</th>
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<tbody>
<tr>
<td>quinolines</td>
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<tr>
<td>NO$_2$</td>
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<td>NO$_2$</td>
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<tr>
<td>O$_2$N</td>
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<td>N-Me</td>
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<td>H$_2$N</td>
<td></td>
<td>NH$_3$</td>
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<tr>
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<td>98.4$^b$</td>
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<td>84.1$^b$</td>
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<tr>
<td>NO$_2$</td>
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<td>NO$_2$</td>
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<td>93.7$^c$</td>
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$^a$ Other reactions were carried out with 8 mol equiv. of TiCl$_3$ in H$_2$O–AcOH (1:1, v/v) at room temperature for 7 min.

$^b$ 5.9 mol equiv. of aqueous TiCl$_3$ (16%) was used.

$^c$ 7.0 mol equiv. of TiCl$_3$ was used.

1) Location: 12-1 Takara-machi, Kanazawa-shi, Ishikawa 920, Japan.
3) This solvent system was found to be the best among those examined.
sure. Under these reaction conditions, nitro-isoquinolines, -quinolines, and -cinnolines were readily reduced to the corresponding amines within 7 min in high yields. The results are summarized in Table I.

It should be noted that in the reductions of 5-nitrocinoline, and 5- and 6-nitroquinoline, excess TiCl₃ effected the reduction of the aromatic ring. Thus, 5-nitrocinoline was converted to 5-amino-1,4-dihydrocinoline by 8 mol equiv. of TiCl₃ in 84% yield.

Although this reagent was already known to reduce aromatic nitro compounds to amines, the procedure was rather tedious, including handling under reduced pressure, or prolonged reaction (~16 hr) at high temperature. Our procedure avoided these disadvantages, and the reagent was successfully applied to heteroaromatic nitro compounds for the first time.

We further found that aromatic nitro compounds were also reduced at room temperature within 7 min, in yields comparable with the reported ones, without tedious procedures (Table II).

| Nitro compound | Amine | Yield | Reported yield
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<td><img src="image6" alt="Amine" /></td>
<td>94.5</td>
<td>89</td>
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</table>

* a) 8 mol equiv. of TiCl₃ (16%) was used at room temperature in AcOH-H₂O (1:1, v/v). The reaction time was 7 min.

Thus, titanium (III) chloride was demonstrated to be a mild and convenient reagent, generally useful for the reduction of nitro compounds other than aliphatic nitro compounds to amines.

**Experimental**

Commercially available aqueous titanium (III) chloride (16%, d = 1.5) was used throughout this work. All melting points are uncorrected. Preparative thin-layer chromatography (p-TLC) was performed on Merck Aluminiumoxid GF₂₅₄ or Kieselgel GF₂₅₄ (type 60).

**5-Aminoisoquinoline**

a) A solution of 5-nitroisoquinoline (102.5 mg) in 3 ml of AcOH-H₂O (1:1, v/v) was treated with 2.7 ml (7 mol equiv.) of aqueous TiCl₃ (added as a single portion), and stirring was continued for 7 min at room temperature (20°). The reaction mixture was basified by the addition of 15% aqueous NaOH solution and extracted with CH₂Cl₂-MeOH (95:5, v/v). The extract was washed with water, dried over Na₂SO₄, and concentrated to leave a crystalline solid (82.5 mg). Purification of the residue by p-TLC on Al₂O₃, using CH₂Cl₂ as a developing solvent, gave 80.6 mg (y. 93.7%) of 5-aminoisoquinoline. Recrystallization from MeOH-H₂O afforded needles, mp 128—130° (lit.⁴ mp 125—127°).

b) A solution of 5-nitroisoquinoline N-oxide (193.0 mg) in 6 ml of AcOH-H₂O (1:1, v/v) was treated with 5.1 ml (8 mol equiv.) of aqueous TiCl₃ (added as a single portion), and the whole was stirred for 7 min at 18°. After usual work-up, 143.0 mg (y. 97.8%) of pure 5-aminoisoquinoline⁵ was obtained.

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c) A solution of 5-nitroisoquinoline hydrobromide (101.0 mg) in 3 ml of AcνOH–H₂O (2: 1, v/v) was treated with 2.0 ml (8 mol equiv.) of aqueous TiCl₄ (added as a single portion), and stirring was continued for 7 min at 20°C. After usual work-up, 55.5 mg of crude product was obtained. Purification by p-TLC on Al₂O₃ using MeOH–CH₂Cl₂ (3: 97, v/v) as a developing solvent gave 49.5 mg (y. 86.8%) of 5-aminoisoquinoline.

8-Aminoquinoline—A solution of 8-nitroquinoline (100.7 mg) in 6 ml of AcνOH–H₂O (1: 1, v/v) was treated with 2.95 ml (8.0 mol equiv.) of aqueous TiCl₄ (added as a single portion), and the whole was stirred for 7 min at 19°C. After usual work-up as described above, 79.0 mg (y. 95.5%) of 8-aminoquinoline was obtained. Recrystallization from hexane gave prisms, mp 66.0—66.5°C (lit. 8 mp 65—67°C).

6-Aminoquinoline—A solution of 6-nitroquinoline (103.5 mg) in 12 ml of AcνOH–H₂O (1: 1, v/v) was treated with 2.2 ml (5.9 mol equiv.) of aqueous TiCl₄ (added as a single portion), and stirring was continued for 7 min at 20°C. After usual work-up, 87.2 mg of crude product was obtained. Purification by p-TLC on Al₂O₃ using MeOH–CH₂Cl₂ (1: 99, v/v) afforded 84.3 mg (y. 98.4%) of 6-aminoquinoline. Recrystallization from benzene gave needles, mp 116—117°C (lit. 9 mp 114°C).

5-Aminoquinoline—A solution of 5-nitroquinoline (104.0 mg) in 6 ml of AcνOH–H₂O (1: 1, v/v) was treated with 2.2 ml (5.9 mol equiv.) of aqueous TiCl₄ (added as a single portion), and the whole was stirred for 7 min at 19°C. After usual work-up, 84.5 mg of crude product was obtained. Purification by p-TLC on Al₂O₃ using MeOH–CH₂Cl₂ (0.5: 99.5, v/v) afforded 72.4 mg (y. 84.1%) of 5-aminoquinoline. Recrystallization from MeOH–H₂O gave prisms, mp 107—109°C (lit. 10 mp 109—110°C).

8-Aminonocinoline—A solution of 8-nitrocinnoline (90.0 mg) in 8 ml of AcνOH–H₂O (1: 1, v/v) was treated with 2.7 ml of aqueous TiCl₄ (added as a single portion), and the whole was stirred for 7 min at 11°C. After usual work-up, 73.0 mg of crude product was obtained. Purification by p-TLC on kieselgel using MeOH–CH₂Cl₂ (5: 95, v/v) afforded 68.5 mg (y. 92.0%) of 8-aminonocinoline. Recrystallization from benzene gave pale yellow prisms, mp 95—96°C (lit. 11 mp 89—92°C).

5-Amino-1,4-dihydrocininnoline—A solution of 5-nitrocinnoline (85.9 mg) in 7 ml of AcνOH–H₂O (1: 1, v/v) was treated with 2.5 ml (8 mol equiv.) of aqueous TiCl₄ (added as a single portion), and stirring was continued for 7 min at 26°C. After usual work-up, 60.5 mg (y. 84.0%) of 5-amino-1,4-dihydrocininnoline was obtained. Recrystallization from MeOH–H₂O afforded pale yellow needles, mp 141—142°C. IR v max cm⁻¹: 3426, 3345, 3226, 1626, 1607, 1592. MS m/z: 147 (M⁺), 130. PMR (CDCl₃) δ: 3.13 (3H, d, J = 3 Hz), 3.27 (2H, br. s, NH₂), 5.97 (1H, d, d, J = 8 and 1 Hz), 6.23 (1H, d, d, J = 8 and 1 Hz), 6.60 (1H, t, J = 3 Hz), 6.85 (1H, t, J = 8 Hz), 7.19 (1H, br. s, NH). Anal. Calcd for C₈H₇N₂: C, 65.28; H, 6.16; N, 28.55. Found: C, 65.09; H, 6.32; N, 28.76.

5-Amino-2-methylisocarbostyril—A solution of 5-nitro-2-methylisocarbostyril (106.8 mg) in 4 ml of AcνOH–H₂O (1: 1, v/v) was treated with 2.7 ml (8 mol equiv.) of aqueous TiCl₄ (added as a single portion), and stirring was continued for 7 min at 21°C. After usual work-up, 78.1 mg (y. 85.7%) of pure 5-amino-2-methylisocarbostyril was obtained. Recrystallization from MeOH–H₂O afforded prisms, mp 152—153°C. IR v max cm⁻¹: 3434, 3236, 3204, 1631, 1593, 1569. MS m/z: 174 (M⁺). PMR (CDCl₃) δ: 3.00—3.66 (2H, br. s, NH₂), 3.55 (3H, s), 6.36 (1H, d, J = 7.5 Hz), 6.86 (1H, d, d, J = 7.5 and 1.5 Hz), 6.98 (1H, d, J = 7.5 Hz), 7.23 (1H, t, J = 7.5 Hz), 7.86 (1H, d, d, J = 7.5 and 1.5 Hz). Anal. Calcd for C₁₆H₁₉N₂O: C, 76.15; H, 7.58; N, 15.66. Found: C, 76.25; H, 5.88; N, 15.74.

5-Amino-4-hydroxyphenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline—A solution of 4-hydroxyphenyl-2-methyl-3-nitro-1,2,3,4-tetrahydroisoquinoline (20.0 mg) in 3 ml of AcνOH–H₂O (1: 1, v/v) was treated with 1 ml (17.2 mol equiv.) of aqueous TiCl₄ (added as a single portion), and the whole was stirred for 7 min at 12°C. After usual work-up, 12.2 mg of crude product was obtained. Purification by p-TLC on Al₂O₃ using MeOH–CH₂Cl₂ (1: 99, v/v) gave 10.1 mg (y. 70.0%) of 5-amino-4-hydroxyphenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline. Recrystallization from acetone afforded prisms, mp 144—145°C. MS m/z: 192 (M⁺). IR v max cm⁻¹: 3380—3100 (NH, OH), 1640, 1502. PMR (CDCl₃) δ: 2.42 (3H, s, N-Me), 2.56 (1H, d, J = 11 and 3.5 Hz), 2.81 (1H, q, J = 3.5 Hz), 3.16 (1H, d, J = 11 Hz), 3.24 and 3.29 (each 1H, d, J = 16 Hz), 4.03 (2H, d, J = 3.5 Hz), 6.52 and 6.57 (each 1H, d, J = 8 Hz), 7.03 (1H, t, J = 8 Hz). Anal. Calcd for C₁₄H₁₄N₂O: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.84; H, 8.42; N, 14.62.

4-Aminoisoquinoline—A solution of 4-nitroisoquinoline (102.3 mg) in 12 ml of AcOH–H₂O (1: 1, v/v) was treated with 3.4 ml (8 mol equiv.) of TiCl₄ (added as a single portion), and stirring was continued for 7 min at 14°C. After usual work-up, 77.7 mg (y. 94.5%) of 4-aminoisoquinoline was obtained. All spectral data were identical with those of an authentic sample.

Aniline—A solution of nitrobenzene (120.0 mg) in 4 ml of AcOH–H₂O (1: 1, v/v) was treated with 5.3 ml (8 mol equiv.) of aqueous TiCl₄ (added as a single portion), and the whole was stirred for 7 min at 15°C. After usual work-up, 83.5 mg (y. 92.0%) of aniline was obtained. All spectral data were identical with those of an authentic sample.

2-Aminotoluene — A solution of 2-nitrotoluene (135.5 mg) in 6 ml of AcOH–H₂O (1:1, v/v) was treated with 5.1 ml (8 mol equiv.) of aqueous TiCl₄ (added as a single portion), and the whole was stirred for 7 min at 15⁰. After usual work-up, 99.5 mg (y. 94.0%) of 2-aminotoluene was obtained. All spectral data were identical with those of an authentic sample.

Acknowledgement The authors are grateful to Prof. Chikara Kaneko for his encouragement throughout this work. Thanks are also due to the staff of the analytical section of our university for the elemental analyses and mass spectra.

Analytical Studies on Pyrimidine Derivatives. V.¹ Simple and Rapid Spectrophotometric Determination of Silver (I) with 5-p-Dimethylaminobenzylidene-2-thiobarbituric Acid²

KENICHIRO NAKASHIMA and SHUZO AKIYAMA

Faculty of Pharmaceutical Sciences, Nagasaki University³

(Received February 25, 1980)

The spectrophotometric determination of silver(I) with 5-p-dimethylaminobenzylidene-2-thiobarbituric acid (DABTB) was studied and two simple and rapid methods are proposed. One is based on photometry of the DABTB-Ag(I) complex in ethanol-buffer (pH 6) solution (method A), and the other is based on measurement of the decrease in absorbance of DABTB due to the complex formation (method B).

Beer’s law holds over the range of 0.04–2 μg/ml of silver(I) at 400 nm in method A, and 0–35 μg of silver(I) at 484 nm in method B. The molar extinction coefficient of the complex is 2.5 × 10⁻⁴ L·mol⁻¹·cm⁻¹ in method A. Hg(I,II), Au(III), Pd(II), Pt(IV), and various anions such as Br⁻, Cl⁻, I⁻, SCN⁻, CN⁻, SO₄²⁻, and S²⁻ interfered with the determination.

These methods were successfully applied to the determination of silver(I) in commercial preparations such as silver nitrate eye lotion and silver protein.

Keywords — 5-p-dimethylaminobenzylidene-2-thiobarbituric acid; silver(I); spectrophotometric determination of silver(I); silver nitrate eye lotion; silver protein

The coloration mechanism of 6-aminouracil derivatives with 9-dimethylaminobenzaldehyde and the application of the coloration in a colorimetric determination method have been reported by one of the authors (K.N.).⁴ In the course of these studies it has become apparent that 9-dimethylaminobenzylidenebarbituric acid derivatives were readily obtained as single reaction products. We investigated the utilization of these compounds as analytical reagents for metal cations. Among these benzylidene derivatives, 5-p-dimethylaminobenzylidene-2-thiobarbituric acid (DABTB)⁵ efficiently forms complexes with heavy metal cations such as silver (I), mercury (I and II), gold (III), palladium (II), and platinum (IV). Silver (I)-DABTB complex⁶ showed the absorption maximum in a wavelength region where the reagent blank

2) A part of this work was presented at the 18th Annual Meeting of the Japan Society for Analytical Chemistry, Koriyama, October 1979, p. 464.
3) Location: I–14, Bunkyo-machi, Nagasaki 852, Japan.
4) K. Nakashima, Yakugaku Zasshi, 97, 202 (1977); idem, ibid., 97, 906 (1977).
6) The structure of this complex is now under investigation.