[Chem. Pharm. Bull.
28(8)2515—2518(1980)]

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[1]

(Received February 18, 1980)

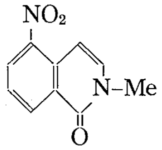
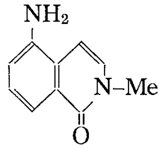
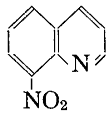
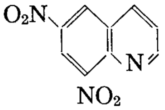
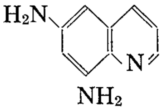
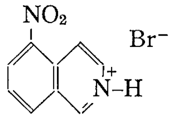
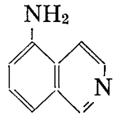
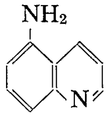
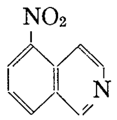
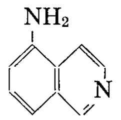
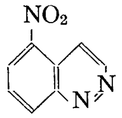
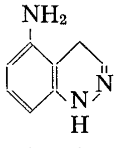
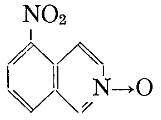
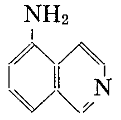
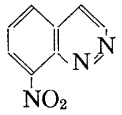
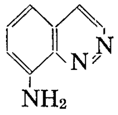
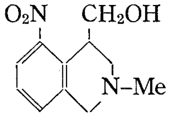
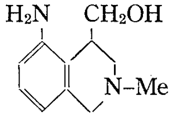
An improved procedure which avoids prolonged reaction at high temperature and handling under reduced pressure was found for the reduction of heteroaromatic and aromatic nitro compounds with aqueous titanium (III) chloride.

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

In the previous communication,[2] 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_2O–AcOH[3] (1: 1, v/v) at room temperature under atmospheric pres-

TABLE I. Reduction of Heteroaromatic Nitro Compounds[a]

Nitro compound	Product, yield %		Nitro compound	Product, yield %	
quinolines					85.7
		95.5			
		98.4[b]			86.8
		84.1[b]	isoquinolines		
cinnolines					93.7[c]
		84.0			97.8
		92.0			70.0

a) Other reactions were carried out with 8 mol equiv. of $TiCl_3$ in H_2O–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.

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[1] Location: *13-1 Takara-machi, Kanazawa-shi, Ishikawa 920, Japan.*
[2] M. Somei, F. Yamada, and C. Kaneko, *Chemistry Lett.*, **1979**, 943.
[3] This solvent system was found to be the best among those examined.

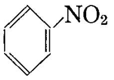
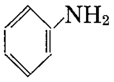
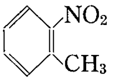
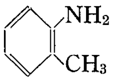
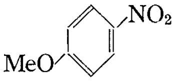
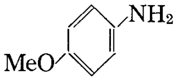
sure. Under these reaction conditions, nitro-isoquinolines, -quinolines, and -cinnolines were readily reduced to the corresponding amines within 7 min in high yields. The results are summarized in Table I.

It should be noted that in the reductions of 5-nitrocinnoline, and 5- and 6-nitroquinoline, excess $TiCl_3$ effected the reduction of the aromatic ring. Thus, 5-nitrocinnoline was converted to 5-amino-1,4-dihydrocinnoline by 8 mol equiv. of $TiCl_3$ in 84% yield.

Although this reagent was already known to reduce aromatic nitro compounds to amines,[4] 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,[4b] without tedious procedures (Table II).

TABLE II. Reduction of Aromatic Nitro Compounds[a]

Nitro compound	Amine	Yield	Reported yield[4]
		92.0	95
		94.0	96
		94.5	89

a) 8 mol equiv. of $TiCl_3$ (16%) was used at room temperature in $AcOH-H_2O$ (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[5] 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 GF_{254} or Kieselgel GF_{254} (type 60).

5-Aminoisoquinoline——a) A solution of 5-nitroisoquinoline (102.5 mg) in 3 ml of $AcOH-H_2O$ (1: 1, v/v) was treated with 2.7 ml (7 mol equiv.) of aqueous $TiCl_3$ (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 CH_2Cl_2–MeOH (95: 5, v/v). The extract was washed with water, dried over Na_2SO_4, and concentrated to leave a crystalline solid (82.5 mg). Purification of the residue by p-TLC on Al_2O_3, using CH_2Cl_2 as a developing solvent, gave 80.6 mg (y. 93.7%) of 5-aminoisoquinoline. Recrystallization from $MeOH-H_2O$ afforded needles, mp 128—130° (lit.[6] mp 125—127°).

b) A solution of 5-nitroisoquinoline N-oxide (193.0 mg) in 6 ml of $AcOH-H_2O$ (1: 1, v/v) was treated with 5.1 ml (8 mol equiv.) of aqueous $TiCl_3$ (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-aminoisoquinoline[6] was obtained.[7]

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4) *a*) J.E. McMurry and M. Silvestri, *J. Org. Chem.*, **40**, 1502 (1975); *b*) T.-L. Ho and C.M. Wong, *Synthesis*, 45 (1974); *c*) F. Sachs and E. Sichel, *Chem. Ber.*, 37, 1861 (1904); *d*) E. Knecht, *Chem. Ber.*, **36**, 166 (1903).

5) J.E. McMurry and J. Melton, *J. Am. Chem. Soc.*, **93**, 5309 (1971).

6) C.F. Koelsch and N.F. Albertson, *J. Am. Chem. Soc.*, **75**, 2095 (1953).

7) Reduction of N-oxide with $TiCl_3$: A. Ohta, Y. Akita, A. Izumida, and I. Suzuki, *Chem. Pharm. Bull.*, **27**, 1316 (1979); J.M. McCall and R.E. TenBrink, *Synthesis*, **1975**, 335.

c) A solution of 5-nitroisoquinoline hydrobromide (101.0 mg) in 3 ml of AcOH–H_2O (2: 1, v/v) was treated with 2.0 ml (8 mol equiv.) of aqueous $TiCl_3$ (added as a single portion), and stirring was continued for 7 min at 20°. After usual work-up, 55.5 mg of crude product was obtained. Purification by p-TLC on Al_2O_3 using MeOH–CH_2Cl_2 (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 AcOH–H_2O (1: 1, v/v) was treated with 2.95 ml (8.0 mol equiv.) of aqueous $TiCl_3$ (added as a single portion), and the whole was stirred for 7 min at 19°. 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° (lit.[8] mp 65—67°).

6-Aminoquinoline——A solution of 6-nitroquinoline (103.5 mg) in 12 ml of AcOH–H_2O (1: 1, v/v) was treated with 2.2 ml (5.9 mol equiv.) of aqueous $TiCl_3$ (added as a single portion), and stirring was continued for 7 min at 20°. After usual work-up, 87.2 mg of crude product was obtained. Purification by p-TLC on Al_2O_3 using MeOH–CH_2Cl_2 (1: 99, v/v) afforded 84.3 mg (y. 98.4%) of 6-aminoquinoline. Recrystallization from benzene gave needles, mp 116—117° (lit.[9] mp 114°).

5-Aminoquinoline——A solution of 5-nitroquinoline (104.0 mg) in 6 ml of AcOH–H_2O (1: 1, v/v) was treated with 2.2 ml (5.9 mol equiv.) of aqueous $TiCl_3$ (added as a single portion), and the whole was stirred for 7 min at 19°. After usual work-up, 84.7 mg of crude product was obtained. Purification by p-TLC on Al_2O_3 using MeOH–CH_2Cl_2 (0.5: 99.5, v/v) afforded 72.4 mg (y. 84.1%)/of 5-aminoquinoline. Recrystallization from MeOH–H_2O gave prisms, mp 107—109° (lit.[10] mp 109—110°).

8-Aminocinnoline——A solution of 8-nitrocinnoline (90.0 mg) in 8 ml of AcOH–H_2O (1: 1, v/v) was treated with 2.7 ml of aqueous $TiCl_3$ (added as a single portion), and the whole was stirred for 7 min at 11°. After usual work-up, 73.0 mg of crude product was obtained. Purification by p-TLC on kieselgel using MeOH–CH_2Cl_2 (5: 95, v/v) afforded 68.5 mg (y. 92.0%) of 8-aminocinnoline. Recrystallization from benzene gave pale yellow prisms, mp 95—96° (lit.[11] mp 89—92°).

5-Amino-1,4-dihydrocinnoline——A solution of 5-nitrocinnoline (85.9 mg) in 7 ml of AcOH–H_2O (1: 1, v/v) was treated with 2.5 ml (8 mol equiv.) of aqueous $TiCl_3$ (added as a single portion), and stirring was continued for 7 min at 26°. After usual work-up, 60.5 mg (y. 84.0%) of 5-amino-1,4-dihydrocinnoline was obtained. Recrystallization from MeOH–H_2O afforded pale yellow needles, mp 141—142°. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3426, 3345, 3226, 1626, 1607, 1592. MS *m/e*: 147 (M^+), 130. PMR ($CDCl_3$) δ: 3.13 (3H, d, $J=3$ Hz), 3.27 (2H, br. s, NH_2), 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), 7.21 (1H, br. s, NH). *Anal.* Calcd for $C_8H_9N_3$: 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 AcOH–H_2O (1: 1, v/v) was treated with 2.7 ml (8 mol equiv.) of aqueous $TiCl_3$ (added as a single portion), and stirring was continued for 7 min at 21°. After usual work-up, 78.1 mg (y. 85.7%) of pure 5-amino-2-methylisocarbostyril was obtained. Recrystallization from MeOH–H_2O afforded prisms, mp 152—153°. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3434, 3326, 3204, 1631, 1593, 1569. MS *m/e*: 174 (M^+). PMR ($CDCl_3$) δ: 3.00—3.66 (2H, br. s, NH_2), 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 $C_{10}H_{10}N_2O \cdot 1/4H_2O$: C, 67.15; H, 5.87; N, 15.66. Found: C, 67.25; H, 5.88; N, 15.74.

5-Amino-4-hydroxymethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline——A solution of 4-hydroxymethyl-2 methyl-5-nitro-1,2,3,4-tetrahydroisoquinoline (20.0 mg) in 3 ml of AcOH–H_2O (1: 1, v/v) was treated with 1 ml (17.2 mol equiv.) of aqueous $TiCl_3$ (added as a single portion), and the whole was stirred for 7 min at 12°. After usual work-up, 12.2 mg of crude product was obtained. Purification by p-TLC on Al_2O_3 using MeOH–CH_2Cl_2 (1: 99, v/v) gave 10.1 mg (y. 70.0%) of 5-amino-4-hydroxymethyl-2-methyl-1,2,3,4-tetrahydroisoquinoline. Recrystallization from acetone afforded prisms, mp 144—145°. MS *m/e*: 192 (M^+). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3380—3100 (NH, OH), 1640, 1592. PMR ($CDCl_3$) δ: 2.42 (3H, s, N–Me), 2.56 (1H, d.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 3.92 (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 $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.64; H, 8.49; N, 14.62.

4-Aminoanisole——A solution of 4-nitroanisole (102.3 mg) in 12 ml of AcOH–H_2O (1: 1, v/v) was treated with 3.4 ml (8 mol equiv.) of $TiCl_3$ (added as a single portion), and stirring was continued for 7 min at 14°. After usual work-up, 77.7 mg (y. 94.5%) of 4-aminoanisole 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–H_2O (1: 1, v/v) was treated with 5.3 ml (8 mol equiv.) of aqueous $TiCl_3$ (added as a single portion), and the whole was stirred for 7 min at 15°. 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.

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[8] J. Howitz, H. Fraenkel, and E. Schroeber, *Ann.*, **396**, 54 (1913).
[9] A. Claus and L. Schnell, *J. Prakt. Chem.*, **53**, 119 (1896).
[10] A. Kaufmann and O. Zeller, *Chem. Ber.*, **50**, 1627 (1917).
[11] E.J. Alford, H. Irving, H.S. Marsh, and K. Schofield, *J. Chem. Soc.*, **1952**, 3009.

2-Aminotoluene——A solution of 2-nitrotoluene (135.5 mg) in 6 ml of AcOH–H_2O (1: 1, v/v) was treated with 5.1 ml (8 mol equiv.) of aqueous $TiCl_3$ (added as a single portion), and the whole was stirred for 7 min at 15°. 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.

[Chem. Pharm. Bull.
28(8)2518—2522(1980)]

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

KENICHIRO NAKASHIMA and SHUZO AKIYAMA

Faculty of Pharmaceutical Sciences, Nagasaki University[3]

(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 $2.5 \times 10^4 \cdot l \cdot mol^{-1} \cdot cm^{-1}$ in method A. Hg(I,II), Au(III), Pd(II), Pt(IV), and various anions such as Br^-, Cl^-, I^-, SCN^-, CN^-, $S_2O_3^{2-}$, and S^{2-} 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 *p*-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 *p*-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 complex[6] showed the absorption maximum in a wavelength region where the reagent blank

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[1] Part IV: K. Nakashima and S. Akiyama, *Yakugaku Zasshi*, **100**, 515 (1980).

[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: *1-14, Bunkyo-machi, Nagasaki 852, Japan.*

[4] K. Nakashima, *Yakugaku Zasshi*, **97**, 202 (1977); *idem, ibid.*, **97**, 906 (1977).

[5] DABTB has been utilized for the qualitative detection of rare earth elements; T. Pavolini and F. Gambarin, *Anal. Chim. Acta*, **3**, 27 (1949).

[6] The structure of this complex is now under investigation.