

Reduction of Some Functional Groups with Titanium(IV) Chloride/Sodium Borohydride

Shinzo KANO, Yasuyuki TANAKA, Eiichi SUGINO, Satsoshi HIBINO

Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

Reducing agents formed by combining transition-metal halides [e.g. Co(II)¹ or Zr(IV)²] with sodium borohydride have recently been applied to the reduction of various functional groups, including C=C double bonds and C≡C triple bonds. These reduction reactions are attracting increasing interest in organic synthesis. The low-valent titanium reagent prepared from titanium(IV)³ or titanium(III)⁴ compounds and lithium alanate [Ti(IV)/LiAlH₄ or Ti(III)/LiAlH₄] have been found to possess particular reducing properties. The combined reagent TiCl₄/NaBH₄ has been used^{5,6,7} for the reduction of carboxylic acids and esters to alcohols and of nitriles to amines; however, unsatisfactory results were obtained in the reduction of nitro compounds and carboxamides. We have now investigated the reducing properties of the TiCl₄/NaBH₄ reagent and have found that this reagent can be used to advantage for the reduction of carboxylic acids, acyl chlorides, carboxamides, oximes, nitro compounds, and sulfoxides.

Treatment of mandelic acid with a mixture of titanium(IV) chloride (2.2 equiv) and sodium borohydride (6.6 equiv) in 1,2-dimethoxyethane at room temperature for 14 h affords phenylethanol in 60% yield without formation of alkanes or C—C coupling products (as is observed when the system TiCl₃/LiAlH₄ is used⁴). In the same manner, we reduced other carboxylic acids to the corresponding alcohols with the system TiCl₄/NaBH₄. In general, the optimum molar ratio of substrate/TiCl₄/NaBH₄ was found to be 1/1.1/3.3 for monofunctional carboxylic acids. Acyl chlorides are readily reduced to alcohols by the reagent; likewise, carboxamides and lactams are reduced to amines, halogen atoms on a benzene ring remaining unaffected. The reduction of oximes to amines is of practical interest for the derivatization of certain organic compounds. The reduction of oximes with diborane usually affords hydroxylamines⁸ whereas the reduction with lithium alanate generally affords amines only in low yields and in some cases, aziridines are obtained⁹. Our reagent reduces oximes to amines without formation of hydroxylamines or aziridines. Further, sulfoxides¹⁰ are smoothly reduced to the corresponding thioethers by our reagent.

Table. Reduction with Titanium (IV) Chloride/Sodium Borohydride

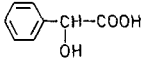
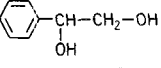
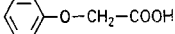
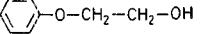
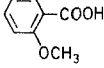

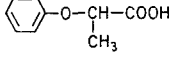
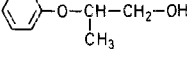
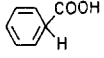
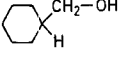
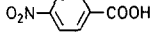
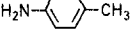
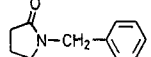
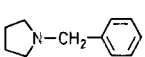
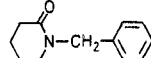
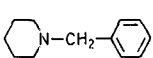
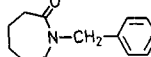
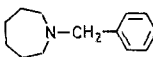
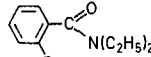
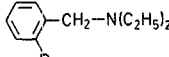
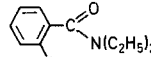
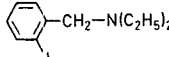
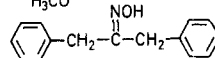
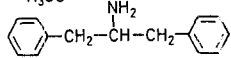
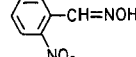
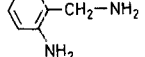
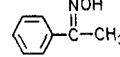
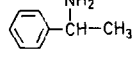
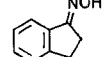
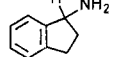
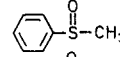
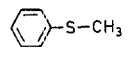
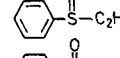
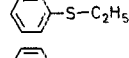
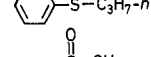
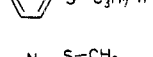
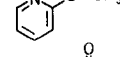
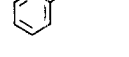
Substrate	Product	Yield ^a [%]	m.p. or b.p./torr [°C]	
			found	reported
		60	m.p. 67–69°	m.p. 68–70° ¹¹
$n\text{-C}_8\text{H}_{17}\text{-COOH}$	$n\text{-C}_8\text{H}_{17}\text{-CH}_2\text{-OH}$	93	b.p. 100–101°/10 torr	b.p. 107.5°/15 torr ¹²
		95	b.p. 102°/10 torr	b.p. 185°/80 torr ¹³
		92	b.p. 95–96°/5 torr	b.p. 180°/250 torr ¹⁴
		95	b.p. 99–101°/5 torr	b.p. 120°/10 torr ¹⁵
		94	b.p. 75–77°/10 torr	b.p. 91–92°/23 torr ¹⁶
		96	m.p. 43°	m.p. 42.8° ¹⁷
$n\text{-C}_7\text{H}_{15}\text{-C(=O)Cl}$	$n\text{-C}_7\text{H}_{15}\text{-CH}_2\text{-OH}$	95	b.p. 100–101°/10 torr	b.p. 107.5°/15 torr ¹²
$n\text{-C}_9\text{H}_{19}\text{-C(=O)NH}_2$	$n\text{-C}_9\text{H}_{19}\text{-CH}_2\text{-NH}_2$	75	b.p. 65–67°/20 torr	b.p. 171–174°/760 torr ¹⁸
$n\text{-C}_9\text{H}_{19}\text{-C(=O)NH-CH}_2\text{-C}_6\text{H}_5$	$n\text{-C}_9\text{H}_{19}\text{-CH}_2\text{-NH-CH}_2\text{-C}_6\text{H}_5$	93	b.p. 154–155°/10 torr	b.p. 156–157°/13 torr ¹⁹
$n\text{-C}_9\text{H}_{19}\text{-C(=O)N(C}_2\text{H}_5)_3$	$n\text{-C}_9\text{H}_{19}\text{-CH}_2\text{-N(C}_2\text{H}_5)_2$	94	b.p. 128–130°/5 torr	b.p. 95–98°/1 torr ²⁰
		93	b.p. 105–106°/5 torr	b.p. 72°/1 torr ²¹
		95	b.p. 118–120°/10 torr	b.p. 122°/15 torr ²²
		92	b.p. 130–132°/5 torr	b.p. 143–144°/13 torr ²²
		96	m.p. 244–246° ^b	m.p. 245° ^b 23
		95	m.p. 256–257° ^b	m.p. 257° ^b 24
$\text{H}_3\text{CO-C}_6\text{H}_4\text{-CH=NOH}$	$\text{H}_3\text{CO-C}_6\text{H}_4\text{-CH}_2\text{-NH}_2$	89	b.p. 136–138°/5 torr	b.p. 160°/14 torr ²⁵
		94	m.p. 199–201° ^b	m.p. 200–202° ^b 26
		82	m.p. 59–61°	m.p. 60–62° ²⁷
		86	b.p. 65–66°/10 torr	b.p. 184.5°/760 torr ²⁸
		91	100–102°/10 torr	b.p. 105–108°/18 torr ²⁹
		91	b.p. 84–85°/15 torr	b.p. 84–85°/15 torr ³⁰
		85	b.p. 85–86°/12 torr	b.p. 85–86°/12 torr ³⁰
		92	b.p. 82–84°/2 torr	b.p. 102–103°/15 torr ³¹
		89	b.p. 61–63°/3 torr	b.p. 197°/760 torr ³²
$n\text{-C}_4\text{H}_9\text{-S-C(=O)C}_2\text{H}_5$	$n\text{-C}_4\text{H}_9\text{-S-C}_2\text{H}_5$	92	b.p. 142°/760 torr	b.p. 43°/16 torr ³³

Table. (Continued)

Substrate	Product	Yield ^a [%]	m.p. or b.p./torr [°C]	
			found	reported
		90	b.p. 78–80°/20 torr	b.p. 80°/20 torr ³⁰
		93	m.p. 49°	m.p. 49–50° ³⁰
		91	b.p. 64°/25 torr	b.p. 62–63°/28 torr ³⁴
		86	b.p. 160°/5 torr	— ^c

^a Yield of isolated purified product

^b Hydrochloride.

^c Compound gave satisfactory microanalysis.

Reduction of Carboxylic Acids, Acyl Chlorides, Carboxamides, and Oximes; General Procedure:

Amounts of Reagent used for 10 mmol of substrate:

for *Carboxylic Acids*: TiCl₄, 2.09 g (11 mmol); NaBH₄, 1.25 g (33 mmol).

for *Acyl Chlorides*: TiCl₄, 2.09 g (11 mmol); NaBH₄, 0.83 g (22 mmol).

for *Carboxamides* and *Lactams*: TiCl₄, 2.85 g (15 mmol); NaBH₄, 1.13 g (30 mmol).

for *Oximes*: TiCl₄, 3.99 g (21 mmol); NaBH₄, 1.59 g (42 mmol).

Procedure: A solution of the substrate (10 mmol) in anhydrous 1,2-dimethoxyethane (10 ml) is added dropwise to an ice-cooled, stirred mixture of titanium(IV) chloride and sodium borohydride in anhydrous 1,2-dimethoxyethane (40 ml). Stirring is continued for 14 h at room temperature and the reaction then quenched by the addition of water (100 ml) with ice cooling. In the case of carboxylic acids, the mixture is extracted with benzene (2 × 60 ml). In the other cases, the mixture is basified with 28% aqueous ammonia and then extracted with benzene (2 × 70 ml). The extract is washed with saturated sodium chloride solution (100 ml), dried with sodium sulfate, and evaporated. The products thus obtained are spectroscopically pure. They are further purified by distillation or recrystallization.

Reduction of Sulfoxides to Sulfides; General Procedure:

A solution of the sulfoxide (10 mmol) in anhydrous 1,2-dimethoxyethane (10 ml) is added dropwise to an ice-cooled, stirred mixture of titanium(IV) chloride (2.09 g, 11 mmol) and sodium borohydride (0.82 g, 22 mmol) in anhydrous 1,2-dimethoxyethane (40 ml). The blue reaction mixture is decolorized within 10–15 min after the addition of the substrate. Stirring is continued for 15 min at room temperature and the reaction then quenched by the addition of water (100 ml) with ice cooling. The mixture is extracted with benzene (2 × 60 ml), the extract washed with saturated sodium chloride solution (100 ml), and dried with sodium sulfate. The solvent is removed to give the spectroscopically pure sulfides which are further purified by distillation or recrystallization.

Received: October 30, 1979

(Revised form: December 17, 1979)

¹ S.-K. Chung, *J. Org. Chem.* **44**, 1014 (1979); and references cited therein.

² F. Sato, S. Sato, M. Sato, *J. Organomet. Chem.* **122**, C25 (1976).

³ T. Mukaiyama et al., *Chem. Lett.* **1975**, 291, 711, 1201.

⁴ J. E. McMurry, M. P. Fleming, *J. Am. Chem. Soc.* **96**, 4708 (1978).

⁵ H. C. Brown, B. C. Subba Rao, *J. Am. Chem. Soc.* **78**, 2586 (1956).

⁶ B. C. Subba Rao, *Curr. Sci.* **30**, 218 (1961).

⁷ B. C. Subba Rao, C. P. Thaker, *J. Sci. Ind. Research* **20B**, 318 (1961).

⁸ H. Feuer, B. F. Vincent, R. S. Bartlett, *J. Org. Chem.* **30**, 2877 (1965).

⁹ K. Kotera et al., *Tetrahedron* **24**, 3681 (1968).

¹⁰ All non-commercial sulfoxides used in this study were prepared by oxidation of thioethers with sodium periodate; see: C. R. Johnson, J. E. Keiser, *Org. Synth. Coll. Vol. V*, 791 (1973).

¹¹ P. Ruggli, K. Knecht, *Helv. Chim. Acta* **27**, 1108 (1944).

¹² F. Kraft, *Ber. Dtsch. Chem. Ges.* **19**, 2218 (1886).

¹³ W. H. Bentley, E. Haworth, W. H. Perkin, *J. Chem. Soc.* **69**, 161 (1896).

¹⁴ W. H. Perkin, *J. Chem. Soc.* **69**, 1198 (1896).

¹⁵ A. R. Sexton, E. C. Britton, *J. Am. Chem. Soc.* **70**, 3606 (1948).

¹⁶ G. S. Hiers, R. Adams, *J. Am. Chem. Soc.* **48**, 2385 (1926).

¹⁷ W. H. Perkin, *J. Chem. Soc.* **69**, 1209 (1896).

¹⁸ A. R. Hofmann, *Ber. Dtsch. Chem. Ges.* **15**, 762 (1882).

¹⁹ R. E. Lutz et al., *J. Org. Chem.* **12**, 760 (1947).

²⁰ H. J. Schneider, H. Adkins, S. M. McElvain, *J. Am. Chem. Soc.* **74**, 4287 (1952).

²¹ L. P. A. Fery, L. van Hove, *Bull. Soc. Chim. Belges* **69**, 63 (1960).

²² V. M. Mićovic, M. L. Mihailović, *J. Org. Chem.* **18**, 1190 (1953).

²³ N. B. Mehta, J. Z. Sterlitz, *J. Org. Chem.* **27**, 4412 (1962).

²⁴ S. L. Shapiro, E. S. Isaacs, V. Bandurco, L. Freedman, *J. Med. Pharm. Chem.* **5**, 793 (1962).

²⁵ L. Rügheimer, P. Schön, *Ber. Dtsch. Chem. Ges.* **41**, 18 (1908).

²⁶ H. Feuer, B. F. Vincent, P. S. Bartlett, *J. Org. Chem.* **30**, 2877 (1965).

²⁷ E. F. M. Stephenson, *J. Chem. Soc.* **1954**, 2354.

²⁸ A. W. Ingersoll, *Org. Synth. Coll. Vol. II*, 503 (1943).

²⁹ T. Takahashi, H. Fujimura, K. Okamura, *Yakugaku Zasshi* **82**, 1597 (1962); *C. A.* **59**, 611 (1963).

³⁰ J. Drabowicz, M. Mikołajczyk, *Synthesis* **1978**, 138.

³¹ J. Drabowicz, M. Mikołajczyk, *Synthesis* **1976**, 527.

³² W. Marckwald, W. Klemm, H. Trabert, *Ber. Dtsch. Chem. Ges.* **33**, 1556 (1900).

³³ H. Normant, T. Cuvigny, *Bull. Soc. Chim. Fr.* **1965**, 1881.

³⁴ M. A. Giantureo et al., *Tetrahedron* **20**, 2951 (1964).