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METAL-COMPLEX CATALYSIS DURING THE REDUCTION OF FUNCTIONAL GROUPS BY SODIUM BOROHYDRIDE IN THE SYNTHESIS OF PYRROLIDINE DERIVATIVES

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A selective method was developed for the reduction of functional groups with sodium borohydride using complexes of $CoCl_2$ and $CuCl_2$ with triethylbenzylammonium chloride and cobalt and copper meso-tetra[4-(2-hydroxyethyl)pyridyl]porphyrinates as catalysts.

Keywords: sodium borohydride, copper and cobalt complexes, metal-complex catalysis, pyrrolidines, porphyrins, reduction.

The development of selective and universal methods for the reduction of functional groups is an important function of organic chemistry.

There are many ways of using the mild and readily available reducing agent sodium borohydride in various catalytic systems with the aim of extending its reducing capabilities, the selectivity of its action, and its other properties. Reducing systems containing sodium borohydride and the salts of metals, such as $CuCl_2$ [1], $CoCl_2$ [2], $NiCl_2$ [3], $ZrCl_3$ [4], and others, are well known and have been well studied. It was demonstrated that the selectivity of reduction depends on the nature of the metal. The mechanism of reduction involving the formation of borides of the respective metals has also been studied [4]. However, the method has a series of important disadvantages, mainly associated with the quantities of the reagents employed. The ratios of the compound being reduced, the metal salt, and sodium borohydride amounted to 1:2:10.

The use of metal complexes as catalysts with sodium borohydride significantly simplifies the process, making it suitable for extensive application. Complexes of $CuCl_2$ [5], $CoCl_2$, and $NiCl_2$ [6] with triphenylphosphine and metal complexes of porphyrins such as iron *meso*-tetraphenylporphyrinate [ClFe(III)TPP] [7] and cobalt *meso*-tetra(*p*-sulfophenyl)porphyrinate [Co(III)TPPS] have been used successfully [8].

As catalysts for reduction in a system containing sodium borohydride we used a series of familiar metal complexes, like the complexes of $CoCl_2$ and $CuCl_2$ with triethylbenzylammonium chloride (**1**) and (**2**) [9] and cobalt and copper *meso*-tetra[4-(2-hydroxyethyl)pyridyl]porphyrinates (CoTOEtPyP) (**3**) and (CuTOEtPyP) (**4**) [10].

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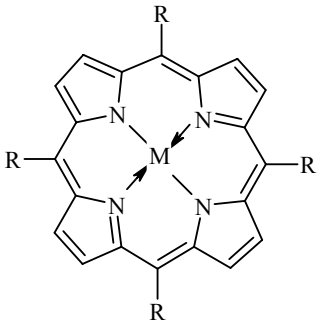


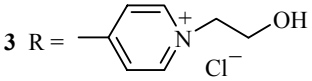
3, **4**

$[CoCl_3]^-[Et_3NBn]^+$

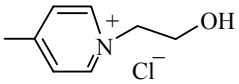
1

$[CuCl_3]^-[Et_3NBn]^+$

2



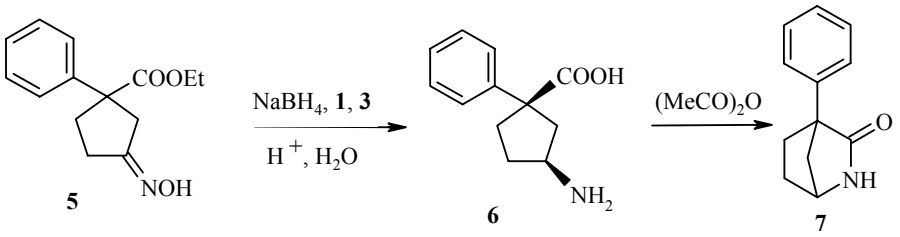
3 R = M = Co



4 R = M = Cu

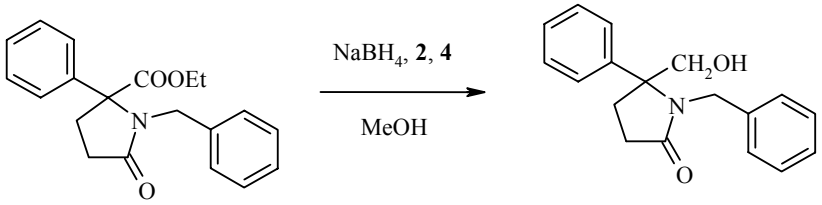
These catalysts were used in the synthesis of new pyrrolidine derivatives.

The reduction of ethyl 3-hydroxyimino-1-phenyl-1-cyclopentanecarboxylate (**5**) [11] with sodium borohydride in the presence of cobalt complexes **1** and **3** gave *cis*-3-amino-1-phenyl-1-cyclopentanecarboxylic acid (**6**) [12], the cyclization of which with acetic anhydride led to the formation of 3-phenyl-1-azabicyclo[2.2.1]heptan-2-one (**7**).



5 **6** **7**

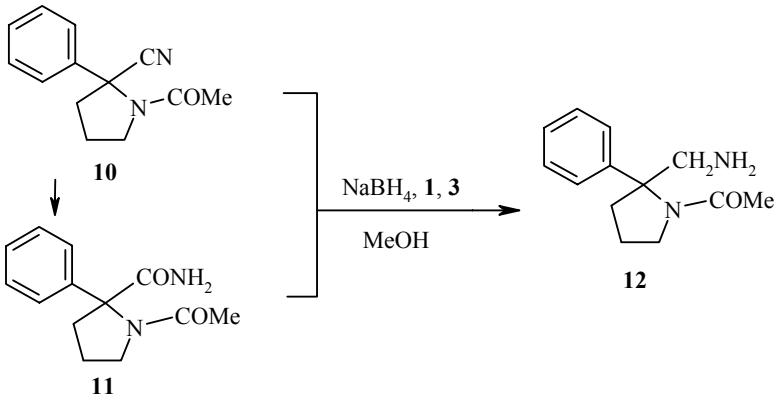
The copper complexes **2** and **4** catalyze the reduction of the ester group without affecting the tertiary amide group, as illustrated by the reduction of ethyl 1-benzyl-5-oxo-2-phenyl-2-pyrrolidinecarboxylate (**8**) [13].



8 **9**

The corresponding hydroxymethyl derivative **9** is formed with a high yield.

Selective reduction of the nitrile and primary amide groups in the presence of a tertiary amide group, catalyzed by cobalt complexes **1** and **3**, was demonstrated in the case of the synthesis of 1-acetyl-2-(2-aminomethyl)-2-phenylpyrrolidine (**12**) from the nitrile of 1-acetyl-2-phenyl-2-pyrrolidinecarboxylic acid (**10**) [13] or the amide of the same acid **11**.



Reduction of the nitrile **10** takes place much more readily and gives a higher yield than reduction of the amide **11**.

The yields of the reduced compounds obtained with the porphyrin catalysts **3** and **4** are somewhat higher than in the case of the metal complexes of triethylbenzylammonium **1** and **2**.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Mercury-300 instrument (300 MHz) at 303 K. The mass spectra were obtained on an MX-1321A instrument at 70 eV. Thin-layer chromatography was conducted on Silufol UV-254 plates. The following systems were used to determine the R_f values: a) 1:1 acetone–hexane; b) 4:1 propanol–water.

***cis*-3-Amino-1-phenyl-1-cyclopentanecarboxylic Acid (6).** To a mixture of ethyl 3-hydroxyimino-1-phenyl-1-cyclopentanecarboxylate (**5**) (10 g, 0.04 mol) [12] and CoTOEtPyP (**3**) (0.2 g, 0.0002 mol) as catalyst [10] in methanol (300 ml) at 25-30°C over 2 h we added in small portions sodium borohydride (6.1 g, 0.16 mol). When all the sodium borohydride had been added the stirring was continued for a further 2 h, the methanol was distilled, water (200 ml) was added to the residue, and the product was extracted with ether. The ether was distilled, conc. hydrochloric acid (300 ml) was added to the residue, and the mixture was refluxed for 3 h. The solution was washed with ether and evaporated to dryness at reduced pressure, and 50 ml of water was added to the residue. The amino acid was precipitated by the addition of a saturated aqueous solution of sodium acetate. The yield of the amino acid **6** was 6.0 g (71%); mp 265-267°C (decomp.); R_f 0.40 (b). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.60-8.20 (3H, m, NH_2, COOH); 7.45-7.20 (5H, m, C_6H_5); 3.55-3.35 (1H, m, CH); 2.70-1.65 (6H, m, $3CH_2$). Found %: C 70.01; H 7.08; N 6.89. $C_{12}H_{15}NO_2$. Calculated %: C 70.24; H 7.31; N 6.83. M^+ 205 (obtained by mass spectrometry). The yield of compound **6** with catalyst **1** amounted to 65%.

3-Phenyl-1-azabicyclo[2.2.1]heptan-2-one (7). To a suspension of compound **6** (4.1 g, 0.02 mol) in water (20 ml) at 25-30°C we gradually added acetic anhydride (20 ml), and the amino acid completely dissolved. The reaction mixture was kept in the refrigerator for 24 h. The crystals that separated were filtered off, washed successively with dilute solutions of sodium bicarbonate and hydrochloric acid, and dried over calcium chloride in a desiccator. The yield of compound **7** was 3 g (80%); mp 191-192°C (ether); R_f 0.55 (a). ^{1}H NMR spectrum (deuterochloroform), δ, ppm: 7.60-7.45 (5H, m, C_6H_5); 7.40-7.25 (1H, m, NH); 4.2-4.0 (2H, m, CH_2); 2.40-1.60 (6H, m, $3CH_2$). Found %: C 77.23; H 7.09; N 7.65. $C_{12}H_{13}NO$. Calculated %: C 77.00; H 6.95; N 7.49. M^+ 187 (found by mass spectrometry).

1-Benzyl-5-hydroxymethyl-5-phenylpyrrolid-2-one (9). To a mixture of ethyl 1-benzyl-5-oxo-2-phenyl-2-pyrrolidinecarboxylate (**8**) (3.2 g, 0.01 mol) [13] and CuTOEtPyP (**4**) (0.2 g, 0.0002 mol) as catalyst [10] in methanol (100 ml) at 25-30°C we added in small portions over 2 h sodium borohydride (1.5 g, 0.04 mol).

When all the sodium borohydride had been added the mixture was stirred for a further 2 h, the methanol was distilled, water (50 ml) was added to the residue, and the product was extracted with ether. The yield of compound **9** was 2.0 g (74%); mp 86-87°C (ethanol); R_f 0.46 (a). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 7.45-7.10 (10H, m, $2C_6H_5$); 5.20 (1H, d, *J* = 17.0, NCH_2); 3.90-3.75 (2H, m, OCH_2); 3.62 (1H, d, *J* = 17.0, NCH_2); 2.70-2.40 (3H, m, CH_2, OH); 1.98-0.97 (2H, m, CH_2). Found %: C 76.73; H 7.00; 4.75. $C_{18}H_{19}NO_2$. Calculated %: C 76.87; H 6.76; N 4.98. M^+ 281 (obtained by mass spectrometry).

Amide of 1-Acetyl-2-phenyl-2-pyrrolidinecarboxylic Acid (11). In conc. sulfuric acid (30 ml) at 10-15°C we dissolved 1-acetyl-2-phenyl-2-pyrrolidinedicarbonitrile (**10**) (10.7 g, 0.05 mol) [13]. The mixture was left at room temperature for 3 h and was then poured slowly into a beaker with water and ice. The crystals that separated were filtered off, washed with a dilute solution of sodium bicarbonate and with water, and recrystallized from ethanol. The yield was 9.3 g (80%); mp 140-141°C (ethanol); R_f 0.30 (a). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.40-7.10 (5H, m, C_6H_5); 7.43 and 6.94 (2H, br. s, NH_2); 3.90-3.60 (2H, m, NCH_2); 2.88-1.60 (4H, m, $2CH_2$); 2.15 (3H, s, CH_3). Found %: C 77.23; H 7.09; N 7.65. $C_{13}H_{16}N_2O_2$. Calculated %: C 67.24; H 6.85; N 12.07. M^+ 232 (obtained by mass spectrometry).

1-Acetyl-2-amino-2-phenylpyrrolidine (12). To a mixture of the nitrile **10** (21.4 g, 0.1 mol) [13] and the catalyst **1** (2.1 g, 0.005 mol), prepared by the known method [9] or *in situ* from equimolar amounts of cobalt and triethylbenzylammonium chlorides, in methanol (500 ml) at 25-30°C we added in small portions over 2 h sodium borohydride (15.2 g, 0.4 mol). When all the sodium borohydride had been added the mixture was stirred for a further 2 h, the methanol was distilled, water (300 ml) was added to the residue, and the product was extracted with ether. The yield of compound **12** in the form of a viscous liquid was 14.8 g (68%), oxalate; mp 134-135°C (ethanol); R_f 0.57 (b). ^{1}H NMR spectrum of compound **12** (DMSO-d_6), δ, ppm (*J*, Hz): 8.17 (1H, t, *J* = 6.0, NH); 7.50-7.25 (5H, m, C_6H_5); 6.7 (3H, br. s, NH_2, OH); 3.90-3.20 (4H, m, $2NCH_2$); 2.50-1.90 (4H, m, $2CH_2$); 1.78 (3H, s, CH_3). Found %: C 71.33; H 8.49; N 12.65. $C_{13}H_{18}N_2O$. Calculated %: C 71.56; H 8.26; N 12.84. M^+ 218 (obtained by mass spectrometry).

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