

Sodium Cyanoborohydride: Scope and Limitations

James S. Drage, Richard A. Earl* and K. Peter C. Vollhardt*

Department of Chemistry, University of California, Berkeley, and the Materials and Molecular Research Division, Lawrence Berkeley Laboratory, Berkeley, California 94720

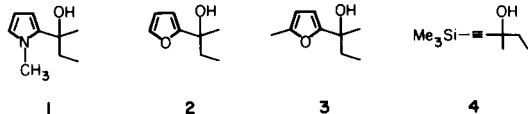
Received February 26, 1982

Acidic sodium cyanoborohydride reduces allylic and other substituted carbinolamides to the corresponding deoxygenated compounds, whereas other similar alcohols are unreactive or undergo alternative transformations.

J. Heterocyclic Chem., **19**, 701 (1982).

A recent report (1) on the reduction of a carbinolamide with sodium cyanoborohydride (2) to the corresponding lactam prompts this disclosure of a general investigation of the deoxygenation of allylic carbinolamides and related compounds. We required the former transformation in connection with a project concerned with the application of the retro-ene-imino-Diels-Alder reaction (3) to the total synthesis of indolizidine alkaloids, and once found successful, attempted to extend it to a variety of related compounds establishing some of its scope and limitations. Table 1 summarizes our results. All new compounds gave satisfactory analytical and/or spectral data (6). It can be seen that for the compounds shown satisfactory (in no case was optimization attempted) conversions may be achieved, making this method a valuable and evidently fairly general addition to the heterocyclic synthetic repertoire. Interestingly, whereas the allylic double bonds in **5** and **10** appear relatively inert, **12** consistently overreduced to the ethyllactam derivative.

On the other hand, extension to other related systems proved unsuccessful. Thus, attempted reduction of 1-methyl or 1-vinylbenzyl alcohol, 1,1-methylvinylbenzyl alcohol, and 1,1-ethylmethylbenzyl alcohol gave recovered starting material. In contrast, the heterocycles **1-3** decomposed under the reaction conditions. The propargyl alcohol **4** was unreactive, its dicobalt hexacarbonyl complex (5) furnished $[\text{HBF}_4 \cdot (\text{CH}_3)_2\text{O}, \text{CH}_2\text{Cl}_2\text{-CH}_3\text{OH}, \text{NaCNBH}_3, 0^\circ\text{C}]$ mainly the products of dehydration.



General Procedure.

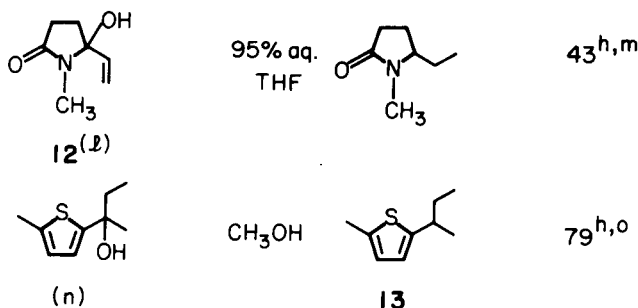
To the substrate dissolved in solvent containing a trace of methylorange indicator and stirred at RT was added sodium cyanoborohydride (1 equivalent). Aqueous hydrochloric acid (6*N*) was dripped in until the indicator changed, and acid addition was continued to maintain its color for about 0.5 hour. Six *N* sodium hydroxide neutralized the acid, the solvent was removed, water added to the residue, and this mixture extracted 3-4 times with ether or

dichloromethane. The organic layer was dried, the solvent removed and the residue in acetone passed through a short column of silica or alumina. The product was then distilled or recrystallized.

Table 1

Reduction of Allylic Carbinolamides and Related Alcohols at pH=3 (Methylorange Indicator)

Starting Material	Solvent	Products	Yield (%) ^a
	CH ₃ OH		53 ^c
		+	
			5 ^d
	CH ₃ OH		70 ^f
	CH ₃ OH		78 ^h
	65% aq. diglyme		63 ^h
	(j) 95% aq. THF		46 ^{h,k}



*All yields refer to isolated analytically pure materials. ^bPrepared from *N*-methyl succinimide and 2-(1,3-butadienyl) magnesium chloride (4), THF, RT, 58%, mp 74.5-76.5°. ^cColorless oil purified by Kugelrohr distillation 80-85°/0.2 torr. ^dIsolated by pgcl. ^ePrepared from *N*-methylsuccinimide and 2-lithio-1,3-dithiane, THF-TMEDA, -78°, 58%, mp 118-121°. ^fmp 80-83°. ^gPrepared from *N*-methylsuccinimide and the dilithium salt of 2(2-hydroxyethyl)-1,3-dithiane, THF, TMEDA, 0°, 13%, mp 128-131°. This compound is in equilibrium with its ketoamide tautomer in solution. ^hColorless oil. ⁱPrepared from *N*-methylphthalimide and 2-(1,3-butadienyl)magnesium chloride, THF, RT, 54%, mp 105-110°. ^jPrepared from *N*-methylsuccinimide and ethylmagnesium bromide, THF, RT, *in situ*. ^kOverall yield from *N*-methylsuccinimide. ^lPrepared from *N*-methylsuccinimide and vinylmagnesium bromide, THF, RT, *in situ*. ^mOverall yield from *N*-methylsuccinimide. Reduction with 0.3 equivalent of NaCNBH₃ gave a mixture of products. ⁿPrepared in two steps from 2-methylthiophene: 1. CH₃COCl, SnCl₄, 64%; 2. CH₃CH₂MgBr, ether, 78%. ^obp 90° (0.1 torr).

Acknowledgements.

This work was supported by NSF-CHE79-03954 and in part by the Director, Office of Energy Research, Office of Basic Energy Sciences, Chemical Sciences Division of the U.S. Department of Energy, under Contract DE-AC03-76SF00098 K.P.C.V. is a Camille and Henry Dreyfus Teacher-Scholar 1978-1983.

REFERENCES AND NOTES

- (1) D. J. Hart and Y.-M. Tsai, *Tetrahedron Letters*, 1567 (1981). This reaction has actually been seen precedent: R. T. La Londe, N. Muhammad, C. F. Wong, and E. R. Sturiale, *J. Org. Chem.*, **45**, 3664 (1980); S. W. Pelletier, N. V. Mody, A. P. Venkov, and H. K. Desai, *Tetrahedron Letters*, 4939 (1979); A. Basha, J. Orlando, and S. M. Weinreb, *Synth. Commun.*, **7**, 549 (1977).
- (2) R. O. Hutchins and N. R. Natale, *Org. Prep. Proc. Int.*, **11**, 201 (1979).
- (3) R. A. Earl and K. P. C. Vollhardt, *Heterocycles*, in press.
- (4) S. Nunomoto and Y. Yamashita, *J. Org. Chem.*, **44**, 4788 (1979);

K. Kondo, S. Dobashi, and M. Matsumoto, *Chem. Letters*, 1077 (1977).

(5) K. M. Nicholas, M. O. Nestle and D. Seyferth, in H. Alper, ed., "Transition Metal Organometallics in Organic Synthesis", Vol 2, Academic Press, New York, p 1.

(6) Selected spectral data: **5**: ir (potassium bromide): 3058, 1667, 1458, 1404, 1263 cm⁻¹; ¹H-nmr (deuteriochloroform): δ 2.19 (m, 4), 2.58 (s, 3), 4.20 (s, 1), 5.00 (dd, 1, J = 2, 17), 5.27 (s, 2), 5.27 (dd, 1, J = 2, 17), 6.03 (dd, 1, J = 11, 17); ¹³C-nmr (deuteriochloroform): δ 24.80, 29.30, 33.45, 92.18, 114.98, 116.58, 134.00, 146.71, 175.47; ms: m/e 167 (M⁺, 3.53), 149 (2.01), 114 (base, 18.53), 86 (4.79), 53 (4.37).

Anal. Calcd. for C₉H₁₃NO₂: C, 64.64; H, 7.85; N, 8.38. Found: C, 64.67; H, 7.91; N, 8.31.

6: ir (neat): 2950, 1690, 1421, 1270, 990, 910 cm⁻¹; ¹H-nmr (perdeuteriobenzene): δ 1.36 (m, 1), 1.61 (m, 1), 2.05 (m, 2), 2.54 (s, 3), 3.62 (dd, 1, J = 8.6, 4.0), 4.64 (s, 1), 4.83 (s, 1), 4.86 (d, 1, J = 11), 4.95 (d, 1, J = 18), 6.05 (dd, 1, J = 11, 18); ¹³C-nmr (deuteriochloroform): δ 24.89, 27.98, 29.21, 61.38, 114.49, 114.73, 135.44, 144.39, 175.20; ms: m/e 151 (M⁺, 2.30), 98 (base, 10.59).

Anal. Calcd. for C₉H₁₃NO: C, 71.47; H, 8.68; N, 9.26. Found: C, 71.09; H, 8.72; N, 9.20.

7: ir (potassium bromide): 3360, 2935, 1670; ¹H-nmr (deuteriochloroform): δ 1.74 (m, 1H), 2.04 (m, 2H), 2.38 (m, 2H), 2.61 (m, 1H), 2.74 (s, 3H), 2.83 (m, 4H), 4.50 (s, 1H), 5.25 (s, 1H); ¹³C-nmr (deuteriochloroform): δ 24.68, 25.56, 29.34, 30.01, 30.25, 55.44, 92.87, 175.29; ms: m/e 233 (M⁺, 0.30), 215 (7.32), 141 (base, 8.54), 119 (6.08), 114 (6.76).

Anal. Calcd. for C₈H₁₅NO₂S₂: C, 46.32; H, 6.49; N, 6.00. Found: C, 46.54; H, 6.50; N, 5.93.

8: ir (potassium bromide): 2935, 2920, 1670, 1420, 1400, 1295, 1280, 1255; ¹H-nmr (deuteriochloroform): δ 2.07 (m, 6), 2.83 (m, 4), 2.83 (s, 3), 3.70 (ddd, 1, J = 3, 6.5, 6.5), 4.42 (d, 1, J = 3); ¹³C-nmr (deuteriochloroform): δ 21.28, 26.14, 28.42, 30.12, 30.28, 30.65, 52.04, 63.04, 175.00; ms: m/e 217 (M⁺, 2.59), 119 (base, 11.82), 98 (11.62).

Anal. Calcd. for C₈H₁₅NOS₂: C, 49.73; H, 6.97; N, 6.45. Found: C, 49.83; H, 6.98; N, 6.35.

9: ir (neat): 3320, 2940, 2910, 1660, 1560, 1445; ¹H-nmr (deuteriochloroform): δ 2.02 (m, 4), 2.40 (m, 3), 2.58 (m, 1), 2.80 (d, 3, J = 4.8), 2.92 (m, 4), 3.95 (m, 3), 6.23 (br s, 1); ¹³C-nmr (deuteriochloroform): δ 25.61, 26.31, 27.42, 27.77, 28.59, 33.46, 42.17, 57.13, 65.73, 86.73, 173.30; ms: m/e 261 (M⁺, 2.47), 146 (base, 7.96), 58 (4.87).

Anal. Calcd. for C₁₁H₁₉NO₂S₂: C, 50.53; H, 7.34; N, 5.36. Found: C, 50.16; H, 7.50; N, 5.26.

11: ir (neat): 3010, 2930, 1690, 1470, 1435, 1390, 700; ¹H-nmr (deuteriochloroform): 3.01 (s, 3), 5.03 (s, 1), 5.04 (d, 1, J = 11), 5.22 (s, 1), 5.26 (d, 1, J = 17), 5.97 (dd, 1, J = 11, 17), 7.44 (m, 3), 7.82 (m, 1); ¹³C-nmr (deuteriochloroform): δ 27.21, 65.62, 116.34, 118.04, 122.43, 123.42, 128.40, 131.61, 132.19, 134.07, 142.08, 144.53, 168.64; ms: m/e 199 (M⁺, 7.22), 146 (base, 27.47), 91 (4.99). Exact mass: Calcd. for C₁₃H₁₃NO: 199.0997. Found: 199.0990.

13: ir (neat): 3066, 2966, 2876, 1454, 1379, 796; ¹H-nmr (deuteriochloroform): δ 0.94 (t, 3, J = 7.5), 1.33 (d, 3, J = 7); 1.65 (m, 2), 2.49 (s, 3), 2.85 (sex, 1, J = 7), 6.60 (s, 2); ms: m/e 154 (M⁺, 5.38), 139 (1.81), 125 (base, 24.45), 97 (2.26).

Anal. Calcd. for C₈H₁₄S: C, 70.07; H, 9.15; S, 20.78. Found: C, 69.94; H, 9.06; S, 20.96.