Reductions of Heterocyclic Systems; I. The Selective Reduction of 4-Substituted Pyridinium Salts with Cyanoborohydride

Robert O. HUTCHINS*, Nicholas R. NATALE

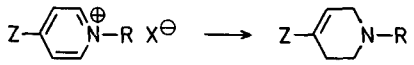
Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104, U.S.A.

Our interest in the synthetic potential of cyanoborohydride for selective reductions[1-4] coupled with the propensity of this reagent to discriminately attack highly electrophilic imminium ions[5,6] prompted a systematic exploration of the utility of cyanoborohydride in the nitrogen heterocyclic area. This communication presents a preliminary report of the typoselective (chemoselective) conversion of certain pyridinium salts to tetrahydro derivatives without damage to most common functional appendages.

For initial investigation, various 4-substituted pyridinium salts bearing a collection of functional groups were chosen in order to limit and direct the hydride attack to the 2-posit-

0039–7881/79/0432–0281 $ 03.00

Table. 1,2,5,6-Tetrahydropyridines **2**

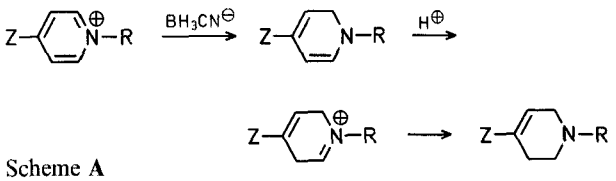


1 **2**

Substrate/Product No.	R	Z	X	Reaction conditions solvent[a]/temperature/time	Yield [%][b] of **2**	m.p. of **2** (m.p. of picrate)	Molecular formula[c]
a	C_6H_5—CH_2	NC—	Cl	H_2O/100°/2 h	82	—	$C_{13}H_{14}N_2$
				1:1 H_2O/C_2H_5OH/25°/2 h	70	(196–198°)	(198.3)
b	4-O_2N—C_6H_4—CH_2	NC—	Br	H_2O/100°/2 h	75	95–97°	$C_{13}H_{13}N_3O_2$
				1:1 H_2O/C_2H_5OH/25°/16 h	91	(215–220° dec.)	(243.3)
c	4-Br—C_6H_4—CO—CH_2	NC—	Br	1:1 H_2O/C_2H_5OH/25°/24 h	75	148–149° (169–171°)	$C_{14}H_{13}BrN_2O$ (305.2)
d	C_6H_5—CH_2	C_2H_5OOC—	Br	H_2O/100°/2 h	61	— (48–50°)	$C_{15}H_{19}NO_2$ (245.3)
e	4-O_2N—C_6H_4—CH_2	C_2H_5OOC—	Br	H_2O/100°/1 h	83	— (141–142°)	$C_{15}H_{18}N_2O_4$ (290.3)
f	2,6-di-Cl—C_6H_3—CH_2	C_2H_5OOC—	Cl	H_2O/100°/2 h	86	— (146–147°)	$C_{15}H_{17}Cl_2O_2$ (300.2)
g	C_6H_5—CH_2	H_2N—CO—	Cl	H_2O/100°/2 h	66	109–110° —	$C_{13}H_{16}N_2O$ (216.3)
h	4-O_2N—C_6H_4—CH_2	H_2N—CO—	Br	H_2O/100°/1 h	94	180–181°	$C_{13}H_{15}N_3O_3$ (261.3)
i	4-Br—C_6H_4—CO—CH_2	H_2N—CO—	Br	H_2O/100°/3 h	50	189–191° (177–179°)	$C_{14}H_{15}BrN_2O_2$ (323.2)
j	4-O_2N—C_6H_4—CH_2	C_6H_5—CH_2—	Br	H_2O/100°/14 h	62	70–71°	$C_{19}H_{20}N_2O_2$
				1:1 H_2O/C_2H_5OH/78°/15 h	80	—	(308.4)
k	4-O_2N—C_6H_4—CH_2	HO—N=CH—	Br	1:1 H_2O/C_2H_5OH/25°/48 h	72	159–161° —	$C_{13}H_{15}N_3O_3$ (261.3)
	4-O_2N—C_6H_4—CH_2	isoquinoline	Br	H_2O/100°/1 h	75[e]	— (171–173°)	$C_{16}H_{16}N_2O_2$ (268.3)
	4-O_2N—C_6H_4—CH_2	quinoline	Br	H_2O/100°/1 h	44[e]	91–93°	$C_{16}H_{16}N_2O_2$ (268.3)

[a] Solutions 0.1 molar in substrate and 0.22 molar in sodium cyanoborohydride.
[b] Isolated and purified by recrystallization or flash distillation.
[c] All products (or the picrates) gave satisfactory microanalysis.
[d] In $CDCl_3$.
[e] Product is the corresponding 1,2,3,4-tetrahydro(iso)quinoline derivative.

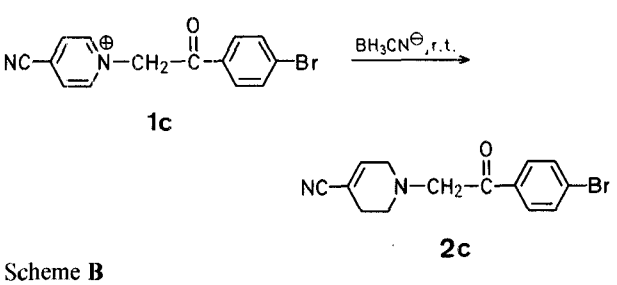
ion leading to intermediate 1,2-dihydropyridines which are subsequently isomerized in protic media and further reduced to 1,2,5,6-tetrahydro derivatives (Scheme **A**)[7,8].



Scheme **A**

Results for a variety of substituted examples, including quinoline and isoquinoline, are presented in the Table. Noteworthy is the extreme chemoselectivity, possibly reflecting the inertness of cyanoborohydride in neutral or basic media toward inactivated carbonyls and related groups. Thus, nitro, amido, cyano, ethoxycarbonyl, and even such normally sensitive groups as ketones and oximes are not affected and allow selective attack of the ring in their presence.

The conversion of 4-cyano-*N*-(*p*-bromophenacyl)-pyridinium bromide (**1c**) to the corresponding tetrahydropyridine **2c** convincingly suggests that such pyridinium reductions should be possible in complex, functional group laden molecules without requiring blocking techniques (Scheme **B**).



1c **2c**

Scheme **B**

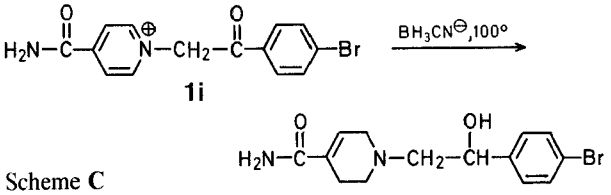
The general experimental procedure is convenient and straightforward. The pyridinium salt and sodium cyanoborohydride (2.2 mol eq) are stirred in solvent (water or 50% aqueous ethanol) for the appropriate time at the temperature listed in the Table. An inert atmosphere is not essential unless the product is air sensitive. The products are either

We thank Ventron Corporation for a generous gift of sodium cyanoborohydride.

Received: November 10, 1978

^{1}H-N.M.R. ($CDCl_3$/DMSO-d_6) δ [ppm] vinylic H	benzylic H	other H
6.44 (1 H)	3.54 (2 H)[d]	—
6.65 (1 H)	3.75 (2 H)	—
6.54 (1 H)	3.90 (2 H)	—
6.81 (1 H)	3.54 (2 H)[d]	—
6.70 (1 H)	3.70 (2 H)[d]	—
6.90 (1 H)	3.87 (2 H)	—
6.51 (1 H)	3.57 (2 H)	—
6.51 (1 H)	3.70 (2 H)	—
6.43 (1 H)		4.68 (1 H, CHOH)
5.30 (1 H)	3.52 (2 H)	—
5.93 (1 H)	3.73 (2 H)	—
—	3.65 (2 H)[d]	—
—	4.47 (2 H)[d]	—

filtered (solids) or extracted into ether. In the presence of other easily reduced groups (i.e. ketones), the reactions are preferably conducted at room temperature. Thus, at 100°, the carbonyl group in **1i** suffers attack concomitantly with the pyridinium ring (Scheme **C**). Other functionalities resist reduction even at 100° (Table).



Scheme **C**

4-Cyano-*N*-(*p*-bromophenacyl)-1,2,5,6-tetrahydropyridine (2c); Typical Procedure:

A solution of **1c** (3.82 g, 10 mmol) and sodium cyanoborohydride (1.38 g, 22 mmol) in 50% aqueous ethanol (100 ml) is stirred at ambient temperature under a nitrogen atmosphere for 24 h. The resulting precipitate is filtered, washed with water, and dried in vacuo. Recrystallization from ethanol affords **2c** as pale yellow needles; yield: 2.30 g (75%); m.p. 148–149°. Characterized as the picrate, m.p. 169–171°. Spectral and microanalysis data are provided in the Table.

[1] R. O. Hutchins et al., *J. Org. Chem.* **42**, 82 (1977).
[2] R. O. Hutchins et al., *J. Org. Chem.* **41**, 3328 (1976).
[3] R. O. Hutchins, D. Kandasamy, *J. Org. Chem.* **40**, 2530 (1975).
[4] A review of cyanoborohydride chemistry is provided by C. F. Lane, *Synthesis* **1975**, 135.
[5] R. F. Borch, M. D. Bernstein, H. D. Durst, *J. Am. Chem. Soc.* **93**, 2897 (1971).
[6] R. O. Hutchins, M. Kacher, L. Rua, *J. Org. Chem.* **40**, 923 (1975).
[7] The reduction of pyridines and related nitrogen heterocycles with hydride reagents, particularly sodium borohydride and lithium aluminum hydride, has received considerable attention; reviews include:
R. E. Lyle, *Heterocyclic Compounds, Pyridine, and Its Derivatives*, R. A. Abramovich, Ed., John Wiley & Sons, New York, Vol. 14, Part 1, p. 137, 1974.
U. Eisner, J. Kuthan, *Chem. Rev.* **72**, 1 (1972).
[8] Recent investigations include sodium borohydride in aqueous methanol, F. Liberatore et al., *J. Org. Chem.* **40**, 559 (1975).
E. E. Knaus, K. Redda, *J. Heterocycl. Chem.* **13**, 1237 (1976).
Sodium borohydride in carboxylic acids, G. W. Gribble, P. Heald, *Synthesis* **1975**, 650.
G. W. Gribble et al., *J. Am. Chem. Soc.* **96**, 7812 (1974).
P. Marchini et al., *J. Org. Chem.* **40**, 3453 (1975).
Borane in carboxylic acids, B. E. Maryanoff, D. F. McComsey, *J. Org. Chem.* **43**, 2733 (1978).
Y. Kikugawa, K. Saito, S. Yamada, *Synthesis* **1978**, 447.
Sodium cyanoborohydride in carboxylic acids, E. Booker, U. Eisner, *J. Chem. Soc. Perkin Trans. 1* **1975**, 929.

0039–7881/79/0432–0283 $ 03.00