Electrophilic Oxidative Additions upon 1,4-Dihydropyridines

Rodolfo Lavilla,* Oscar Coll, Rakesh Kumar, and Joan Bosch*

Laboratory of Organic Chemistry, Faculty of Pharmacy, University of Barcelona, 08028 Barcelona, Spain

Received October 22, 1997

1,4-Dihydropyridines are interesting compounds playing important roles in synthetic, therapeutic, and bioorganic chemistry.[1] The reactivity of this heterocyclic system has involved mainly selective reductions[2] and electrophilic additions[3] and has allowed the completion of remarkable total syntheses of alkaloids belonging to different structural and biogenetic types.[2−4] A general drawback that severely restricts the use of 1,4-dihydropyridines in organic synthesis is their easy oxidation to the corresponding pyridinium salts (NADH is oxidized to NAD in many metabolic reactions). We have recently reported a useful method for the nonbiomimetic oxidation of *N*-alkyl-1,4-dihydropyridines that overcomes this problem and allows the introduction of oxygen atoms at positions 2 and 3 of the dihydropyridine ring.[5,6] Continuing our studies on "alternative" oxidations of these compounds with regard to the synthesis of substituted piperidines, in this paper we report several oxidative electrophilic additions leading to 3-halo-2-substituted-1,2,3,4-tetrahydropyridines.

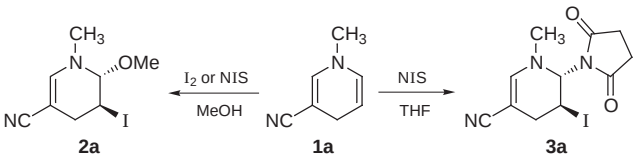
Practically no information is available for this kind of transformation from *N*-alkyl-1,4-dihydropyridines.[7,8] It is interesting to note that the oxidation of these compounds (supposedly to the pyridinium salts) with iodine has been proposed as a quantitative estimation method for 1,4-dihydropyridines.[1a,9]

Table 1. Electrophilic Addition Reactions from Dihydropyridines 1

entry	dihydropyridine	reagent/solvent	product	yield (%)
1	**1a**	I_2/MeOH	**2a**	90
2	**1a**	NIS/MeOH	**2a**	82
3	**1a**	FPTf[a]/MeOH	**2f**	85
4	**1a**	FBDS[b]/MeOH	**2f**	74
5	**1c**	I_2/MeOH	**2g**	79
6	**1a**	NIS/THF	**3a**	74
7	**1b**	NIS/THF	**3b**	77
8	**1a**	NBS/THF	**3c**	70
9	**1b**	NBS/THF	**3d**	76
10	**1b**	NCS/THF	**3e**	75

[a] FPTf refers to *N*-fluoropyridinium triflate. [b] FBDS refers to $(PhSO_2)_2NF$.

Scheme 1



However, adding a stochiometric amount of iodine to a methanol solution of dihydropyridine **1a** gave the iodinated tetrahydropyridine **2a** in a stereoselective manner and with 90% yield (Table 1, entry 1). The only stereoisomer detected arose from an anti addition, and the stereochemistry was ascertained by spectroscopical analysis (including $^1H-^1H$ COSY and $^1H-^{13}C$ correlation experiments). These experiments showed a coupling constant pattern (H_2-H_3) normally around 2−3 Hz, indicating a trans stereochemistry and a preferred conformation with the substituents at positions 2 and 3 being axial. Traces of the corresponding pyridinium salt were also detected. The same result was obtained when the reaction was performed with NIS (*N*-iodosuccinimide) as the halogenating agent (**2a**, 82%; entry 2). Interestingly, when the process was carried out in THF (Scheme 1), the incorporation of a succinimide moiety at position 2 was observed to give the 3-iodo-2-succinimidotetrahydropyridine **3a** (74%; Table 1, entry 6).[10] Again the reaction was highly stereoselective, and the trans isomer isolated showed an H_2-H_3 coupling constant of ≅ 6 Hz, thus indicating an average of two conformers in equilibrium.[11] These remarkable transformations presumably take place by electrophilic addition to the more reactive enaminic double bond,[12,13] thus bypassing (probably via kinetic control) the well-known oxidation process to pyridinium salts, with further nucleophilic trapping of

* Authors to whom correspondence should be addressed. Phone: (343)4024537. Fax: (343)4021896. E-mail: lavilla@farmacia.far.ub.es.

(1) For reviews on the chemistry of dihydropyridines, see: (a) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1. (b) Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223. (c) Sausins, A.; Duburs, G. *Khim. Geterotsikl. Soedin.* **1993**, 579. (d) Sausins, A.; Duburs, G. *Heterocycles* **1988**, *27*, 291. (e) Kutney, J. P. *Heterocycles* **1977**, *7*, 593. (f) Comins, D. L.; O'Connor, S. *Adv. Heterocycl. Chem.* **1988**, *44*, 199.

(2) (a) For a review, see: Bennasar, M.-L.; Lavilla, R.; Alvarez, M.; Bosch, J. *Heterocycles* **1988**, *27*, 789. (b) Lavilla, R.; Gotsens, T.; Gullón, F.; Bosch, J. *Tetrahedron* **1994**, *50*, 5233. (c) Bennasar, M.-L.; Vidal, B.; Lázaro, A.; Kumar, R.; Bosch, J. *Tetrahedron Lett.* **1996**, *37*, 3541.

(3) (a) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Am. Chem. Soc.* **1993**, *115*, 5340. (b) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Org. Chem.* **1995**, *60*, 4280. (c) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Org. Chem.* **1996**, *61*, 1916. (d) Bennasar, M.-L.; Vidal, B.; Bosch, J. *J. Org. Chem.* **1997**, *62*, 3597.

(4) For reviews, see: (a) Wenkert, E. *Pure Appl. Chem.* **1981**, *53*, 1271. (b) Bosch, J.; Bennasar, M.-L. *Synlett* **1995**, 587.

(5) Lavilla, R.; Gullón, F.; Barón, X.; Bosch, J. *Chem. Commun.* **1997**, 213.

(6) Some oxidative transformations have been achieved from the more stable *N*-acyl dihydropyridines: (a) Natsume, M.; Sekine, Y.; Ogawa, M.; Soyagimi, H.; Kitagawa, Y. *Tetrahedron Lett.* **1979**, 3473. (b) Tschamber, T.; Backenstrass, F.; Neuburger, M.; Zehnder, M.; Streith, J. *Tetrahedron* **1994**, *50*, 1135.

(7) Some reports, however, have appeared in the literature dealing with related transformations upon the more stable *N*-acyl dihydropyridines: (a) Natsume, M.; Wada, M. *Chem. Pharm. Bull.* **1976**, *24*, 2651. (b) Urbanski, J.; Wrobel, L. *Pol. J. Chem.* **1985**, *59*, 1099. (c) Urbanski, J.; Wrobel, L. *Pol. J. Chem.* **1985**, *59*, 1107.

(8) For early studies on electrophilic additions upon dihydropyridines, see: (a) Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, *215*, 1. (b) Benary, E. *Chem. Ber.* **1918**, *51*, 567. (c) Kaufmann, H. P., Liepe, J. *Chem. Ber.* **1923**, *56*, 2514. (d) Negievich, L. A.; Grishin, O. M.; Yasnikov, A. A. *Ukr. Khim. Zh.* **1968**, *34*, 684 (*Chem. Abstr.* **1969**, *70*, 11513). (e) Negievich, L. A.; Grishin, O. L.; Yasnikov, A. A. *Ukr. Khim. Zh.* **1968**, *34*, 802 (*Chem. Abstr.* **1969**, *70*, 28776).

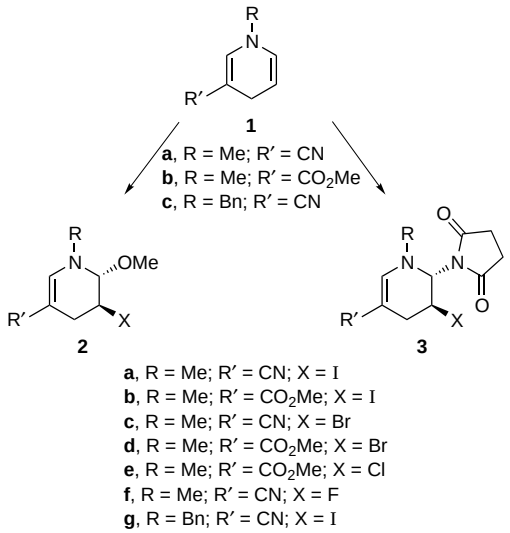
(9) It has been reported that reaction of NBS with *N*-substituted 1,4-dihydropyridines yields the corresponding pyridinium salts: Chupakhin, O. N.; Balykov, V. G.; Klyuev, N. A.; Materi, A. I. *Khim. Geterosikl. Soedin.* **1989**, 1083.

(10) For a recent NIS addition to enol ethers, see: Erbeck, S.; Prinzbach, H. *Tetrahedron Lett.* **1997**, *38*, 2653. It should be noted that *N*-haloimides have been added under thermal or photochemical conditions to enol ethers with opposite regioselectivity: Liebig, U.; Kirsch, A. *Chem. Ber.* **1993**, *126*, 1171.

(11) For a similar situation, see the stereochemical analysis of substituted dioxanes: Adam, W.; Blancafort, L. *J. Org. Chem.* **1996**, *61*, 8432.

S0022-3263(97)01947-6 CCC: $15.00
Published on Web 03/28/1998

Scheme 2

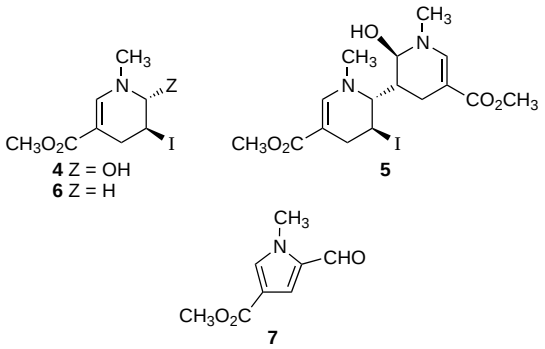


the resulting iminium species. When 1-benzyl-1,4-dihydronicotinamide was used as starting material, low yields of unstable addition compounds were obtained, and we were not able to improve the reaction conditions. However the reaction seems to be quite general, being also effective on dihydropyridines with different substituents at the nitrogen and/or at position 3 (Table 1, entries 5 and 7; Scheme 2).

Furthermore, it is feasible to introduce bromine and chlorine atoms at the 3-position of the dihydropyridine ring through this procedure, using NBS and NCS respectively (Table 1, entries 8, 9, and 10). Even electrophilic fluorinations of dihydropyridines were achieved using *N*-fluoropyridinium triflate[14] (85%) or *N*-fluorodibenzenesulfonimide[15] (74%), thus allowing the stereocontrolled formation of fluorinated tetrahydropyridines (Table 1, entries 3 and 4). Apart from the interest of the selective fluorine labeling of heterocycles in medicinal chemistry,[16] it is worth mentioning that this approach may lead to a wide range of halogenated analogues of bioactive piperidine-based compounds.[17]

In some cases, when poorly nucleophilic species were present in the reaction medium, the formation of byproducts in these processes was observed. For instance, when attempting a fluoride attack upon the initially formed iminium ion using different combinations of fluoride sources (KF, AgF, TBAF, BF_4^-, etc.) and halogenating species (NIS, iodine, stabilized iodonium ions), in no case

Scheme 3



were 2-fluoro-3-iodotetrahydropyridines detected. In the course of these experiments, the hydroxy derivative **4** and dimer **5** were formed instead (Scheme 3). The formation of **4** (19%), which was obtained through interaction of **1b** with bis(collidine)iodonium tetrafluoroborate,[18] may be rationalized by considering that, once the dihydropyridine was halogenated, the resulting iminium ion was trapped by water during the aqueous workup. On the other hand, the production of dimer **5** (20%) may be explained by a nucleophilic attack of unreacted dihydropyridine on the above-mentioned iminium intermediate, followed again by a water quenching of the second iminium ion thus produced.[19] A redox interference was observed in one experiment (attempted iodofluorination of **1b** with iodine and silver fluoride in acetonitrile), leading to the isolation of 3-iodotetrahydropyridine **6** (5%). Also pyrrole **7** (10%)[20] was obtained, its formation probably being the result of a ring-opening, ring-closure, oxidation sequence from intermediate **4**.

The new reactivity of dihydropyridines described in this paper opens interesting perspectives from a preparative standpoint, allowing stereocontrolled transformations, which complement the usual two-electron-transfer processes seen in nature and in the vast majority of oxidations of these compounds. We feel that this method will have useful applications in the synthesis of important natural and/or bioactive piperidines.[21]

Experimental Section

General. All solvents were purified and dried by standard methods. All reagents were of commercial quality from freshly opened containers. Organic extracts were dried with anhydrous sodium sulfate. TLC and column chromatography were carried out using SiO_2. Melting points were determined in a capillary tube and are uncorrected. Microanalyses and HRMS were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona. Unless otherwise quoted, NMR spectra (Table 2) were recorded in $CDCl_3$ solution with TMS as an internal reference at 200, 300, or 500 MHz (^{1}H) and 50.3 or 75 MHz (^{13}C). Only noteworthy IR absortions are listed (cm^{-1}). UV spectra were obtained in MeOH solution. The starting *N*-alkyl-1,4-dihydropyridines **1** were prepared by sodium dithionite reduction

(12) (a) For an excellent review on the oxidation of enamines, see: Pitacco, G.; Valentin, E. In *The Chemistry of Enamines*, Rappoport, Z., Ed. (*The Chemistry of Functional Groups*, Patai, S.; Rappoport, Z., Eds.); Wiley: Chichester, 1994; p 923. (b) For a general overview on the halogenation of enamines, see: Hickmott, P. W. In *The Chemistry of Enamines*; Rappoport, Z., Ed. (*The Chemistry of Functional Groups*, Patai, S.; Rappoport, Z., Eds.); Wiley: Chichester, 1994; p 727.

(13) However, some allylic halogenations have been reported on treatment of enamines with NCS. See, for instance: Tetzlaff, C.; Vilsmaier, E.; Schlag, W. R. *Tetrahedron* **1990**, *46*, 8117.

(14) (a) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990**, *112*, 8563. (b) Umemoto, T. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. E., Ed.; Wiley: Chichester, 1995; Vol. 4, p 2564.

(15) (a) Differding, E.; Ofner, H. *Synlett* **1991**, 187. (b) Differding, E. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. E., Ed.; Wiley: Chichester, 1995; Vol. 4, p 2563.

(16) For a recent example, see: Hodson, H. F.; Madge, D. J.; Slawin, A. N. Z.; Widdowson, D. A.; Williams, D. J. *Tetrahedron* **1994**, *50*, 1899.

(17) Dockner, M.; Sasaki, N. A.; Riche, C.; Potier, P. *Liebigs Ann./Recueil* **1997**, 1267.

(18) Evans, R. D.; Schauble, J. H. *Synthesis* **1987**, 551.

(19) For related processes, see: (a) Anderson, A. C.; Berkelhammer, G. *J. Am. Chem. Soc.* **1958**, *80*, 992. (b) Lyle, R. E.; Nelson, D. A. *J. Org. Chem.* **1963**, *28*, 169.

(20) González-Rosende, E.; Jones, R. A.; Sepúlveda-Arques, J.; Zaballos-García, E. *Synth. Commun.* **1988**, *18*, 1669.

(21) With respect to the synthetic manipulation of the α-alcoxyamino moiety as an iminium ion precursor, see, for instance: (a) Grierson, D. S.; Royer, J.; Guerrier, L.; Husson, H.-P. *J. Org. Chem.* **1986**, *51*, 4475. (b) Gnecco, D.; Marazano, C.; Das, B. C. *J. Chem. Soc. Chem. Commun.* **1991**, 625. (c) See also ref 5.

(22) Brewster, M. E.; Simay, A.; Czako, K.; Winwood, D.; Farag, H.; Bodor, N. *J. Org. Chem.* **1989**, *54*, 3721.

Table 2. ^{1}H and ^{13}C NMR Chemical Shift Data for Tetrahydropyridines 2 and 3

	H2 C2	H3 C3	H4 C4	C5	H6 C6	N−R	R′	succinimide	OMe
2a	4.40	4.35	2.85, 2.38		6.72	3.11			3.43
	90.8	18.1	27.4	74.5	144.2	42.8	121.4		56.0
2f	4.33	4.79	2.50, 2.38		6.76	3.15			3.44
	86.5	81.6	23.8	74.0	144.7	42.6	121.5		56.6
2g	4.37	4.37	2.91, 2.40		6.78	4.37			3.33
	89.1	17.8	27.8	74.8	143.6	57.8	121.6		56.0
3a	5.36	4.73	2.72		6.84	2.86		2.79	
	69.5	17.4	32.1	75.5	147.2	40.5	120.1	175.6; 27.9	
3b	5.36	4.85	2.84		7.35	2.85	3.68	2.77	
	70.1	20.0	31.0	96.3	145.3	40.3	167.4; 51.0	175.8; 27.9	
3c	5.32	4.66	2.74		6.81	2.85		2.80	
	68.2	40.8	30.6	74.6	147.2	40.1	120.7	175.7, 27.9	
3d	5.33	4.78	2.85		7.32	2.84	3.69	2.78	
	68.8	42.8	29.6	95.4	145.4	39.8	167.5; 51.0	175.8; 27.9	
3e	5.23	4.73	2.86		7.31	2.83	3.69	2.79	
	68.6	51.8	28.9	94.7	145.4	39.5	167.6; 51.0	175.9; 27.9	

of the corresponding pyridinium salts, following published procedures.[22]

General Method for Oxidative Addition Reactions. A solution of iodine (1 mmol) or *N*-halosuccinimide (1 mmol) in THF (40 mL) was added dropwise under an N_2 atmosphere to a stirred solution of dihydropyridine **1** (1 mmol) in THF (40 mL) or MeOH (40 mL) at 0 °C, and stirring was continued for 1 h at this temperature. Water (150 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic extracts were washed with aqueous $Na_2S_2O_3$ solution (100 mL, 0.5 M), water (100 mL), and a saturated aqueous Na_2CO_3 solution (100 mL), dried (Na_2SO_4), and then concentrated under reduced pressure. The residue was purified by crystallization from CH_2Cl_2−hexanes or by column chromatography (SiO_2, elution with CH_2Cl_2) to yield pure tetrahydropyridines **2** (from reactions performed in MeOH) or **3** (from reactions performed in THF).

***trans*-3-Iodo-2-methoxy-1-methyl-1,2,3,4-tetrahydropyridine-5-carbonitrile (2a)** was obtained as an oil (90% yield): IR (KBr) 2189, 1633; UV 263 (4.39); MS (EI) *m*/*z* (relative intensity) 278 (M^+, 34), 247 (8), 151 (43), 119 (100); HRMS (EI) mass calcd for $C_8H_{11}N_2OI$ 277.9916, found 277.9910.

***trans*-1-Benzyl-3-iodo-2-methoxy-1,2,3,4-tetrahydropyridine-5-carbonitrile (2g)** was obtained as an oil (79% yield): IR (KBr) 2192, 1632; UV 269 (4.30); MS (EI) *m*/*z* (relative intensity) 354 (M^+, 2), 227 (13), 196 (9), 91 (100); HRMS (EI) mass calcd for $C_{14}H_{15}N_2OI$ 354.0229, found 354.0216.

***trans*-3-Iodo-1-methyl-2-succinimido-1,2,3,4-tetrahydropyridine-5-carbonitrile (3a)** was obtained as a white solid (74% yield): mp 142−143 °C; IR (KBr) 2188, 1712, 1702, 1635; UV 262 (4.08); MS (CI) *m*/*z* (relative intensity) 346 ($M + H^+$). Anal. Calcd for $C_{11}H_{12}N_3O_2I$: C, 38.28; H, 3.50; N, 12.17. Found: C, 38.01; H, 3.54; N, 11.91.

Methyl *trans*-3-iodo-1-methyl-2-succinimido-1,2,3,4-tetrahydropyridine-5-carboxylate (3b) was obtained as a white solid (77% yield): mp 125−126 °C; IR (KBr) 1718, 1675, 1632; UV 279 (4.39); MS (EI) *m*/*z* (relative intensity) 378 (M^+, 4), 347 (14), 251 (22), 152 (100). Anal. Calcd for $C_{12}H_{15}N_2O_4I$: C, 38.11; H, 4.00; N, 7.41. Found: C, 38.00; H, 3.98; N, 7.18.

***trans*-3-Bromo-1-methyl-2-succinimido-1,2,3,4-tetrahydropyridine-5-carbonitrile (3c)** was obtained as a white solid (70% yield): mp 141−142 °C; IR (KBr) 2191, 1708, 1702, 1638; UV 266 (4.47); MS (EI) *m*/*z* (relative intensity) 299 and 297 (M^+, 16), 119 (100). Anal. Calcd for $C_{11}H_{12}N_3O_2Br$: C, 44.31; H, 5.06; N, 14.09. Found: C, 44.23; H, 4.07; N, 13.89.

Methyl *trans*-3-bromo-1-methyl-2-succinimido-1,2,3,4-tetrahydropyridine-5-carboxylate (3d) was obtained as a white solid (76% yield): mp 105−106 °C; IR (KBr) 1714, 1673, 1632; UV 283 (4.44); MS (EI) *m*/*z* (relative intensity) 332 and 330 (M^+, 10), 301 and 299 (36), 152 (100). Anal. Calcd for $C_{12}H_{15}N_2O_4Br$: C, 43.52; H, 4.56; N, 8.46. Found: C, 43.35; H, 4.50; N, 8.30.

Methyl *trans*-3-chloro-1-methyl-2-succinimido-1,2,3,4-tetrahydropyridine-5-carboxylate (3e) was obtained as a white solid (75% yield): mp 149.5−150.5 °C; IR (KBr) 1708, 1681, 1634; UV 281 (4.50); MS (EI)) *m*/*z* (relative intensity) 286 (M^+, 4), 255 (8), 249 (8), 152 (100). Anal. Calcd for $C_{12}H_{15}N_2O_4Cl$: C, 50.27; H, 5.27; N, 9.77. Found: C, 50.29; H, 5.33; N, 9.62.

***trans*-3-Fluoro-2-methoxy-1-methyl-1,2,3,4-tetrahydropyridine-5-carbonitrile (2f).** A solution of 1-fluoropyridinium triflate (227 mg, 0.91 mmol) in MeOH (5 mL) was added dropwise to a solution of dihydropyridine **1a** (99 mg, 0.82 mmol) in anhydrous CH_2Cl_2 (10 mL), and the resulting solution was stirred overnight at room temperature under a nitrogen atmosphere. Water (100 mL) was added, and the mixture was extracted with CH_2Cl_2. The organic extracts were dried, filtered, and evaporated to give 120 mg (85%) of practically pure tetrahydropyridine **2f**. Further purification may be achieved by column chromatography (SiO_2, CH_2Cl_2): IR (KBr) 2195, 1635; UV 263 (4.05); MS (EI)) *m*/*z* (relative intensity) 170 (M^+, 51), 139 (100), 119 (52); HRMS (EI) mass calcd for $C_8H_{11}N_2OF$ 170.0855, found 170.0852.

Acknowledgment. This work was supported by the DGICYT, Spain (project PB94-0214). Thanks are also due to the Comissionat per Universitats i Recerca (Generalitat de Catalunya) for Grant SGR95-00428. O.C. and R.K. thank the Ministerio de Educación y Cultura, Spain, for fellowships. Professor J. Sepúlveda-Arques (University of Valencia) is thanked for sending us a sample of pyrrole **7**.

Supporting Information Available: Characterization data for compounds **4**−**7** (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO971947V