Pergamon

Tetrahedron Letters 39 (1998) 5089–5092

TETRAHEDRON LETTERS

Iodocyclization of 1,4-Dihydropyridines

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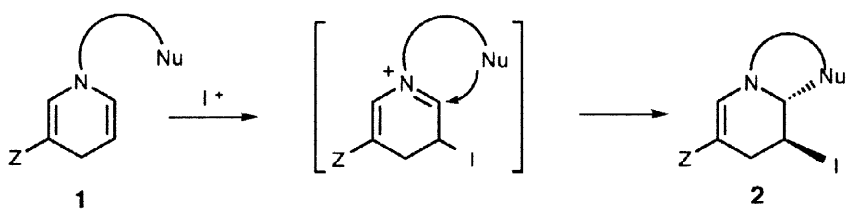
Received 27 February 1998; revised 27 April 1998; accepted 1 May 1998

Abstract

Iodine (or related species) addition to 1,4-dihydropyridines, with properly attached substituents at the nitrogen atom, leads to the corresponding 3-iodotetrahydropyridinium ions, which undergo an internal nucleophilic attack to furnish regio- and stereoselectively iodobi(poly)heterocyclic ring systems in good yields.

Keywords: Cyclization; Halogenation; Pyridines; Oxazolidines

The chemistry of dihydropyridines shows a broad variety of synthetic transformations[1 - 6], involving reductions, concerted reactions, Lewis or protic acid promoted additions, etc., which make these compounds valuable synthetic intermediates, especially in the fields of Natural Product Synthesis and Medicinal Chemistry [7 - 10]. However, the easy oxidation of 1,4-dihydropyridines to the corresponding pyridinium salts (NADH is converted to NAD^+ in many metabolic reductions) seriously restricts their use in organic synthesis. Recently, we have accomplished "non-biomimetic" oxidations of *N*-alkyl-1,4-dihydropyridines, including formal epoxidations [11], diaminations [12], and alcoxyhalogenations [13], in simple experimental procedures that effectively avoid the natural oxidation route. Here we report the extension of this methodology to the preparation of polycyclic β-iodotetrahydropyridines through an intramolecular nucleophilic attack upon the initially generated iminium ion (Scheme 1).



1 **2**

Scheme 1

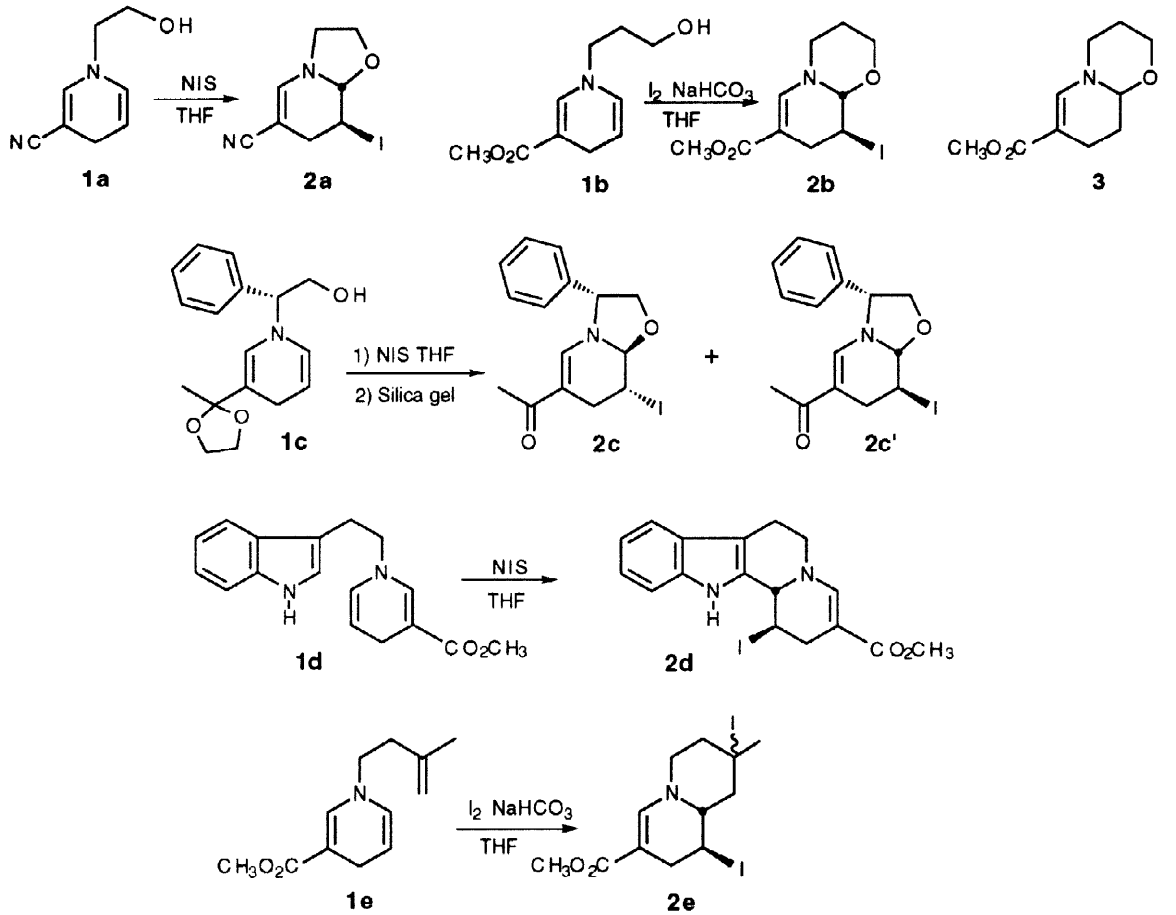
The starting 1,4-dihydropyridines **1** were prepared from the corresponding pyridinium salts by sodium dithionite reduction [14, 15]. Special care should be taken with the hydroxy substituted derivatives **1a-c** because of their propensity to undergo cyclization [16].

The first experiments were performed from 1-(2-hydroxyethyl)-1,4-dihydropyridine **1a**, which was treated with NIS in THF solution to stereoselectively afford the *trans* oxazolidine **2a**

0040-4039/98/$19.00
PII: S0040-4039(98)00912-5

(30 %, Scheme 2).[1,2]

The *anti* addition observed is well precedented in intramolecular (as well as intermolecular) additions to iminium ions [17], and was also confirmed by the ^1H-^1H coupling constant analysis and COSY and ROESY experiments. Similarly, treatment of dihydropyridine **1b** with iodine (1 equivalent) gave the iodinated oxazine **2b** (22%) and compound **3** (33%). When the reaction was performed in the presence of excess $NaHCO_3$ (to scavenge the acid produced in the cyclization step) the latter product was not detected, and the yield of **2b**[3] went up to 67%.



Scheme 2

Chiral dihydropyridines have emerged as powerful tools in alkaloid synthesis [18 - 21]; to further expand the scope of the above iodocyclizations, we envisaged a similar process starting from the chiral non-racemic dihydropyridine **1c**, which was prepared from the corresponding 1-(2,4-dinitrophenyl)pyridinium salt and (*R*)-(-)-2-phenylglycinol following a previously reported procedure [16]. This unstable compound was immediately allowed to react with NIS in THF

1. All new compounds gave satisfactory spectroscopic data (^1H and ^{13}C NMR, IR, UV, MS) as well as elemental analysis or HRMS.
2. Oxazolidine **2a**. ^1H NMR ($CDCl_3$, 300 MHz) 7.02 (d, J = 1.2 Hz, 1H), 4.90 (d, J = 8.9 Hz), 4.16 (m, 1H), 3.99 (m, 1H), 3.83 (m, 1H), 3.66 (m, 1H), 3.47 (m, 1H), 2.86 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 142.9, 119.9, 90.5, 65.1, 62.6, 49.1, 33.8, 19.4; IR (KBr) 2189, 1615; UV (MeOH) 270 (4.0); MS (EI) 276 (M^+, 59), 149 (100). HRMS Calcd for $C_8H_9N_2OI$ 275.9760, found 275.9760.
3. Oxazine **2b**. ^1H NMR ($CDCl_3$, 300 MHz) 7.23 (d, J = 1.5 Hz, 1H), 4.66 (d, J = 3.6 Hz, 1H), 4.29 (m, 1H), 4.16 (m, 1H), 3.84 (m, 1H), 3.70 (s, 3H), 3.49 (m, 2H), 2.98 (m, J = 17.5, 4.8, 1.5 Hz, 1H), 2.80 (dd, J = 17.5, 4.1 Hz, 1H), 1.97 (m, 1H), 1.49 (d, J = 13.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 168.0, 142.5, 98.1, 87.4, 67.9, 51.7, 51.0, 28.0, 26.5, 20.7; IR (KBr) 1689, 1628; UV (MeOH) 279 (4.22); MS (EI) 323 (M^+, 22), 292 (13), 196 (100). HRMS Calcd for $C_{10}H_{14}NO_3I$ 323.0018, found 323.0020.

solution to afford a diastereomeric mixture of iodotetrahydropyridines, which were subjected to ketal hydrolysis by stirring a CH_2Cl_2 solution over silica gel, yielding **2c**[4] with moderate diastereoselection (3 : 1 ratio) over the minor isomer **2c'** (overall yield, 38%).

The stereochemistry was determined by mono- and bidimensional NMR experiments (COSY, NOE, ROESY, HMQC), and follows trends similar to those previously described for the non-iodinated analogs [16] (see Figure 1).

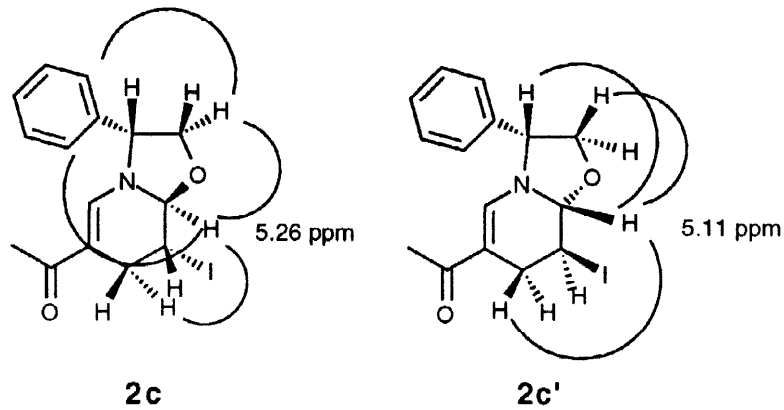


Figure 1. Selected NOE's for **2c** and **2c'**

Next, we explored the possibility of trapping the oxidatively formed iminium ion through electrophilic addition upon an aromatic ring. After several unsuccessful attempts to cyclize diversely substituted *N*-phenethyl-1,4-dihydropyridines, in which only intermolecular addition was observed [22],[5] the interaction of *N*-tryptophyl derivative **1d** with NIS was studied and, to our delight, indoloquinolizidine **2d**[6] was stereoselectively obtained in 85% yield (Scheme 2). This result opens interesting synthetic approaches towards indole alkaloids with the above-mentioned framework (vincamine and tacamine types).

The interaction of an olefin moiety upon the iminium ion was then tested with homoallyl dihydropyridine **1e**. Although treatment with iodine in the presence of methanol afforded the corresponding 2-methoxy-3-iodotetrahydropyridine, a THF solution of iodine cleanly yielded the somewhat unstable quinolizidine diiodide **2e**[7] (43% isolated yield) as an epimeric mixture at

4. **2c**. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.41 - 7.33 (m, 5H), 7.22 (d, J = 1.5 Hz, 1H), 5.26 (d, J = 9 Hz, 1H), 4.69 (m, 1H), 4.53 (m, 1H), 3.89 (m, 1H), 3.81 (m, 1H), 3.43 (dd, J = 16.7, 5.2 Hz, 1H), 2.73 (m, J = 16.7, 12.5, 1.5 Hz, 1H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 192.7, 140.8, 136.9, 129.3, 128.9, 126.8, 111.8, 92.8, 73.7, 64.6, 32.0, 24.2, 21.9; UV (MeOH) 306 (4.20); MS (EI) 369 (M+, 30), 242 (100); $[\alpha]^{20}_D$ -145.3 (c 0.6, MeOH); HRMS Calcd for $C_{15}H_{16}NO_2I$ 369.0226, found 369.0226.

5. For instance, treatment of methyl 1-phenethyl-1,4-dihydropyridine-3-carboxylate with iodine in MeOH afforded the corresponding 3-iodo-2-methoxytetrahydropyridine, whereas when using NIS the corresponding 3-iodo-2-succinimide adduct was formed. The use of activated aromatic rings (4-methoxy and 3,4-dimethoxy substituted) and/or iodinating agents with less nucleophilic counterparts [bis(collidine)iodonium tetrafluoroborate] did not improve the situation, no benzoquinolizidines being detected from these experiments.

6. Indoloquinolizidine **2d**. ^{1}H NMR ($CDCl_3$, 300 MHz) 8.80 (bs, 1H), 7.54 (s, 1H), 7.50 - 7.09 (m, 4H), 4.99 (d, J = 7.7 Hz, 1H), 4.57 (m, 1H), 3.74 (m, 1H), 3.68 (s, 3H), 3.50 (m, 1H), 3.12 (dd, J = 16.5, 5.0 Hz, 1H), 2.99 (dd, J = 16.5, 8.1 Hz, 1H), 2.97 - 2.75 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 168.5, 144.9, 135.8, 130.7, 126.4, 121.9, 119.3, 118.0, 111.2, 108.9, 96.6, 60.2, 51.4, 50.8, 30.0, 22.6, 21.8; IR (KBr) 3380, 1675, 1604; UV (MeOH) 292 (4.40), 221 (4.69); MS (EI) 408 (M^+, 6), 280 (100), 221 (59); mp 137 - 138 °C (acetone - Et_2O); correct combustion analysis.

7. Quinolizidine **2e** (major stereoisomer). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.28 (s, 1H), 4.16 (m, J = 7.1, 5.5 Hz, 1H), 3.68 (s, 3H), 3.40 (m, 1H), 3.36 - 2.31 (m, 9H), 2.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) 167.6, 144.2, 95.8, 58.5, 51.5, 50.9, 50.2, 46.5, 41.3, 31.7, 31.5, 24.1; IR (NaCl) 1683, 1622; UV (MeOH) 289 (4.18); MS (EI) 461 (M^+, 7), 334 (46), 206 (100); HRMS Calcd for $C_{12}H_{17}NO_2I_2$ 460.9348, found 460.9340.

the tetrasubstituted sp^3 carbon atom. This remarkable result suggests a stereocontrolled addition (*anti*) of the olefin moiety upon the iminium ion, followed by a non-stereospecific trapping of the resulting tertiary carbocation by iodide.

The methodology here disclosed is based on the "non-biomimetic" oxidation of dihydropyridines, and represents a new synthetic entry to a wide range of functionalized heterocyclic systems, potential precursors of bioactive or natural products.

Acknowledgement

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. thanks the "Ministerio de Educación y Cultura", Spain, for a fellowship.

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