Vicinal diamination of 1,4-dihydropyridines

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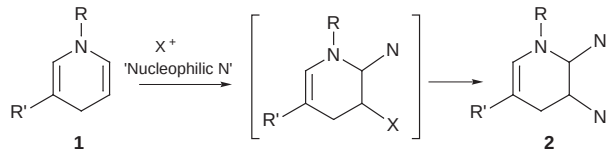
Electrophilic interaction of iodine with *N*-alkyl-1,4-dihydropyridines 1 in the presence of secondary amines stereoselectively leads to the corresponding *trans*-2,3-diamino-1,2,3,4-tetrahydropyridines 2 in satisfactory yields (79–94%); the method allows the synthesis of piperidine, pyrrolidine, morpholine and piperazine derivatives.

Continuing our research on the development of new transformations of 1,4-dihydropyridines,[1] we have recently described some 'non-biomimetic' oxidations of these compounds, in which the normal production of the corresponding pyridinium salt is avoided.[2–4] As a consequence, several unusual transformations of these heterocyclic systems have emerged as useful synthetic tools. For instance, the oxidative addition of halonium ions (*N*-halosuccinimide or related alkoxyhalogenations) was investigated, and the method was successful for the preparation of 2-substituted 3-halo-1,2,3,4-tetrahydropyridines, which, in turn, may be considered as valuable synthetic intermediates.[3] In these reactions, we observed the formation of some byproducts, arising from the nucleophilic trapping of the iminium ion produced in the interaction of the enamine moiety with the halogenating agent. We reasoned that the use of nitrogenated species in these processes would result in the formation of interesting tetrahydropyridines bearing amino substituents at positions 2 and 3 (Scheme 1).[5]

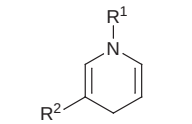
The use of amines as nucleophiles in this type of transformation is normally avoided,[6,7] because of the easy oxidation of the nitrogen atom or its coordination with the electrophile. We felt, however, that this process could be dramatically reduced due to the high reactivity of the enamine moiety present in dihydropyridines **1**, which may rapidly attack the halogen to form a 3-halo-3,4-dihydropyridinium ion. In good agreement with our expectations, when dihydropyridine **1a**[8] was treated in THF solution with iodine (3.5 equiv.) in the presence of an excess of pyrrolidine, the 2,3-diaminotetrahydropyridine **2a**† was stereoselectively formed in 87% yield (Scheme 2 and Table 1).‡ The stereochemistry of the addition was ascertained by NMR methods (including homo- and hetero-correlation techniques). The small H^2–H^3 coupling constant observed suggests a *trans* relationship between the two pyrrolidine groups and a major conformation in which these substituents are axial (it should be noted that in a tetrahydropyridine ring such a substitution pattern displays no serious 1,3-diaxial interactions).

The formation of **2a**§ could be rationalized by considering the initial formation of a *trans*-2-amino-3-iodotetrahydropyridine, which would undergo an internal nucleophilic substitution reaction followed by a stereoselective ring opening of the resulting aziridinium ion promoted by a second equivalent of the secondary amine.[9]

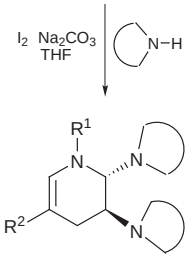
The reaction seems to be quite general, and works well with different alkyl groups at the dihydropyridine nitrogen (methyl and benzyl) and electron-withdrawing groups at the 3 position (methoxycarbonyl and cyano). Several cyclic secondary amines¶ were tested, including pyrrolidine, piperidine, morpholine and *N*-methylpiperazine, and the corresponding *trans* vicinal diamines were isolated in good yields. It should be noted that the diamination of olefins usually involves multistep sequences and/or the use of expensive organometallic reagents. The yields were slightly improved by adding solid Na_2CO_3 to the reaction mixture, but efforts to reduce the amount of iodine and/or secondary amine to stochiometric amounts resulted in decreased yields, even after longer reaction times.



Scheme 1



1 a R^1 = Me R^2 = CO_2Me
b R^1 = Me R^2 = CN
c R^1 = Bn R^2 = CN



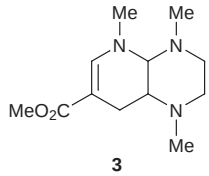
2 a R^1 = Me R^2 = CO_2Me R_2N = pyrrolidinyl
b R^1 = Me R^2 = CO_2Me R_2N = piperidino
c R^1 = Me R^2 = CN R_2N = pyrrolidinyl
d R^1 = Me R^2 = CN R_2N = piperidino
e R^1 = Me R^2 = CN R_2N = morpholino
f R^1 = Bn R^2 = CN R_2N = pyrrolidinyl
g R^1 = Bn R^2 = CN R_2N = 4-methylpiperazin-1-yl

Scheme 2

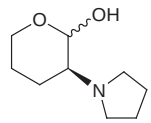
This remarkable process is also suitable for the formation of cyclic adducts. Thus, when **1a** was allowed to react with iodine in the presence of *N*,*N*′-dimethylethylenediamine, the bicyclic adduct **3** was obtained (80% yield) as a slightly unstable oil, probably as a mixture of two isomers. Column chromatography (SiO_2, elution with CH_2Cl_2–EtOAc) allowed the purification of the major component. The stereochemistry of the ring fusion in

Table 1 Vicinal diamination reactions from dihydropyridines **1**

Entry	Dihydropyridine	Secondary amine	Product	Yield (%)
1	**1a**	pyrrolidine	**2a**	87
2	**1a**	piperidine	**2b**	90
3	**1b**	pyrrolidine	**2c**	94
4	**1b**	piperidine	**2d**	89
5	**1b**	morpholine	**2e**	84
6	**1c**	pyrrolidine	**2f**	79
7	**1c**	1-methylpiperazine	**2g**	86
8	**1a**	$MeNH(CH_2)_2NHMe$	**3**	80



3



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the major isomer was determined to be *cis*,‖ as the coupling constant between the ring fusion hydrogens is small (J < 1 Hz; a *trans*-decalin type fusion would result in a much larger coupling constant). This was confirmed by NOE and NOESY experiments. The difference with respect to the previous acyclic systems (where only *trans* products **2** were obtained) may reflect the fact that, in the present case, the intramolecular nucleophilic attack in the initially formed *trans*-2-amino-3-iodotetrahydropyridine takes place faster from the remaining secondary amino group to form the more stable 6-membered ring. Alternatively, an aziridinium intermediate could undergo ring-opening to give a 3-amino-3,4-dihydropyridinium cation, which could be intramolecularly trapped by the remaining secondary amino group.

The use of this methodology with enol ethers was tested next, and when 3,4-dihydro-2*H*-pyran was treated with iodine and pyrrolidine, an unstable compound was obtained (presumably the corresponding 2,3-diaminotetrahydropyran), which decomposed during column chromatography to furnish the hemiacetal **4**** (27%, non-optimized yield) as an anomeric mixture.[10] It is worth mentioning that cyclohexene failed to yield significant amounts of the corresponding addition product[11] on treatment with iodine and pyrrolidine under the usual reaction conditions, thus suggesting that only electron-rich olefins are good substrates for this kind of oxidative additions.

In summary, we have described a new 'non-biomimetic' oxidation of 1,4-dihydropyridines that allows the vicinal diamination of these substrates in an efficient and stereocontrolled manner.

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Notes and references

† All new compounds were characterized by ^{1}H and ^{13}C NMR, IR, UV, MS and HRMS or elemental analysis.

‡ *General procedure* for oxidative diamination reactions. A solution of iodine (3.5 mmol) in THF (50 ml) was added dropwise under N_2 atmosphere to a stirred suspension of dihydropyridine **1** (1 mmol), secondary amine (25 mmol), and Na_2CO_3 (95 mmol) in THF (50 ml) kept at 0 °C, and stirring was continued at room temperature until no dihydropyridine is detected by TLC (usually 1–3 h). Water (150 ml) was added, and the mixture was extracted with EtOAc (3 × 75 ml). The combined organic extracts were washed with aq. $Na_2S_2O_3$ solution (100 ml, 0.5 M) and brine (100 ml), and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2, elution with CH_2Cl_2–EtOAc) to yield pure 2,3-diaminotetrahydropyridines.

§ *Selected data* for **2a**: δ_H 7.39 (s, 1H, H-6), 3.66 (s, 3H, OCH_3), 3.57 (br s, 1H, H-2), 3.09 (s, 3H, NCH_3), 2.59 (m, 10H), 2.30 (m, J 16.8, 4.4, 1.4, 1H, H-4), 1.75 (m, 8H); δ_C 168.4 (CO), 144.9 (C-6), 93.1 (C-5), 78.0 (C-2), 58.4 (C-3), 51.8 (OCH_3), 50.1, 50.0, 43.2 (NCH_3), 22.9, 22.8, 20.5 (C-4).

¶ The use of primary amines (pentylamine, hexylamine, methylamine) resulted in complex reaction mixtures, from which the desired products, as well as the corresponding aziridines, were detected in trace amounts.

‖ *Selected data* for *cis*-**3**: δ_H 7.23 (s, 1H, H-6), 3.61 (s, 3H, OCH_3), 3.13 (br s, 1H, H-4a), 2.99 (s, 3H, NCH_3), 2.86 (m, 1H, H-8a), 2.76 (m, 2H), 2.43–2.19 (m, 4H), 2.38 (s, 3H, NCH_3), 2.22 (s, 3H, NCH_3); δ_C 168.0 (CO), 144.3 (C-6), 94.4 (C-7), 78.6 (C-4*a*), 56.1 (C-8*a*), 50.6 (OCH_3), 47.3, 42.2, 42.0, 41.9, 24.7 (C-8).

** *Selected data* for **4** (major anomer): δ_H 5.16 (d, J 3.3, 1H, H-2), 3.91 (m, 1H, H-6), 3.53 (m, 1H, H-6), 2.57 (m, 4H), 2.26 (m, 1H, H-3), 1.80–1.60 (m, 9H); δ_C (data for the major anomer) 91.4 (C-2), 64.1 (C-6), 58.9 (C-3), 50.9, 24.1 (C-5), 23.6, 23.0 (C-4).

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