ONE-POT ACCESS TO 2,3-DISUBSTITUTED 1,2,3,4-TETRAHYDROQUINOLINES BY REDUCTIVE AMINATION OF ALDEHYDES WITH SODIUM CYANOBOROHYDRIDE

Guy Lewin*[a,b] and Corinne Schaeffer[c]

Laboratoire de Pharmacognosie, Faculté de Pharmacie, boulevard Becquerel, 14032 Caen France [a]. Laboratoire de Pharmacognosie, Faculté de Pharmacie, av. J.B. Clément, 92296 Châtenay-Malabry France [b]. Institut de Recherches Servier, 11 rue des Moulineaux, 92150 Suresnes, France [c]

Abstract- Slight modification of the reductive amination Borch method (delayed addition of $NaBH_3CN$) provided an easy one-pot synthesis of 1,2,3,4-tetrahydroquinoline derivatives from enolizable aldehydes.

The method of choice for the one-pot conversion of aldehydes and ketones to amines is the Borch reduction which consists in attack of the intermediate iminium adduct by $NaBH_3CN$.[1-3] In other respects, synthesis of 1,2,3,4-tetrahydroquinoline derivatives has been described through acid-catalyzed [4+2] cycloaddition between some enamines and a benzylidene aniline.[4] Surprisingly, access to 1,2,3,4-tetrahydroquinoline derivatives by condensation between an enamine and its own tautomeric Schiff base has hardly been related to our knowledge.[5] In this note, we report a slight modification of the Borch reductive amination of enolizable aldehydes, which allows a one-pot synthesis of 2,3-disubstituted 1,2,3,4-tetrahydroquinolines.

General Procedure: To a mixture of 0.25 mmol of carbonyl compound and aniline hydrochloride (5 or 0.5 eq) in solution in MeOH (5 mL) at room temperature, $NaBH_3CN$ (50 mg, 0.8 mmol) was added (immediately or 20 min after) then the reaction was left at room temperature for 16 h. The reaction mixture was taken up in water (20 mL), raised to pH 10 with 0.5N NaOH and extracted with CH_2Cl_2. Standard work-up of the organic layer provided a dried residue which was purified by flash or thin layer chromatography on silica gel. Four experimental conditions (A, B, C and D) were investigated according to aniline:aldehyde ratio and moment of $NaBH_3CN$ addition (see legend of the Table).

This study was carried out with five enolizable carbonyl compounds, propionaldehyde, phenylacetaldehyde, *N*-benzyl-2-methylindole-3-acetaldehyde (**1**),[6,7] acetone and cyclohexanone. As shown on Table, results

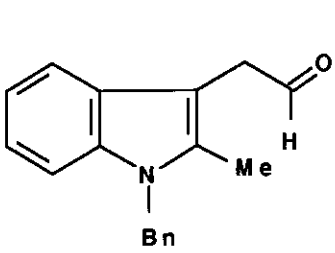
were closely dependent on starting carbonyl compounds (aldehyde or ketone), aniline:aldehyde ratio and moment of $NaBH_3CN$ addition. Three kinds of reduction products were isolated: expected reductive monoamination compounds (type I), symmetrical reductive diamination compounds (type II) and 2,3-disubstituted 1,2,3,4-tetrahydroquinoline compounds (type III). Compounds of the type III (**2-5**, **8**)[8] were obtained only from aldehydes and 5 eq of aniline hydrochloride (conditions A and B, entries 2-4,7-8). These 1,2,3,4-tetrahydroquinoline derivatives were always the major isolated compounds when $NaBH_3CN$ was added 20 min after the mixture of reagents (condition B, entries 2,4,8). In the case of an immediate addition of $NaBH_3CN$, these 1,2,3,4-tetrahydroquinoline derivatives were all the more abundant that the starting aldehyde could generate a stabilized intermediate enamine: **8** was isolated in 7% yield (entry 7), **4** and **5** only as traces (entry 3) while **2** and **3** were not detected (entry 1). Stereochemistry of the 1,2,3,4-tetrahydroquinolines at C2 and C3 seemed highly dependent on the size of the starting aldehyde: propionaldehyde led to the 1:1 mixture of diastereoisomers (**2**) and (**3**) (entry 2), phenylacetaldehyde to the 4:1 mixture of 2,3-*trans* (**4**) and 2,3-*cis* (**5**) derivatives (entry 4) whereas the bulky indoloacetaldehyde (**1**) yielded only the 2,3-*trans* disubstituted isomer (**8**) (entry 8). Under the Borch original conditions (immediate addition of $NaBH_3CN$), the expected type I compounds were always the major reaction products (*N*-propylaniline, *N*-phenethylaniline, **6**). Using 0.5 eq of aniline hydrochloride (conditions C and D) provided also the symmetrical type II compounds (*N,N*-diphenethylaniline, **7**) and a same final reaction mixture whenever $NaBH_3CN$ was added (entries 5 and 6). Lastly, ketones furnished only the reductive amination type I compounds without production of any 1,2,3,4-tetrahydroquinoline derivatives (entries 10-13).

Table

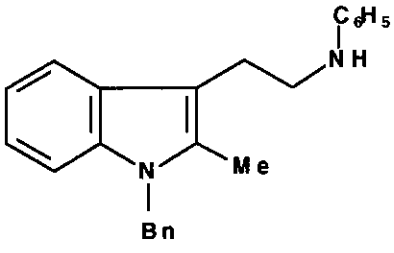
entry	Substrate	Conditions[a]	Products (% yield[b])		
			Type I	Type II	Type III
1	Propionaldehyde	A	*N*-Propylaniline (53)		
2	"	B			**2** (24), **3** (24)[5,9]
3	Phenylacetaldehyde	A	*N*-Phenethylaniline (57)		**4** and **5** (traces)
4	"	B	" (12)		**4** (34), **5** (8.5)
5, 6	"	C or D	" (44)	*N,N*-Diphenethylaniline (17)	
7	**1**	A	**6** (49)	**7** (3)	**8** (7)
8	"	B	**6** (traces)		**8** (58)
9	"	C	**6** (35)	**7** (22)	
10, 11	Acetone	A or B	*N*-Isopropylaniline (63)		
12, 13	Cyclohexanone	A or B	*N*-Cyclohexylaniline (62)		

[a] A: aniline, HCl 5 eq, $NaBH_3CN$ added immediately. B: aniline, HCl 5 eq, $NaBH_3CN$ added after 20 min. C: aniline, HCl 0.5 eq, $NaBH_3CN$ added immediately. D: aniline, HCl 0.5 eq, $NaBH_3CN$ added after 20 min.[b] Yield of isolated compound after flash chromatography or tlc (silica gel, cyclohexane-CH_2Cl_2 1:1 or 2:1).

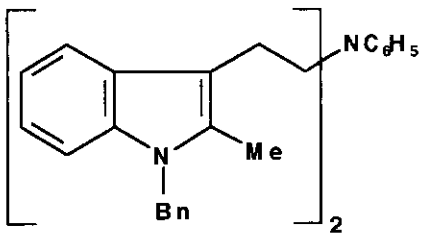
Mechanism (Scheme): The mild and neutral experimental conditions exclude a first crotonaldehyde-type intermediate by self-condensation of the aldehyde. The lack of any cyclization compound with a



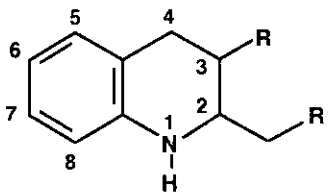
1



6

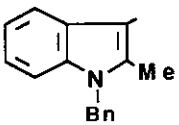


7

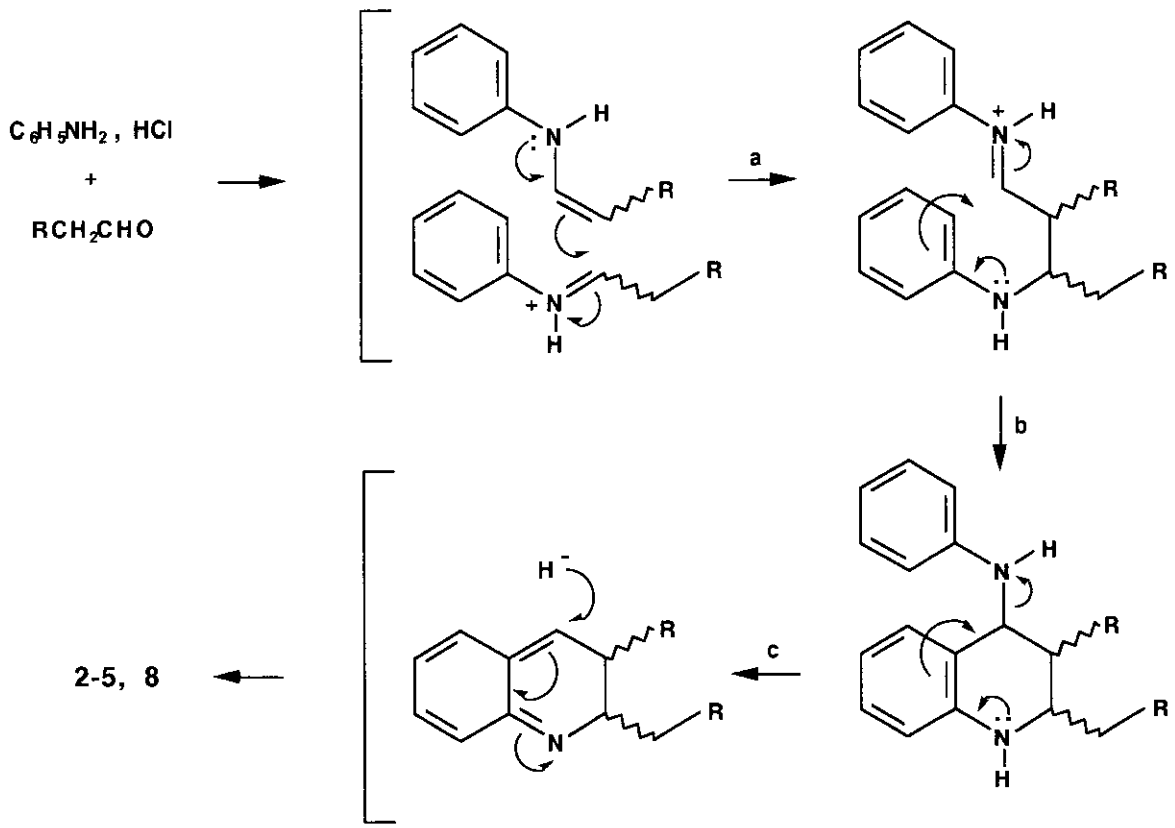


R = CH_3- (2,3-*trans*) **2** (2,3-*cis*) **3**

R = C_6H_5- (2,3-*trans*) **4** (2,3-*cis*) **5**

R = 

(2,3-*trans*) **8**



aniline:aldehyde 0.5 ratio is strongly in favour of a Schiff base intermediate. So, the cyclization into 1,2,3,4-tetrahydroquinoline ring may result from a) the addition of the enamine form to the tautomeric Schiff base, as iminium salt; b) the electrophilic aromatic substitution at the ortho position by the iminium intermediate; c) the reduction at the benzylic C4 center by $NaBH_3CN$. Sequences a and b of this mechanism have already been suggested,[4] particularly as possible key steps in the Doebner-von Miller synthesis of the quinoline ring.[10] Lastly, the lack of 1,2,3,4-tetrahydroquinoline synthesis from ketones under these conditions is related to the known more difficult formation of intermediate enamines which requires higher temperature and longer reaction times.[11]

REFERENCES AND NOTES

1. R.F. Borch, M.D. Bernstein, and H.J.D. Durst, *J. Am. Chem. Soc.*, 1971, **93**, 2897.
2. C.L. Barney, E.W. Huber, and J.R. McCarthy, *Tetrahedron Lett.*, 1990, **31**, 5547.
3. R.J. Mattson, K.M. Pham, D.J. Leuck, and K.A. Cowen, *J. Org. Chem.*, 1990, **55**, 2552.
4. Y. Nomura, M. Kimura, Y. Takeuchi, and S. Tomoda, *Chem. Lett.*, 1978, 267.
5. O. Doebner, and W. von Miller, *Ber.*, 1884, **17**, 1714.
6. M. Ihara, K. Noguchi, K. Fukumoto, and T. Kametani, *Tetrahedron*, 1985, **41**, 2109.
7. Compared with indole-3-acetaldehyde, *N*-benzylation increases stability and 2-methylation prevents side reactions at C2.
8. **Typical Procedure** (entry 4 in the Table): To a mixture of 0.25 mmol of phenylacetaldehyde (30 mg) and 1.25 mmol of aniline hydrochloride (162 mg) in solution in MeOH (5 mL) at room temperature for 20 min, $NaBH_3CN$ (50 mg, 0.8 mmol) was added then the reaction was left at room temperature for 16 h. The reaction mixture was taken up in water (20 mL), raised to pH 10 with 0.5N NaOH and extracted with CH_2Cl_2. Standard work-up of the organic layer provided a residue (35 mg) which was purified by thin layer chromatography on silica gel (cyclohexane-CH_2Cl_2 2:1) to yield the diastereoisomers (**4**) (16.5 mg, 34%) and (**5**) (4.5 mg, 8.5%) and *N*-phenethylaniline (6 mg, 12%).
***trans*-2-Ethyl-3-methyl-1,2,3,4-tetrahydroquinoline (2)**: amorphous; ^1H NMR ($CDCl_3$) δ ppm: 0.95 (t, J = 7.4 Hz, and d, J = 6.7 Hz, 6H); 1.45/1.63 (m, 2H); 1.82 (m, 1H, H3); 2.43 (dd, J = 16 and 9.6 Hz, H4); 2.71 (dd, J = 16 and 5.5 Hz, H4); 2.84 (dt, J = 8 and 3.7 Hz, 1H, H2); 3.83 (s, 1H, H1); 6.45 (d, J = 7.9 Hz, 1H, H8); 6.55 (t, J = 7.9 Hz, 1H, H6); 6.93 (m, 2H, H5 and H7); HRMS calcd for $C_{12}H_{17}N$ 175.1361, found 175.1359; Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.15; H, 9.84; N, 8.06. ***cis*-2-Ethyl-3-methyl-1,2,3,4-tetrahydroquinoline (3)**: amorphous; ^1H NMR ($CDCl_3$) δ ppm: 0.92 (d, J = 6.6 Hz, 3H); 0.98 (t, J = 7.4 Hz, 3H); 1.45 (m, 2H); 2.05 (m, J = 6.6, 5 and 3 Hz, 1H, H3); 2.41 and 2.93 (2d, J = 16 and 5 Hz, 2H, H4); 3.09 (m, J = 7 and 3 Hz, 1H, H2); 3.82 (s, 1H, H1); 6.45 (d, J = 7.9 Hz, 1H, H8); 6.62 (t, J = 7.9 Hz, 1H, H6); 6.95 (m, 2H, H5 and H7); nOe observed between H2 and H3; HRMS calcd for $C_{12}H_{17}N$ 175.1361, found 175.1353; Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.12; H, 9.87; N, 8.01. ***trans*-2-Benzyl-3-phenyl-1,2,3,4-tetrahydroquinoline (4)**: amorphous; ^1H NMR ($CDCl_3$) δ ppm: 2.38 (dd, J = 13.5 and 10 Hz, 1H, benzyl group); 2.65 (dd, J = 13.5 and 3.8 Hz, 1H, benzyl group); 3.13 (d, J = 7 Hz, 2H, H4); 3.42 (dt, J = 7 and 3.8 Hz, 1H, H3); 3.69 (dt, J = 10 and 3.8 Hz, 1H, H2); 6.41 (d, J = 7.9 Hz, 1H, H8); 6.68 (t, J = 7.9 Hz, 1H, H6); 7.03 (m, 4H); 7.30 (m, 8H); HRMS calcd for $C_{22}H_{21}N$ 299.1674, found 299.1671; Anal. Calcd for $C_{22}H_{21}N$: C, 88.25; H, 7.07; N, 4.68. Found: C, 88.32; H, 7.13; N, 4.61. ***cis*-2-Benzyl-3-phenyl-1,2,3,4-tetrahydroquinoline (5)**: amorphous; ^1H NMR ($CDCl_3$) δ ppm: 2.38 (dd, J = 10 and 7 Hz, 1H, benzyl group); 2.75 (dd, J = 7 and 3 Hz, 1H, benzyl group); 2.91 (m, 1H, H3); 3.08 (m, 2H, H4); 3.65 (m, J = 10, 5.5 and 3 Hz, 1H, H2); 6.42 (d, J = 7.9 Hz, 1H, H8); 6.65 (t, J = 7.9 Hz, 1H, H6); 7.02 (t, J = 8 Hz, 2H); 7.30 (m, 10H); nOe observed between H2 and H3; Anal. Calcd for $C_{22}H_{21}N$: C, 88.25; H, 7.07; N, 4.68. Found: C, 88.19; H, 7.08; N, 4.73. ***trans*-3-(1-Benzyl-2-methylindol-3-yl)-2-(1-benzyl-2-methylindol-3-ylmethyl)-1,2,3,4-tetrahydroquinoline (8)**: amorphous; ^1H NMR ($CDCl_3$) δ ppm: 2.18 and 2.43 (2s, 6H); 2.56 (dd, J = 16 and 11 Hz, 1H); 2.93 (m, 2H); 3.34 (m, J = 11 and 6 Hz, 1H, H3); 3.61 (dd, J = 17.6 and 11 Hz, 1H, H4); 4.21 (m, J = 11 and 6 Hz, 1H, H2); 5.31 and 5.38 (2d and s, 4H, *N*-benzyl groups); 6.32 (d, J = 7.9 Hz, 1H, H8); 6.61 (t, J = 7.9 Hz, 1H, H6); 6.92 (m, 2H); 7.00 (m, 3H); 7.12 (m, 3H); 7.25 (m, 10H); 7.39 (d, J = 8 Hz, 1H); 7.77 (d, J = 8 Hz, 1H); HRMS calcd for $C_{42}H_{39}N_3$ 585.3144, found 585.3142; Anal. Calcd for $C_{42}H_{39}N_3$: C, 86.11; H, 6.71; N, 7.17. Found: C, 86.27; H, 6.78; N, 7.28.
9. S.D. Lesesne, and H.R. Henze, *J. Am. Chem. Soc.* 1942, **64**, 1897.
10. Rodd's Chemistry of Carbon Compounds, 2nd Edition, Vol.IV Part F; ed. by S. Coffey, Elsevier, Amsterdam, Oxford, New York, 1976, p. 239.
11. J. March, Advanced Organic Chemistry, John Wiley, New York, 1992, p. 897.

Received, 17th September, 1997