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AN EASY AND VERSATILE ACCESS TO 8-SUBSTITUTED ISOQUINOLINES

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Summary : Lithiation of *N*-(2,2-diethoxyethyl)benzylamines and subsequent reaction with electrophiles allow to introduce a variety of carbo- and heterofunctional groups in the *ortho*-position. Subsequent acid-catalyzed cyclization leads to isoquinolines having an uncommon substitution pattern.

N-Alkyl-*N*-(2,2-diethoxyethyl)benzylamines readily cyclize to afford 4-hydroxy-1,2,3,4-tetrahydroisoquinolines [1]. Their preparation from the corresponding aldehydes is extremely simple. In this way, a large number of new heterocyclic compounds was obtained. [1]

Left aside a few exceptions, polyfunctionalized aromatic aldehydes carrying one *ortho* substituent are commercially not available. They have to be synthesized by lengthy procedures unless a simpler aldehyde is accessible into which the lacking substituents may be introduced at an early or later stage [2]. It occurred to us that tertiary benzylamines are prone to selective *ortho* metalation [3]. An electronegative *meta* substituent provides additional activation. The piperonal derived aminoacetals 1 and butyllithium were indeed found to undergo a rapid and virtually quantitative hydrogen/metal exchange. The resulting aryllithium reagent was trapped with a variety of electrophiles to give *ortho* substituted intermediates 2 and, after cyclization with 20% aqueous hydrochloric acid [4], the expected tetrahydroisoquinolines 3 (see Table, next page).

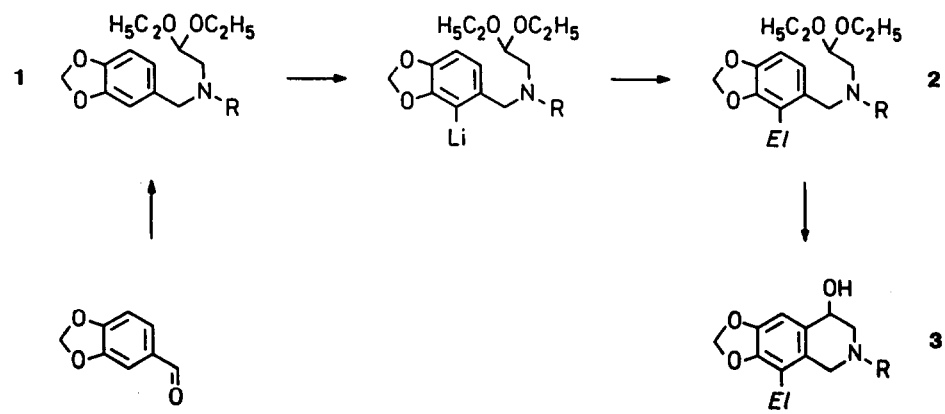


Table. 8-Substituted 4-hydroxy-1,2,3,4-tetrahydroisoquinolines **3** as obtained after *ortho*-lithiation, electrophilic substitution (by *El*-X) and acid catalyzed cyclization of *N*-alkyl-*N*-(2,2-diethoxyethyl)-3,4-methylenedioxybenzylamines **1** [R = CH_3, $CH_2C_6H_5$].

Cpd.nr.	R	*El*	[*El*-X used]	yield [a]	mp [b]
3a	CH_3	CH_3	[$H_3COSO_2OCH_3$]	67%	175 - 176 °C (C_2H_5OH)
3b	$CH_2C_6H_5$	CH_3	[$H_3COSO_2OCH_3$]	62%	139 - 140 °C ($H_3CCOOC_2H_5$)
3c	CH_3	CH_2OH	[-$(CH_2O)_{oo}$ -]	37%	175 - 176 °C (C_2H_5OH)
3d	CH_3	OCH_3	c)	36%	151 - 152 °C ($H_3CCOOC_2H_5$)
3e	CH_3	SCH_3	[H_3CS-SCH_3]	72%	137 - 138 °C ($H_3CCOOC_2H_5$)
3f	CH_3	Cl	[Cl_3C-CCl_3]	52%	172 - 173 °C (C_2H_5OH) [d]
3g	CH_3	Br	[Br_2]	50%	174 - 175 °C (C_2H_5OH) [e]
3h	CH_3	I	[I_2]	75%	203 - 204 °C (C_2H_5OH) [f]

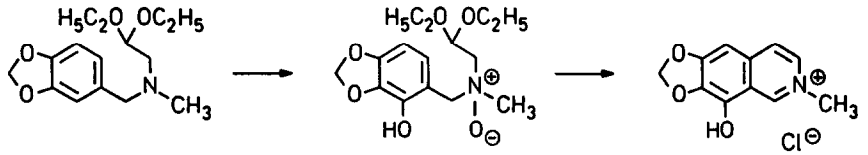
a) Yield (with respect to **1**) of isolated product, the identity and purity of which was confirmed by spectral data (NMR, IR, MS) and combustion analyses.
b) Corrected melting ranges and, in parentheses, the solvent from which the compound was crystallized.
c) By consecutive treatment with trimethoxyborane, alkaline hydrogen peroxide, dimethyl sulfate, sodium dithionite (for reduction of the concomitantly formed *N*-oxide) and half-concentrated hydrochloric acid.
d) Some dimethylformamide being added.
e) Hydrochloride : mp 242 - 243 °C (dec.).
f) Hydrochloride : mp 214 - 215 °C (dec.).

In a strictly analogous sequence of transformations, 3-methoxybenzaldehyde and veratraldehyde (3,4-dimethoxybenzaldehyde) were converted to 4-hydroxy-7-methoxy- and 4-hydroxy-6,7-dimethoxy-2,8-dimethyl-1,2,3,4-tetrahydroisoquinoline, respectively (**4**, 61%, mp 164 - 165 °C, and **5**, 71%, mp 123 - 124 °C, both after recrystallization from ethyl acetate). Thus, one single donor substituent at the future 7-position suffices to direct the metalation to the site flanked by the two heteroatom bearing substituents and afterwards to facilitate the ultimate cyclization step.

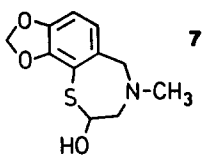
X = H : **4**
X = H_3CO: **5**

Tetrahydroisoquinolines **3** - **5** are useful intermediates for the synthesis of more elaborate heterocyclic compounds. Derivative **3d**, for example, can be readily converted to alkaloids such as cotarnine and narcotine [5].

When the β-aminoacetal **1** [R = CH_3] was submitted to consecutive lithiation, dimethoxyborylation and treatment with hydrogen peroxide in alkaline medium, not only a hydroxy group was introduced into the aromatic nucleus but also the amino function was oxidized to the corresponding *N*-oxide (mp 78 - 80 °C). Cyclization of the latter compound under strongly acidic conditions was accompanied by dehydration and afforded directly the *N*-alkylisoquinolinium salt **6** [6] (chloride : mp 265 - 267 °C, dec.).



We have identified one source of possible complications which may set a limit to the applicability of the method. If a strongly nucleophilic group is introduced at the position flanked by the two substituents, it may intercept the aldehyde function liberated by acetal hydrolysis and thus prevent the ordinary cyclization (*e.g.*, **2** [*El* = SH] → **7**, hydrochloride : mp 194 -195 °C, dec.).



Typical working procedure : At 0 °C, a 1.5 M solution (73 mL) of butyllithium (0.11 mol) in hexane was added to the β-aminoacetal **1** [R = CH_3] [7] (28 g, 0.10 mol) dissolved in diethyl ether (0.15 L). After 1 h, the formation of a precipitate was complete. The suspension was treated with dimethyl disulfide (13 mL, 14 g, 0.15 mol) and stirred 1 h at 25 °C. The mixture was washed with water (0.05 L) and evaporated. The residue was dissolved in 20% hydrochloric acid (0.50 L). After 16 h at 25 °C, the solution was cleared with charcoal, filtered and basified with 40% aqueous sodium hydroxide (the temperature being kept below 40 °C). Extraction with dichloromethane (3 × 0.25 L), evaporation and crystallization from ethyl acetate afforded 18.1 g (72%) of 4-hydroxy-2-methyl-6,7-methylenedioxy-8-methylthio-1,2,3,4-tetrahydroisoquinoline (**3e**); mp 137 - 138 °C. - ^{1}H-NMR ($CDCl_3$, 360 MHz) : δ 6.82 (1 H, s), 6.01 (2 H, symm.m), 4.45 (1 H, symm.m), 3.87 (1 H, d, *J* 15.5), 3.60 (1 H, s, broad), 3.08 (1 H, d, *J* 15.5), 2.92 (1 H, dd, *J* 11.5, 3.0), 2.47 (1 H, dd, *J* 11.5, 3.0), 2.47 (3 H, s), 2.38 (3 H, s). - MS (*m/e*) : 253 (42%, M^+), 238 (58%), 220 (11%), 210 (100%). - Analysis : calc. for $C_{12}H_{15}NO_3S$ (253.31) C 56.90, H 5.97; found C 57.03, H 5.94%.

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[2] For example, aromatic aldehydes can be protected as hemiaminals and then submitted to consecutive *ortho*-lithiation and electrophilic substitution. Although quite attractive in princple, this route implies a great number of reaction steps, gives frequently only moderate yields and is not always predictable as far as its regioselective outcome is concerned [D.L. Comins, J.D. Brown, *J. Org. Chem.* **54** (1989), 3730, and references quoted therein].

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