STUDY ON THE COUPLING REACTIONS OF BENZYLISOQUINOLINES WITH LEAD TETRAACETATE

Gábor Blaskó, Gábor Dörnyei, Marietta Bárczai-Beke, Péter Péchy and Csaba Szántay*

Institute of Organic Chemistry, Technical University, Budapest XI., Gellért tér 4. H-1521. Central Research Institute for Chemistry, Hungarian Academy of Sciences, Budapest II., Pusztaszeri u. 59-67. H-1525, Hungary

Abstract - Lead tetraacetate (LTA) oxidation of different mono- or non-phenolic tetrahydrobenzylisoquinolines containing secondary amino group leads to dibenzopyrrocoline derivative or oxoaporphine, respectively. The substrate selectivity of LTA has been discussed.

Benzylisoquinolines are well known intermediates in the biosynthesis of different isoquinoline alkaloids[1,2]; their regioselective in vivo oxidative couplings afford the various type isoquinoline alkaloids e.g. proaporphines and aporphines, morphinanedienones, dibenzopyrrocolines, cularines, pavines etc. The in vitro realization of these selective coupling reactions are steadily under investigation[3,4].

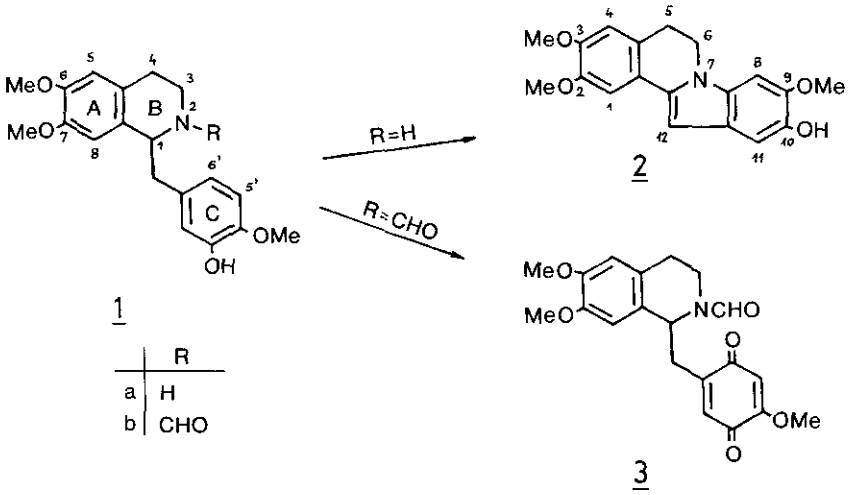
Earlier experiments could realize only non-selective oxidative couplings of phenolic benzylisoquinolines in low yields using ferric chloride[5], potassium ferricyanide[6] or manganese dioxide[7] as oxidizing agent.

One of the first selective oxidation methods was reported by Umezawa and co-workers[8], concerning the cyclization of various benzylisoquinolines with lead tetraacetate (LTA) in acetic acid. It has been found, that tertiary N-methyl-7-hydroxy-tetrahydrobenzylisoquinolines resulted selectively in p-quinol-acetates which on subsequent treatment with trifluoroacetic acid (TFA) afforded mainly aporphines.

Recently LTA in dichloromethane solution in the presence of trichloro- or trifluoroacetic acid proved to be proper reagent for the oxidation of reticuline into aporphinic isoboldine as well as salutaridine having morphinanedienone skeleton[9].

This different regioselectivity of LTA depending on the reaction conditions inspired us to study the substrate selectivity of the reagent with non-phenolic or monophenolic tetrahydrobenzylisoquinolines containing secondary amino group.

At the outset racemic N-norlaudanine (1a) containing phenol group on ring C was treated with LTA in the presence of TFA. As a result of the reaction only one compound could be isolated in moderate yield. On the basis of spectral data the coupling took place between the nitrogen and the 6' position of ring C resulting in 2 dibenzopyrrocoline derivative.



1

	R
a	H
b	CHO

2

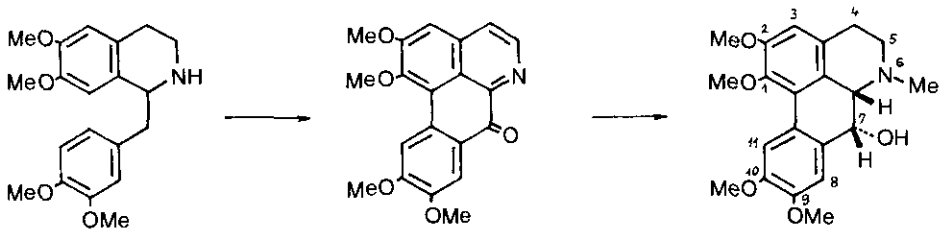
3

If the secondary amino group was protected by formylation no ring closure could be observed, however 1b afforded quinone derivative 3 in high yield.

In the similar oxidation of the non-phenolic tetrahydropapaverine (4) the formation of aporphine skeleton is accompanied by further oxidation resulting in oxoglaucine (5)[10]. Beside the unreacted starting material 5 is the only isolable product even if one mole equiv. of LTA is applied. The conversion can be improved by the use of LTA in excess.

This successful ring closure to build up aporphine skeleton opens a new approach for the simple total synthesis of 7-hydroxy-aporphines, a small and

interesting subgroup of the widespread aporphine alkaloids[11]. The final steps of the transformation are shown on the example of oxoglaucine (5).



4 5 6

Quaternarization and subsequent sodium borohydride reduction affords 6 smoothly in good overall yield. The relative cis position of C_{6a}-H and C_7-H in 6 was determined by ^{1}H NMR measurements (see coupling constants of the corresponding proton signals in the Experimental).

On the basis of the above results it can be stated, that the presence or the absence of free phenolic group determines the regioselectivity of the oxidative coupling of different benzylisoquinolines containing secondary amino group. When the substrate contains OH group on ring C (1a), the unprotected nitrogen takes part in the reaction yielding 2 dibenzopyrrocoline derivative.

The oxidative coupling can be accomplished on non-phenolic benzylisoquinoline 4, and in the reaction aporphine skeleton is formed. In both cases the unprotected secondary amino function is likely to be responsible for the further oxidation of the skeletons.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on Spectromom 2000 infrared spectrophotometer. NMR spectra were determined on a Varian XL 100-15 instrument. Deuterochloroform was used as solvent and TMS as internal standard. Chemical shifts are reported in δ values relative to TMS. Mass spectra were obtained with an AEI-MS-902 instrument. Silica gel PF_{254} coated plates (E.Merck) were used for thin layer chromatography (TLC).

General Procedure for Lead Tetraacetate Oxidation: Tetrahydrobenzylisoquinoline (1.5 mmol) was dissolved in dry dichloromethane (100 mL) and a 9:1

mixture of trifluoroacetic acid and trifluoroacetic anhydride (3 mL) was added at -20 °C. Lead tetraacetate (709 mg, 1.6 mmol) was added to the mixture in two portions. The solution was stirred at -20 °C for 4 h and kept in refrigerator at 4 °C overnight. The reaction mixture was treated with 10 % ammonium hydroxide. The organic layer was separated and washed with water then dried and evaporated under reduced pressure. The residue was purified by column chromatography using aluminium oxide (Brockmann II-III, E.Merck) adsorbent and dichlorometane-methanol 100:1 v/v solvent system as eluent.

1. The oxidation of 1a (494 mg) and subsequent purification resulted in 2 (80.4 mg, 16.5 %), $C_{19}H_{19}NO_4$; mp 197-199 °C (EtOAc-ether); ^{1}H NMR ($CDCl_3$) δ 3.11 (t, J=6.5Hz, 2H, C_5-H), 4.14 (t, J=6.5Hz, 2H, C_6-H), 3.88, 3.93 and 3.95 (3 x s, 3 x 3H, methoxyls), 6.61 (s, 1H, C_{12}-H), 6.76, 6.78, 7.11 and 7.19 (4 x s, 4 x 1H, aromatic protons); mass spectrum m/e (rel.int.) 325 (100, M^+), 310 (80), 294 (3), 288 (3), 266 (10), 252 (3), 249 (3), 191 (3), 176 (3), 155 (3).

2. The oxidation of 1b[12] (536 mg) gave uniformly 3 (473 mg, 85 %), $C_{20}H_{21}NO_6$; mp 182-183 °C (MeOH); IR(KBr) 1605 (C=$C_{conj.}$), 1650 (C=$O_{conj.}$), 1660 cm^{-1} (N-C=O); ^{1}H NMR ($CDCl_3$)[13] δ 3.82, 3.85 and 3.88 (3 x s, 3 x 3H, methoxyls), 5.52 (dd, J_1=5Hz, J_2=12Hz, 1H, C_1-H), 5.96 and 5.98 (s, s, 1H, C_5-H), 6.45 and 6.48 (s, s, 1H, C_8-H), 6.58 and 6.62 (s, s, 1H, =C-H), 6.77 and 6.85 (s, s, 1H, =C-H), 7.98 and 8.08 (s, s, 1H, CHO); mass spectrum m/e (rel. int.) 371 (3, M^+), 353 (15), 352 (4), 343 (100), 338 (6), 328 (45), 326 (80), 310 (17), 300 (8), 220 (68), 192 (7).

3. The oxidation of 4 (515 mg) supplied 5 (127 mg, 24.1 %), $C_{20}H_{17}NO_5$; mp 224-225 °C (MeOH), (lit. mp[10] 225-226 °C), ^{1}H NMR ($CDCl_3$) δ 4.02, 4.05, 4.06 and 4.10 (4 x s, 4 x 3H, methoxyls), 7.18 (s, 1H, C_3-H), 7.76 (d, J=6.5Hz, 1H, C_4-H), 8.04 (s, 1H, C_8-H), 8.82 (s, 1H, C_{11}-H), 8.91 (d, J=6.5Hz, 1H, C_5-H); ^{13}C NMR see Table 1.; mass spectrum m/e (rel.int.) 351 (100, M^+), 350 (13), 336 (22), 322 (4), 308 (13), 292 (5), 277 (4), 222 (4), 151 (4). From the reaction mixture unreacted starting material (4) (173 mg, 33.6 %) could be recovered.

Preparation of 7-Hydroxy-aporphine (6) from Oxoglaucine (5): To a solution of oxoglaucine (200 mg, 0.57 mmol) in acetonitrile (50 mL) methyl iodide was added in two portions (with a 2 h delay) and the reaction mixture was kept at 80 °C for 5 h. The solvent was removed under reduced pressure. The residue

was dissolved in methanol (20 mL) and sodium borohydride was added to the stirred solution in small portions over a 1 h period and the reaction was monitored by TLC using dichloromethane-methanol 10:1 system. The reaction mixture was neutralized with acetic acid and the solvent was removed in vacuo. The residue was triturated with chloroform (15 mL), washed with water, dried and evaporated. The remaining material was purified by preparative TLC to supply amorphous 6 (131.4 mg, 62.1 %), $C_{21}H_{25}NO_5$; ^{1}H NMR ($CDCl_3$) δ 2.62 (s, 3H, NCH_3), 3.25 (d, J=2.6Hz, 1H, C_{6a}-H), 3.68, 3.77, 3.82 and 3.84 (4 x s, 4 x 3H, methoxyls), 4.76 (d, J=2.6Hz, 1H, C_7-H), 6.62 (s, 1H, C_3-H), 6.96 (s, 1H, C_8-H), 8.21 (s, 1H, C_{11}-H); ^{13}C NMR see Table 1.; mass spectrum m/e (rel.int.) 371 (100, M^+), 370 (26), 356 (30), 353 (36), 340 (99), 338 (20), 206 (64).

Table 1.

^{13}C NMR of 5 and 6 in $CDCl_3$

carbons	5	6
1	149.37	144.68
2	150.98	152.73
3	106.51	110.32
3a	128.88	129.04
4	123.26	28.79
5	144.17	53.11
6a	145.50	66.57$^+$
7	180.52	66.97$^+$
7a	135.00	130.77
8	110.56*	112.07^o
9	153.69	149.30*
10	156.47	148.41*
11	109.60*	112.43^o
11a	126.48	124.21
11b	118.76	116.20
11c	121.24	121.47
CH_3	-	43.37
OCH_3	60.16	60.17
OCH_3	56.04	56.24
OCH_3	55.73	55.99
OCH_3	55.73	55.89

The values signed with identical symbols are interchangeable

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12. Formylation of N-norlaudanine (1a) hydrochloride with chloral in dichloromethane solution in the presence of triethylamine gave 1b, $C_{20}H_{23}NO_5$; mp 194-196 °C (EtOAc); IR (KBr) 1665 cm^{-1} (N-C=O); ^1H NMR ($CDCl_3$+DMSO-d_6)[13] δ 3.65, 3.82 and 3.84 (3 x s, 3 x 3H, methoxyls), 6.35-6.85 (m, 5H, aromatic protons), 7.71 and 8.02 (s, s, 1H, CHO); mass spectrum m/e (rel.int.) 357 (0.6, M^+), 355 (0.7), 340 (0.6), 328 (0.5), 326 (0.5), 254 (0.7), 221 (21), 220 (100), 192 (8), 177 (2), 176 (4), 148 (2).
13. The characteristic formyl and aromatic proton singulets appear as doubled signals with different intensities in the ^1H NMR spectrum due to the hindered rotation of the N-formyl group[14].
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