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SYNTHESIS OF *N*-TRIFLUOROACETYL-2-HYDROXYNORAPORPHINE BY RADICAL REACTION OF *p*-QUINOL ACETATE OF *N*-TRIFLUORO-ACETYL-1-(2-IODOVERATRYL)METHYL-1, 2, 3, 4-TETRAHYDRO-7-METHOXYISOQUINOLIN-6-OL †

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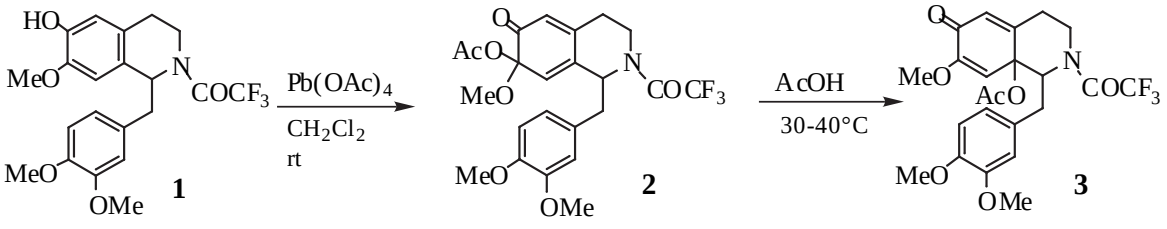
Abstract — Radical reaction of *p*-quinol acetate (**8b**) of *N*-trifluroroacetyl-1-(2-iodoveratryl)methyl-1, 2, 3, 4-tetrahydro-7-methoxyisoquinolin-6-ol (**7b**) using tributyltin hydride gave the corresponding noraporphine (**9**)(45 %), while that of the bromo congener (**8a**) failed. Similar reaction of **8b** using tris(trimethylsilyl)silane improved the yield (75 %) of **9**.

Previously,[2] we reported that lead tetraacetate (LTA) oxidation of *N*-trifluoroacetyl-1-veratrylmethyl-tetrahydro-7-methoxyisoquinolin-6-ol (**1**) in CH_2Cl_2 gives rise to the corresponding *o*-quinol acetate (*o*-

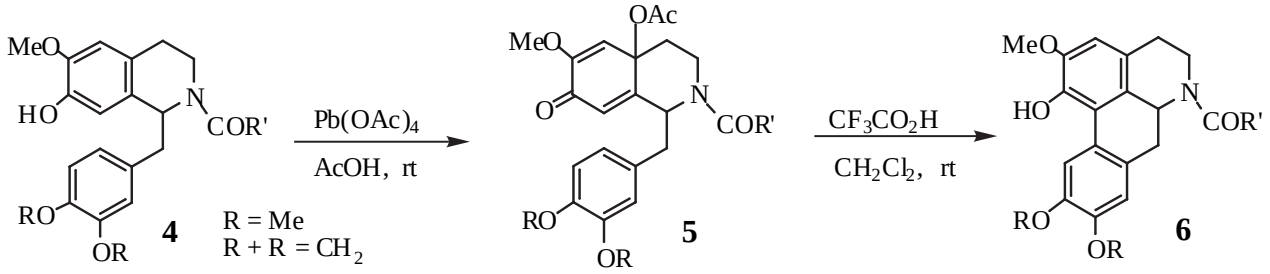


Scheme 1

† Dedicated to Dr. Pierre Potier on the occasion of his 70th birthday.

QA)(**2**) in good yield, reaction of which with AcOH at 30-40°C produces *p*-QA (**3**)(Scheme 1).

Although treatment[3] of *p*-QAs (**5**) of *N*-acyltetrahydroisoquinolin-7-ols (**4**) with CF_3CO_2H in CH_2Cl_2

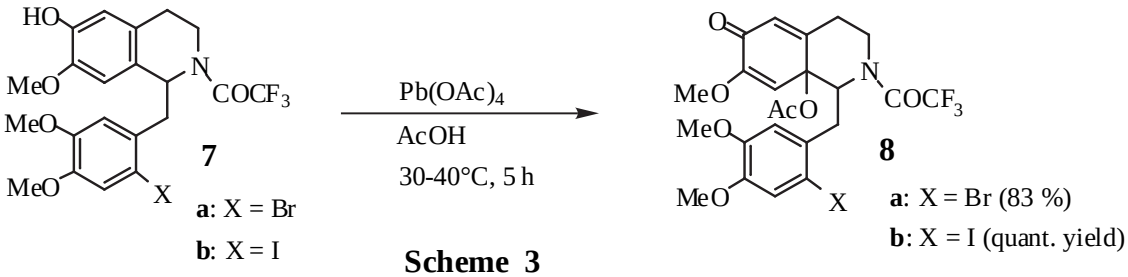


Scheme 2

afforded the corresponding 1-hydroxynoraporphines (**6**)(Scheme 2), attempts[4] to synthesize 2-hydroxynoraporphine by reaction of **2** or **3** under a variety of acidic conditions were unfruitful, in which the reaction gave only undetermined complex mixtures along with reversed **1**.

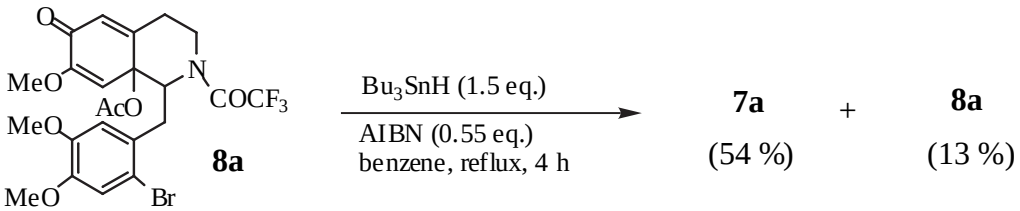
Therefore, in order to synthesize 2-hydroxynoraporphine from *p*-QA (**8**) and to examine its reactivity, radical reaction of 1-(2-bromo- and iodoveratryl)methyl *p*-QAs (**8**)[5] was performed. This paper deals with successful formation of *N*-trifluroacetyl-2-hydroxynoraporphine (**9**) from 1-(2-iodoveratryl)methyl *p*-QA (**8b**).

LTA oxidation of *N*-trifluoroacetyl-1-(2-bromo- and iodoveratryl)methyltetrahydro-7-methoxyisoquinolin-6-ols (**7**)(**7a**,[6, 7] mp 157-158°C; **7b**,[6, 9] mp 190-191°C) in AcOH at 30-40°C for 5 h furnished the corresponding 1-(2-haloveratryl)methyl *p*-QAs (**8**)(**8a**,[6] mp 162-163°C; **8b**,[6] mp 175-176°C) in good yield (Scheme 3).



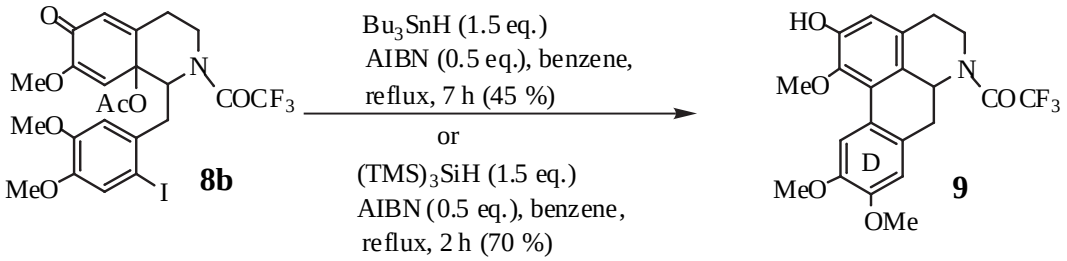
Scheme 3

Unexpectedly, reaction of **8a** in boiling benzene (1 mmol %) containing AIBN (0.55 eq.) and tributyltin hydride (1.5 eq.) for 4 h and purification on preparative TLC (SiO_2; developing solvent: benzene : EtOAc = 1 : 1) gave reversed **7a** (54 %) and untact **8a** (13 %), respectively (Scheme 4).



Scheme 4

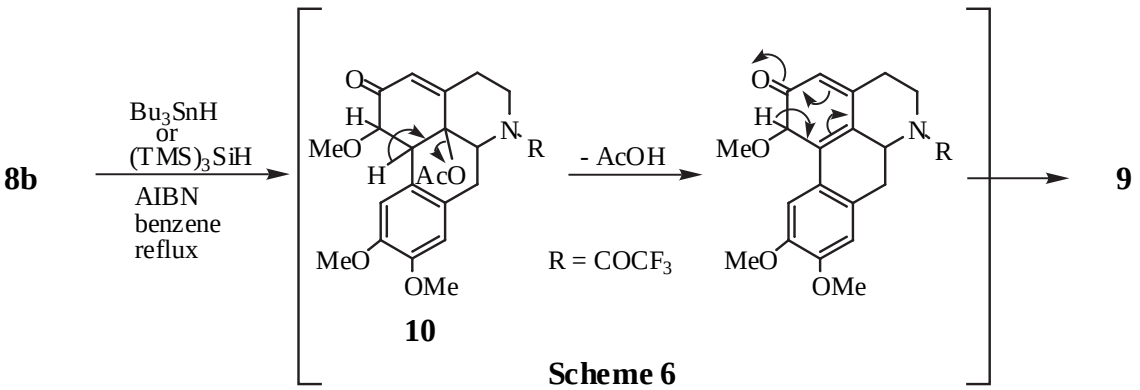
However, similar reaction[10] of **8b** followed by purification gave desired *N*-trifluroacetyl-2-hydroxy-noraporphine (**9**) in 45 % yield, in which starting material (**8b**) and reversed **7b** were not determined (Scheme 5). Furthermore, an analogous reaction of **8b** in boiling benzene (1 mmol %) using $(TMS)_3SiH$ (1.5 eq.) in place of Bu_3SnH afforded **9** in 70 % yield (Scheme 5).



Scheme 5

The difference in reaction would be attributable to the reactivity[11] of aryl bromide and iodide in radical reaction. Also this assumption is supported by formation of reversed **7a**, which would be produced by reductoin of a carbonyl group in **8a** with Bu_3SnH followed by elimination of AcOH.

A pathway on formation of **9** is considered to proceed *via* an intermediate (**10**)(Scheme 6), although a pathway *via* direct cyclization of **7b**, which might be formed from **8b** by reaction similar to that described for **8a**, could not be excluded completely. Because reaction of **7b** with AIBN (0.5 eq.) and Bu_3SnH (1.5 eq.) in boiling benzene (1 mmol %) for 7 h gave **9** (11 %) together with **1** (24 %).



Scheme 6

In conclusion, synthesis of noraporphine (**9**) by radical reaction of 1-(2-iodoveratryl)methyl *p*-QA (**8b**) was accomplished successfully. Thus, the reaction promises the preparation of noraporphine bearing no substituent(s) in D ring, which has been not yet synthesized by acid treatment of *p*- QA.

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REFERENCES AND NOTES

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5. Since *p*-QA was more stable than *o*-QA, the former was used in the reaction.
6. All new compounds described in this text gave satisfactory ^{1}H- and ^{13}C-NMR, and HRMS spectral data.
7. Starting material (**7a**) was prepared by *N*-trifluoroacetylation (trifluoroacetic anhydride, K_2CO_3, CH_2Cl_2; K_2CO_3, MeOH) of 1-(2-bromoveratryl)methyltetrahydroisoquinolin-6-ol[8] from benzyloxyphenethylamine and 2-bromohomoveratric acid in a usual manner (Bischler-Napieralski reaction, $NaBH_4$ reduction, and debenzylation with conc. HCl).
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9. Starting material (**7b**) was prepared from benzyloxyphenethylamine and 2-iodohomoveratric acid in a manner similar to that noted for **7a**.
10. A solution of **8b** (50 mg, 0.08 mmol) in benzene (8 mL) containing AIBN (6.7 mg, 0.04 mmol) and Bu_3SnH (35.8 mg, 0.12 mmol) was refluxed for 7 h. A residue remained on removal of the solvent *in vacuo* was dissolved in MeCN. The MeCN solution was washed with hexane. Usual work-up of the MeCN layer gave an oily product, which was purified on preparative TLC (SiO_2; developing solvent: benzene : EtOAc = 1 : 1) to produce **9** (15.5 mg, 45 %, mp 177-178°C); ^{1}H-NMR (270 MHz)($CDCl_3$) δ: 3.61 (3H, s), 3.93 (6H, s), 5.90, 6.72, 6.80, and 7.99 (each 1H, s); ^{13}C-NMR (62.5 MHz)($CDCl_3$) δ: 30.1, 32.8, 41.4, 52.6, 55.8, 56.1, 60.2, 110.8, 111.5, 113.2, 123.3, 123.4, 126.8, 128.9, 129.7, 142.8, 148.0, 148.6, 148.8, and 156.3; EI MS *m/z* (M^+): 423; HRMS *m/z* calcd for $C_{21}H_{20}NO_5F_3$ (M^+) 423.1293, found: 423.1302.
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