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SHORT-CUT IN THE POMERANZ-FRITSCH SYNTHESIS OF 1-BENZYL-ISOQUINOLINES; SHORT AND EFFICIENT SYNTHESES OF NORRETICULINE DERIVATIVES AND OF PAPAVERINE

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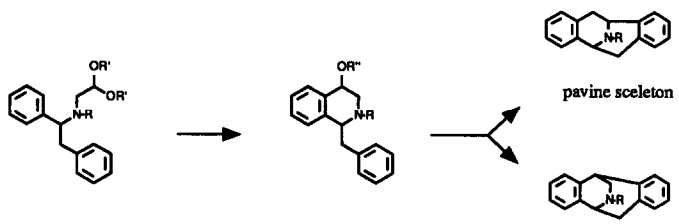
Summary: A new methodology for the Pomeranz-Fritsch synthesis of 1-benzyl-1,2-dihydroisoquinolines avoiding pavine or isopavine troubles, has been developed. These intermediates could be reduced to their 1,2,3,4-tetrahydro congeners or aromatized to give isoquinolines, as it was demonstrated by the synthesis of some norreticuline derivatives **4 - 7** and of papaverine **8.**

The Pomeranz-Fritsch cyclization is one of the major methodologies for the synthesis of isoquinolines.[1] Unfortunately, the synthesis of pharmacologically important 1-benzyl-1,2,3,4-tetrahydroisoquinolines on this route is not practicable on a preparative scale. Further reaction of the Pomeranz-Fritsch intermediates, the corresponding 4-hydroxy-isoquinolines, normally gives pavines and isopavines[2] (scheme 1). These severe side reactions can be avoided by N-acylation making the reaction feasible.[3] However, as many of the naturally occurring isoquinoline alkaloids carry an alkyl group at the ring nitrogen, this is an indirect route, which requires additional steps. Now we have found an interesting short-cut in these series.

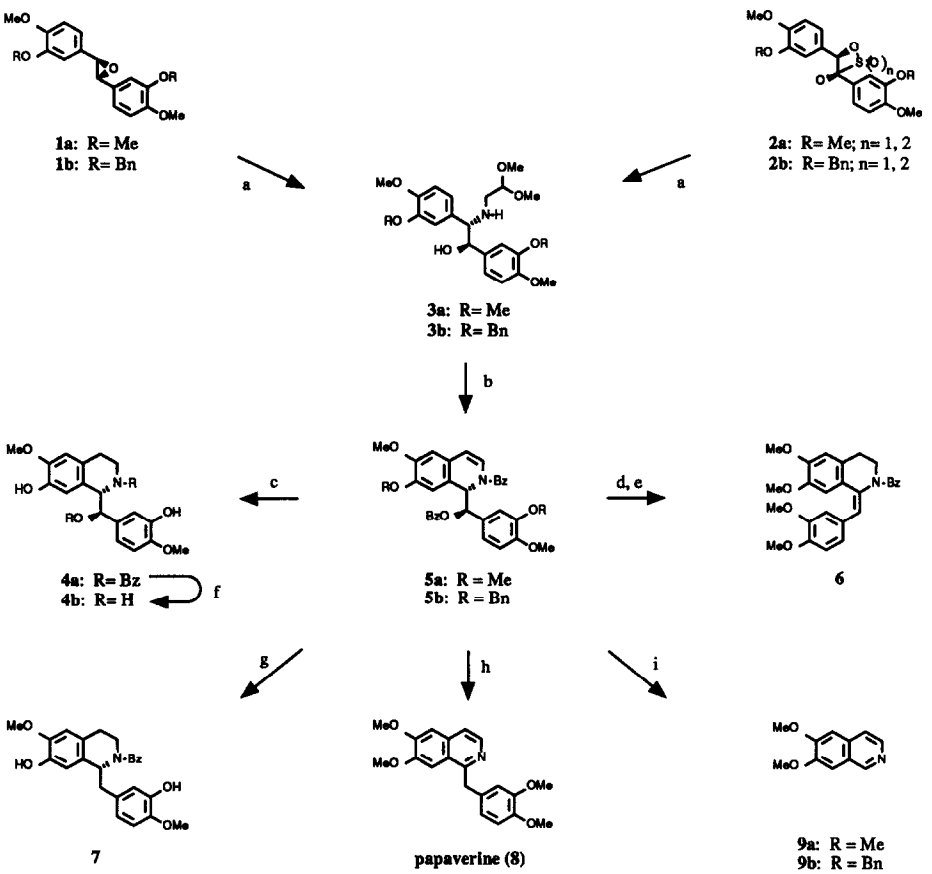
Scheme 1



pavine sceleton

isopavine sceleton

On our way to the total synthesis of morphine alkaloids we have recently developed a short and efficient route for the synthesis of isoquinolines,[4] starting from either racemic or enantiomeric stilbene oxides **1a,b**[5] or epoxide analogues **2a,b.**[6] Aminolysis of these epoxides (**1a,b**) or cyclic sulfates (**2a,b**) with aminoacetaldehyde dimethylacetal proceeded smoothly to give the aminoalcohols **3a,b** in high yield and high stereospecifity[4,7a,7b] (scheme 2). In order to protect both the alcohol and the amino function we used an excess of benzoyl chloride (6 eq.) and pyridine (6 eq.). To our surprise the reaction ended up with the 1,2-dihydroisoquinoline derivatives **5a,b.**[7b,8] Thus, bis-protection, cyclization and elimination were accomplished in a single step. As we assume, the result of this reaction may be caused by the presence of pyridine hydrochloride, which may be responsible for the hydrolysis of the acetal, and of benzoyl chloride, which facilitates the elimination during the work-up procedure. These 1,2-dihydroisoquinolines **5a,b,**[7b] which are now available on this exceptional short route, are precious intermediates in the synthesis of 1,2,3,4-tetrahydroisoquinolines and of aromatized isoquinolines.



Scheme 2

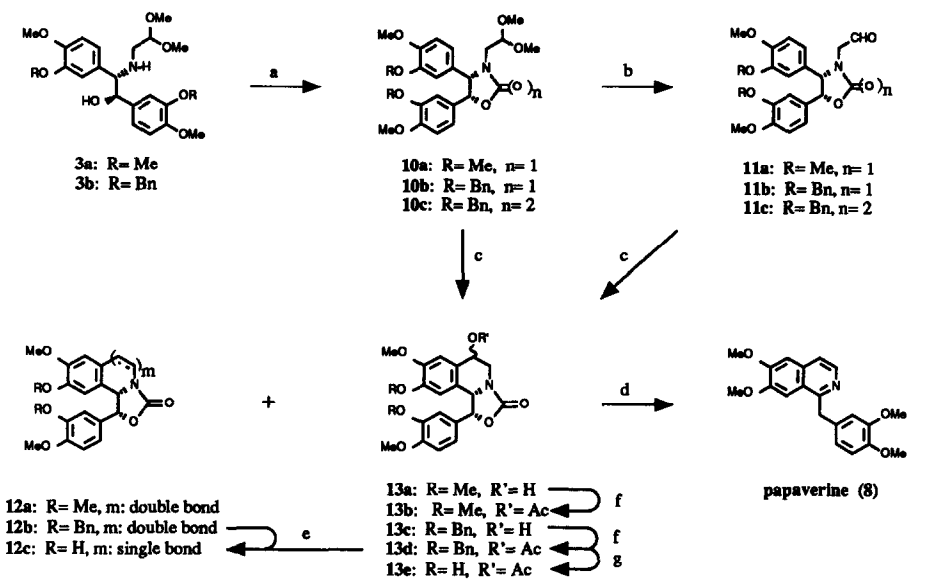
Reagents: (a) 5eq. aminoacetaldehyde dimethylacetal, CH_2Cl_2, n-butanol, r.t. to 140°C, 2h, 78%, m.p.= 117°C (methanol); (b) 6eq. benzoyl chloride, 6eq. pyridine, CH_2Cl_2, 59%; (c) cat. Pd(10%)/C, H_2(110atm), iso-propanol/water (3:2), 70°C, 18h, 78%; (d) cat. Pd(10%)/C, H_2(7atm), THF, r.t., 88%; (e) $CuSO_4$ on SiO_2, xylene, reflux, 5h; (f) HCl_g in ethanol, 90°C, 8h, 61%; (g) cat. Pd(10%)/C, H_2(85atm), iso-propanol/conc. HCl (3:2), 70°C, 18h; (h) KOH/N_2H_4, ethyleneglycol, 160°C, 90min., 56% [(8)/(9) = 1:1]; (i) NaOMe, methanol, r.t.;

Thus, catalytic hydrogenation of **5b** followed by acidic hydrolysis afforded α-hydroxy-norreticuline **4b**,[7b] which has attracted both synthetical and pharmacological interest.[9] Under enforced conditions, hydrogenation proceeded to give mixtures (1:1) of N-benzoyl-norreticuline **7** and its α-benzoyloxy congener **4a**. Investigations to push the hydrogenation towards completion are currently under way. The analysis of the product mixture was complicated due to the atropisomeric behaviour of these N-acylated derivatives.[7c]

By starting from optically active epoxides **1a,b** or analoga **2a,b** it should be possible to obtain optically active intermediates **3a,b** and target compounds **4a,b** , **5a,b** , **7**.[4] An alternate way for the introduction of asymmetry was demonstrated by the synthesis of the "Noyori-type" isoquinoline *E*-**6**, simply obtained by elimination of benzoic acid.[10] After photochemical isomerization to the Z-isomer,[11a] this compound should give access to the enantioselective Noyori synthesis (95% ee) via asymmetric hydrogenation on Ru/BINAP catalysts.[11b]

Further interesting targets in the surroundings of the Pomeranz-Fritsch intermediates **5a,b** are aromatic isoquinolines like papaverine (**8**), for instance. For the purpose of synthesizing papaverine, elimination of benzoic acid and removal of the N-benzoyl protecting group were necessary. Because hydrolysis under various alkaline or acidic conditions caused fragmentation and aromatization ended up with isoquinoline **9**, reductive removal of the N-benzoyl group was aspired. Thus Wolff-Kishner reduction afforded a mixture (1:1) of papaverine (**8**) and fragmentation product **9**. As the yield of this papaverine synthesis, which is, by the way, the shortest ever been described,[12] remained rather low after several optimizations, an alternate approach was developed.

In a straightforward synthesis, which is outlined in scheme 3, more easily removable N-protecting groups were introduced. Pomeranz-Fritsch cyclizations of these intermediates (**10a-c**),[7b] however, required stronger conditions than usually,[4] probably due to ring strain in the formation of the tricycles **12** and **13**. As a consequence of these harsh conditions mixtures of dihydro- and tetrahydoisoquinolines **12a/13a** and **12b/13c** were obtained besides some hydrolytic by-products. Employing milder conditions the cyclization stopped at the aldehyde intermediates **11a-c**. Acylation of the Pomeranz-Fritsch mixture **12a/13a** then gave the papaverine precursors **12a/13b**. Finally, simultaneous elimination of acetic acid and of CO_2 under acidic conditions led to the target compound **8**. Hydrogenation of the Pomeranz-Fritsch mixture **12b/13c** afforded interesting bridged, conformatively rigid norreticuline derivatives **12c**[7b] and **13e**.[13]



Scheme 3

Reagents: (a) Me_2CO, NaOMe, toluene, reflux, 6h, 91%; (b) HCl_{aq}/acetone 4:6, 0°C to r.t.; (c) HCl_{aq}/acetone 4:6, 0°C to 40°C, tlc-control, 63%; (d) p-TosOH(cat), toluene, reflux, 5h; (e) cat. Pd(10%)/C, H_2(10atm), methanol, 40°C, 2h, 68%; (f) pyridine/Ac_2O 1:1, r.t., 87%; (g) cat. Pd(10%)/C, H_2(1atm), methanol, r.t., 2h, tlc-control, 75%;

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7. (a) aminolysis of the epoxides proceeded stereospecifically, erythro-aminoalcohols; (b) ^{1}H NMR spectra (300MHz, $CDCl_3$, TMS): **3b:** δ 2.49 (m, 2H, $NCH_2CH(OCH_3)_2$), 3.21, 3.23 (2s, 6H, $NCH_2CH(OCH_3)_2$), 3.63 (d, 1H, H-2, $J_{1,2}$= 6.0Hz, erythro), 3.85 (s, 6H, Ar-OCH_3), 4.30 (t, 1H, $NCH_2CH(OCH_3)_2$), 4.60 (d, 1H, $J_{1,2}$= 6.0Hz, erythro), 4.95, 5.03 (2d, 2H, OCH_2Ph, J= 10.5Hz), 5.05 (s, 2H, OCH_2Ph), 6.6-6.9 (m, 6H, Ar), 7.25-7.5 (m, 10H, OCH_2Ph); **4b:** δ 2.5-3.8 (m, 4H, H-3, H-4), 3.80, 3.87 (2s, 6H, Ar-OCH_3), 3.89 (d, 1H, H-1, $J_{1,\alpha}$= 6.5Hz), 4.39 (d, 1H, H-α, $J_{1,\alpha}$= 6.5Hz), 5.87, 6.51 (2s, 2H, H-5, H-8), 6.61, 6.77 (2d, 2H, Ar, J= 8.0Hz), 6.86 (sb, 1H, Ar); **5b:** δ 3.88 (2s, 6H, Ar-OCH_3), 4.63, 4.73 (2d, 2H, OCH_2Ph, J= 11.5Hz), 5.08, 5.19 (2d, 2H, OCH_2Ph, J= 12.0Hz), 5.61 (d, 1H, H-4, $J_{3,4}$= 8.0Hz), 6.00 (d, 1H, H-1, J= 5.0Hz), 6.15 (d, 1H, H-3, $J_{3,4}$= 8.0Hz), 6.22 (s, 1H, H-5 or H-8), 6.33 (d, 1H, H-α, J= 5.0Hz), 6.65 (s, 1H, H-5 or H-8), 6.85 (d, 1H, Ar), 6.93 (d, 1H, Ar), 6.96 (s, 1H, Ar), 7.15-7.6 (m, 18H, Bn and Bz), 7.92 (d, 2H, Bz); **10b:** δ 2.61 (dd, 1H, $NCH_2CH(OCH_3)_2$, J= 14.5Hz, 6.5Hz), 3.28, 3.29 (2s, 6H, $NCH_2CH(OCH_3)_2$), 3.65 (dd, 1H, $NCH_2CH(OCH_3)_2$,J= 14.5Hz, 4.0Hz), 3.74 (2s, 6H, Ar-OCH_3), 4.47 (dd, 1H, $NCH_2CH(OCH_3)_2$, J= 6.2Hz, 4.5Hz), 4.78, 4.87 (2d, 2H, OCH_2Ph, J= 12.0Hz), 4.85 (s, 2H, OCH_2Ph), 4.99 (d, 1H, Ar-CH-N, J= 8.0Hz), 5.65 (d, 1H, Ar-CH-O, J= 8.0Hz), 6.22 (d, 1H, J= 2.0Hz), 6.31 (dd, 1H, J= 8.5Hz, 2.0Hz), 6.42 (d, 1H, J= 1.7Hz), 6.47 (dd, 1H, J= 9.5Hz, 1.7Hz), 6.56 (d, 1H, J= 1.0Hz), 6.58 (d, 1H, J= 8.5Hz), 7.2-7.45 (m, 19H, OCH_2Ph); **12c:** δ 2.55 (dd, 1H, J= 16Hz, 3.5Hz), 2.8-3.2 (m, 2H), 3.79 (2s, 6H, Ar-OCH_3), 4.18 (ddd, 1H, J= 12Hz, 6Hz, 2Hz), 5.28 (d, 1H, J= 8.5Hz), 5.4, 5.6 (2sb, 2H, OH), 6.71 (d, 1H, ArCH-O, J= 8.5Hz), 6.17, 6.46 (2s, 2H, H-5, H-8), 6.61 (m, 3H, Ar); (c) ^{1}H NMR spectra of N-benzoylated compounds **4a** and **7** showed the typical atropisomeric behaviour of N-acyl-1-benzyl-1,2,3,4-tetrahydroisoquinolines;
8. typical procedure: 5.0g (8.7mmol) **3b**, dissolved in dichloromethane (30ml), 6.2ml (50mmol) benzoyl chloride and 4.25ml (50mmol) pyridine, was stirred at r.t. overnight. The reaction mixture was evaporated (bath temperature 60°C, vacuum); this evaporation was repeated twice with 30ml toluene. Finally the residue, dissolved in dichloromethane, was washed twice with water and evaporated. The product was purified by filtration over silica gel (dichloromethane/methanol 99:1).
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