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Facile Synthesis of 7-Hydroxy -1- (2-Bromobenzyl) -N- Methyl Tetrahydroisoquinolines via BF_3 Complexation Lithiation Protocol- Precursors to Dibenzopyrrocoline Alkaloids

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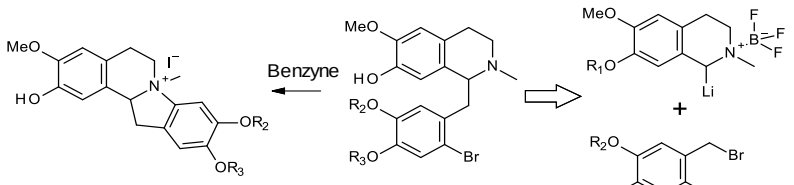
***Abstract*—** Appropriately substituted N-methyl tetrahydroisoquinolines where functionalized via BF_3 complexation and lithiation technique to access substituted 7-hydroxy -1(2-bromobenzyl -N- methyl tetrahydroisoquinolines **3a** & **3b**; precursors to dibenzopyrrocoline alkaloids, (±) cryptaustoline and (±) cryptowoline.



***Keywords*—** Benzyl tetrahydroisoquinolines; BF_3 complex; Dibenzopyrrocolines; α-Lithiation; Tertiary amine

I. INTRODUCTION

Dibenzopyrrocoline alkaloids form a part of isoquinoline alkaloid family and have been studied for antitumour and antileukemic activities as well as tubulin polymerization inhibitory properties [1]. Cryptowoline and Cryptaustoline are the two naturally occurring alkaloids which possess a 5, 6, 12,12a-tetrahydro-indolo [2,1-a] isoquinoline skeleton (Fig.1) and are reported to cause neurological paralysis by acting as respiratory poison [2].

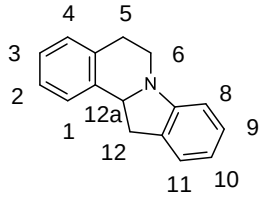


Figure 1

Among several approaches to synthesize dibenzopyrrocolines [3] and tetrahydrodibenzopyrrocolines [4a,4b] benzyne mediated cyclisation of phenolic benzyl isoquinoline precursors **3a** and **3b** are known to give (±) cryptaustoline [4c] and (±) cryptowoline [4d] respectively as the major products. Also, photocyclisation of **3a** and **3b** is known to generate aporphine alkaloids (±) thaliporphine and (±) domesticine [5]. Lately, Braslow et al. [6] have observed aporphine formation from tetrahydroisoquinolines with basic nitrogen (i.e., NH or NMe), though in low yield, on photo stimulation in liquid NH_3 and ^{t}-BuOK. Apart from the synthetic interest, precursor, such as, **3a**, has been used in radiotracer study and is reported to exhibit selective dopamine D-1 receptor antagonist activity [7]. It was, therefore, of interest to study the elaboration of BF_3 complexed tertiary amines **1** to benzyl isoquinolines **3** via C-1 (sp^3) C-H deprotonation protocol using s-BuLi as the base (**scheme-1**), a technique [8] earlier established in

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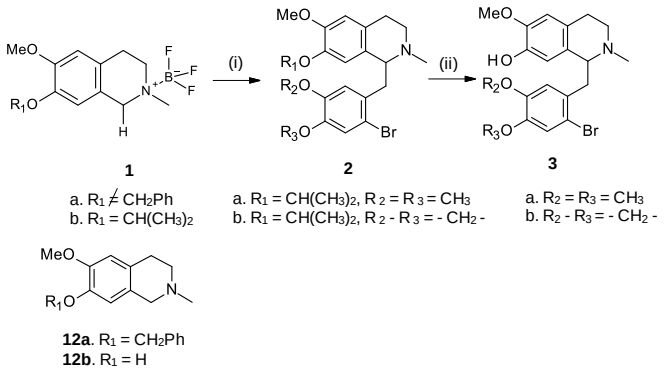
our group to access aporphine, phthalide isoquinoline and spiro alkaloids [9].

Scheme – 1

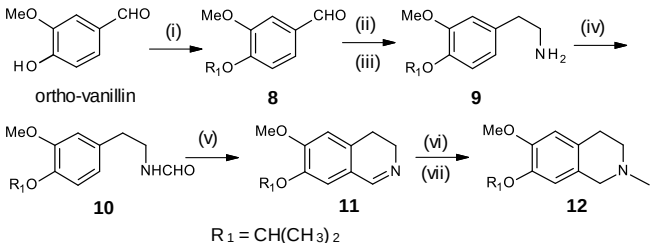


Reagents and conditions: (i) s-BuLi (1.4 N sol in pentane, 2.2 equiv.), - 78°C,1 h, 7a / 7b (2.2 equiv.), - 78°C (0.5 h) to - 40°C / H_2O/H^+. (ii) AcOH / 47% HBr, 80-90°C, 1 h.

II. RESULTS AND DISCUSSION

The amine complex **1a**, obtained as a white suspension by treating an ice cold solution of amine **12a** in anhydrous THF with 1.1 equivalent of BF_3 etherate, on exposure to 2.2 equivalents of s-BuLi at -78^{0}C for 1h resulted in a red colored solution. Subsequent treatment with **7a** or **7b** at -78^{0}C for 0.5 h and warming the reaction mass to -40^{0}C afforded, after acid base work-up, a crude reaction mass. Analysis of the crude reaction mass by thin layer chromatography indicated it to be mixture of products along with some unreacted amine **12a**. Attempted purification of the crude reaction mass by column chromatography did not result in the expected 1-benzyl tetrahydroisoquinolines; instead debenzylated amine **12b** was recovered in 60% and 52 % yield respectively [10]. Although debenzylation of phenolic OH in presence of Lewis acids at ambient and higher temperature is reported [11], the same is not expected in our case as complexation of amine **12a** with BF_3 etherate was carried out at 0^{0}C and subsequent deprotonation reaction at -78^{0}C. However, in a separate experiment, the above generated BF_3 complexed amine **1a** was stirred at 0-5^{0}C for 1.5 h and quenched with H_2O; only to liberate starting amine **12b** in near quantitative yield (97%) after simple work-up. This clearly indicates that benzyl protection of OH group in **1a** is not compatible under strongly basic reaction conditions owing to the introduction of another competitive deprotonation site. Consequently, isopropyl group was introduced to protect hydroxyl function and the required tertiary amine **12** [13] was prepared starting from ortho-vanillin in a series of steps analogous to the known series of steps to prepare amine **12a [**14] (**scheme-2**).

Scheme – 2



Reagents and conditions: (i) Isopropyl bromide (1.8 equiv.), K_2CO_3 (1.2 equiv.), DMF, 100°C, 3 h, yield **8** (17.2 g, 88.6%), oil, bp 118-120°C/0.5 mm. (ii) NH_4OAc (1.5 equiv.), CH_3NO_2 (1.75 equiv.), glacial AcOH (30 ml),100°C, 6.5 h, yield **8a** (11.6 g, 61%) yellow cryst., mp (EtOAc/pet-ether) 81-83°C. (iii) Anhyd. THF (250 ml), LAH (2.66 equiv.), reflux, 0.5 h, yield **9** (9.6 g, 60%), oil, bp 100°C/0.5 mm.(iv) $CHCO_2C_2H_5$, (10.6 equiv.), yield **10** (7 g, 86%), oil bp 158-160°C/0.5 mm. (v) 10 (7.0 g, 29.5 mmol), $POCl_3$ (9.75 equiv.), anhyd. benzene, 75 -80°C, 2.5 h, yield **11** (3.6 g, 55.5%), viscous oil. (vi) CH_3I (1.02 equiv.), anhyd. ether, ambient temp., 24 h, yield **11a** (4.5 g, 90.5%), yellow cryst., mp (ethanol) 195 - 196°C. (vii) $NaBH_4$ (1.5 equiv), MeOH/H_2O (5:1, 25 ml), yield **12** (1.96 g, 76%), colorless oil, bp160°C/0.5 mm, picrate (EtOH) mp, 142°C.

A similar treatment of amine **12** with BF_3 etherate in anhydrous THF resulted in amine BF_3 complex **1b** and exposing it to 2.2 equivalents of s-BuLi at -78^{o}C for 1 h followed by reaction with **7b** afforded a crude reaction mass after acid base workup. Purification of the crude by column chromatography resulted in the isolation of the desired benzyl tetrahydroisoquinoline **2b** as a solid in 65% yield, m. p. (pet-ether/benzene, 4:1) 158^{0}C. It was characterized by ^{1}H NMR, ^{13}C NMR, MS and elemental analysis [15a]. The reaction of amine BF_3 complex **1b** with **7a** under identical conditions resulted in the isolation of **2a**, after column purification as a viscous oil in 46% yield which solidified on standing, mp, (n-hexanes) 81-82^{0}C; its identification by ^{1}H NMR, ^{13}C NMR, MS and

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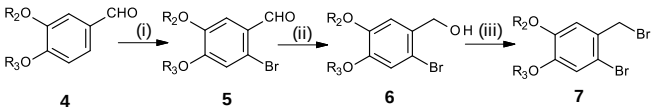
elemental analysis was in conformity with the assigned structure [15b]. The inferior yield of **2a** under identical conditions may be ascribed to the presence of two methoxy groups in **7a** rendering it less electrophilic in comparison to **7b** carrying a methylenedioxy group. A facile deprotection of 7- isopropoxyl group of **2a** & **2b** in AcOH/HBr completed the synthesis of desired benzyl isoquinoline precursors **3a** [16b] & **3b** [16a] in good yields. The required electrophiles **7a** & **7b**, used in this transformation were amenable from easily available veratraldehyde **4a** and piperonal **4b** (**scheme-3**).

Scheme – 3



a. $R_2 = R_3 = CH_3$
b. $R_2 - R_3 = -CH_2-$

Reagents and conditions: (i) AcOH (35 ml), Br_2 (1.04 equiv.), 0°C to RT 3 h, yield **5a** (53.7%), solid, mp (acetone) 147-148°C (lit [17b] 149-151°C); yield **5b** (65%), solid, mp(ethanol) 123-125°C (lit [18a] 126°C). (ii) MeOH (30 ml), $NaBH_4$ (1.14 equiv.) 0°C to RT, 1.5 h, yield **6a** (97%), solid, mp (EtOAc) 92°C (lit [17b] 88-91°C); yield **6b** (94%), solid, mp (EtOAc) 92°C (lit [18b] 88-91°C). (iii) Anhyd. ether (45 ml), PBr_3 (2.4 equiv.) 0°C to RT, 1.5 h, yield **7a** (76%), solid, mp (EtOH) 90-91°C (lit [17b] 88-91°C); **7b** (80%), solid, mp (EtOH) 92°C (lit [18b] 94°C).

III. CONCLUSION

In summary, we have extended the scope of BF_3 complexation and lithiation methodology to construct C-C bond leading to 7- hydroxy-N-methyl-1-benzyl tetrahydroisoquinolines. It clearly emerges that benzyl group protection of phenolic OH in the tertiary amine substrate **12a** is not compatible under the reaction conditions described whereas, in amine **12,** isopropyl group is well tolerated. Besides, a discrete choice of substituents may result in substituted 1-benzyl tetrahydroiso-quinolines of significant biological interest.

IV. ACKNOWLEDGEMENT

A useful discussion with Prof. Paramjit Singh on the subject matter of this communication is highly appreciated.

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[13] The amine **12** was prepared from o-vanillin and isolated as colorless oil, b.p.160^{0}C/0.8 mm, picrate (ethanol) m.p. 142^{0}C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.31-1.33 (d, 6H, -CH($C\underline{H}_3$)$_2$); 2.42 (s, 3H, -N$C\underline{H}_3$); 2.64 (t, 2H, ArC$\underline{H}_2$); 2.82 (t, 2H, -CH_2N); 3.46 (s, 2H, ArCH_2N); 3.79 (s, 3H, O$C\underline{H}_3$); 4.43 (septet, 1H, -C$\underline{H}$(CH_3)$_2$); 6.55 (s, 1H, Ar$\underline{H}$); 6.9 (s, 1H, Ar$\underline{H}$). MS, m/z (relative intensity): 235 (M^+, 52.4); 234 (45.6); 192 (47.8); 150 (100); 135 (12.1). HRMS: calculated for $C_{14}H_{21}NO_2$, m/z 235.1573. Found 235.1569.

[14] (a) T. Kametani, K. Ohkubo., "The Structure of Sendaverine and Its Total Syynthesis" *Chem. Pharm. Bull.*, 15(5), 608 - 612, **1967**. (b) The amine **12a** was prepared from o-vanillin and isolated as a solid, m. p. (EtOAc/pet-ether) 102^{0}C (lit [17a] 102-103^{0}C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.42 (s, 3H, N$C\underline{H}_3$); 2.62-2.66 (t, 2H, ArC$\underline{H}_2$-); 2.81-2.85 (t, 2H, -$CH_2C\underline{H}_2$N); 3.43 (s, 2H, ArC$\underline{H}_2$N); 3.85 (s, 3H, O$C\underline{H}_3$): 5.09 (s, 2H, O$C\underline{H}_2$Ph); 6.53 (s, 1H, C-8 Ar$\underline{H}$); 6.62 (s, 1H, C-5 Ar$\underline{H}$); 7.26-7.44 (m, 5H, Ar$\underline{H}$). Anal. Calcd, for $C_{18}H_{21}NO_2$: C, 76.32; H, 7.42; N, 4.94. Found: C, 76.58; H, 6.99; N, 4.84.

[15] (a) **General representative procedure:** compound **2a** & **2b**; Into a flame dried two-neck round bottom flask, equipped with a septum cap and a stir bar, was placed a solution of amine **12b** (0.210 g, 0.89 mmol) in anhydrous THF (10 ml) under N_2 atmosphere. The contents where cooled to 0^{0}C and BF_3 etherate (0.11 ml, 0.97 mmol, 1.1 equiv.) added, resulting in a white suspension. The contents where further cooled to -78^{0}C and s-BuLi, 1.4 N sol in n- pentane, (1.4 ml, 2.2 equiv.) added slowly. The resulting red colored solution was stirred for 1h at -78^{0}C and reacted with **7b** (0.575 g, 1.9 mmol, 2.2 equiv.) dissolved in anhyd. THF (2 ml) and continued to stir for 0.5 h at the same temperature. The reaction mixture was gradually warmed to -40^{0}C and quenched with H_2O (5 ml). The reaction contents where poured into aq. HCl 10% solution (30 ml) under stirring at 0^{0}C and extracted with EtOAc (3x10 ml). The acidic aq. phase was basified with $NaHCO_3$ and extracted with $CHCl_3$ (2x20 ml).The combined organic extract was washed with H_2O (2x15 ml), sat. brine (15 ml), dried over anhyd Na_2SO_4 (0.8 g) and filtered. The filtrate was concentrated on Rota vapor to give a crude material which on purification by column chromatography (eluent, 40% EtOAc in pet-ether) resulted in pure **2b**, solid (0.260 g, 65%), mp (pet-ether/benzene, 4:1) 158^{0}C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.24-1.28 (2xd, 6H, -OCH($C\underline{H}_3$)$_2$); 2.47 (s, 3H, N$C\underline{H}_3$); 2.54-2.61 (m, 1H), 2.78-2.94 (m, 3H), 3.09-3.16 (m, 1H), 3.22-3.29 (m, 1H) Ar$C\underline{H}_2C\underline{H}_2$N & C-1 $C\underline{H}_2$Ph; 3.81 (s, 3H, O$C\underline{H}_3$); 3.76-3.81 (t, 1H, C-1 $\underline{H}$); 4.19-4.25 (septet, 1H, -OC$\underline{H}$(CH_3)$_2$); 5.90-5.93 (dd, 2H, O$C\underline{H}_2$O,jem J=7.9, 1.36 Hz); 6.26 (s, 1H, Ar$\underline{H}$); 6.57 (s, 1H, Ar$\underline{H}$); 6.59 (s, 1H, Ar$\underline{H}$); 7.0 (s, 1H, Ar$\underline{H}$). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 22.09; 22.29; 24.54; 41.27; 42.52; 45.94; 55.94; 62.40; 71.62; 101.58; 111.93; 112.53; 114.98; 115.94; 126.63; 129.05; 132.50; 144.99; 146.78; 147.00; 148.97. MS, m/z (relative intensity): 234 (100); 192 (45.9), 177 (19.4); 150 (18.6); 149 (15.9). Anal. Calcd for $C_{26}H_{26}BrNO_4$: C, 58.93; H, 5.83; N, 3.12 Found: C, 58.79; H, 5.85; N, 3.03. (b) The amine BF_3 complex **1b** was exposed to s-BuLi (2.2 equiv.) and reacted with **7a** (2.2 equiv.) as above to give **2a** as a viscous liquid after column purification which solidified on standing, mp (n-hexanes) 81-82^{0}C. **Data for compound 2a:** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.21-1.24 (2d, 6H, -OCH($C\underline{H}_3$)$_2$); 2.51 (s, 3H, N$C\underline{H}_3$); 2.57-2.64 (m, 1H), 2.75-2.83 (m, 1H), 2.86-2.95 (m, 1H), 3.14-3.28 (m, 1H) Ar$C\underline{H}_2C\underline{H}_2$N & C-α $C\underline{H}_2$Ph; 3.72 (s, 3H, O$C\underline{H}_3$); 3.80 (s, 3H, O$C\underline{H}_3$); 3.84 (s, 3H, O$C\underline{H}_3$); 3.77-3.82 (t, 1H, C-1 $\underline{H}$); 4.11-4.19 (septet, 1H, -OC$\underline{H}$(CH_3)$_2$); 6.18 (s, 1H, Ar$\underline{H}$); 6.55 (s, 1H, Ar$\underline{H}$); 6.57 (s, 1H, Ar$\underline{H}$); 6.99 (s, 1H, Ar$\underline{H}$). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 22.07; 22.13; 25.17; 40.42; 42.64; 46.48; 55.94; 56.12; 62.65;

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63.68; 71.65; 109.76; 111.94; 114.26; 114.84; 115.32; 115.93; 126.62; 128.90; 131.11; 144.92; 147.96; 148.93. MS, m/z (relative intensity): 234 (100); 192 (30.5), 177 (14.4). Anal. Calcd for $C_{23}H_{30}BrNO_4$: C, 59.49; H, 6.51; N, 3.02 Found: C, 59.10; H, 5.98; N, 3.22.

[16] (a) **General representative procedure,** compound **3a** & **3b**: A solution of **2b** (0.150 g, 0.33 mmol) in AcOH (10 ml) and HBr (47% sol in AcOH, 1 ml) was heated for 1 h at 80-90^{0}C. The reaction mass was poured into H_2O (20 ml) at 0^{0}C, basified with liq. NH_3 and extracted with $CHCl_3$ (2x10 ml). The organic extract was dried over anhyd. Na_2SO_4, filtered and the solvent evaporated on Rota vapor to leave a brown solid. It was purified by passing through a pad of silica-gel (eluent, EtOAc, 0.5% $CHCl_3$) to give **3b,** white solid (0.098 g, 72%), mp (ethanol) 169^{0}C (lit [5d] mp 169-170^{0}C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.41 (s, 3H, NC$\underline{H}_3$); 2.47-2.61 (m, 1H), 2.78-2.95 (m, 3H), 3.0-3.07 (m, 1H), 3.23-3.31 (m, 1H) ArC$\underline{H}_2$C$\underline{H}_2$N & C-1 C$\underline{H}_2$Ph; 3.73-3.83 (t, 1H, C-1 $\underline{H}$); 3.85 (s, 3H, OC$\underline{H}_3$); 5.93 (s, 2H, OC$\underline{H}_2$O); 6.44 (s, 1H, Ar$\underline{H}$); 6.55 (s, 1H, Ar$\underline{H}$); 6.64 (s, 1H, Ar$\underline{H}$); 6.9 (s, 1H, Ar$\underline{H}$). Anal. Calcd for $C_{19}H_{20}BrNO_4$: C, 56.17; H, 4.95; N, 3.44 Found: C, 56.34; H, 4.75; N, 3.34. (b) The compound **3a** was prepared from **2a** as per the general procedure above and isolated as viscous oil, HCl salt, mp (ethanol) 140^{0}C, (lit [5d] mp 137-138^{0}C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.49 (s, 3H, NC$\underline{H}_3$); 2.55-2.65 (m, 1H), 2.81-2.97 (m, 3H), 3.02-3.21 (m, 1H), 3.27-3.35 (m, 1H); 3.74 (s, 3H, OC$\underline{H}_3$); 3.83-3.85 (1H, C-1 $\underline{H}$); 3.85 (s, 6H, 2xOC$\underline{H}_3$); 6.30 (s, 1H, Ar$\underline{H}$); 6.56 (s, 1H, Ar$\underline{H}$); 6.60 (s, 1H, Ar$\underline{H}$); 6.99 (s, 1H, Ar$\underline{H}$).

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[18] (a) W. F. Barthel, *C A.*, 53, 1621i, **1957**. (b) R. G. Naik, T. S. Wheeler., "Reactivity of the ω-halogen atom in *p*-alkoxybenzyl halides: preparation of phenylacetic acids" *J. Chem. Soc.*, 1780 - 178, **1938**.