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A process for the preparation of 1,2,3,4,8,9,10,10a-octahydro-7b*H*-cyclopenta[*b*][1,4]diazepino[6,7,1-*hi*]indole

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Abstract—A synthesis of 1,2,3,4,8,9,10,10a-octahydro-7b*H*-cyclopenta[*b*][1,4]diazepino[6,7,1-*hi*]indole is described exemplifying a new synthetic route to medicinally interesting compounds. The key step involves a cyclization of 2-(2,3,3a,8b-tetrahydrocyclopenta[*b*]indol-4(1*H*)-yl)-ethanamine with aqueous formaldehyde in the presence of trifluoroacetic acid.

1. Introduction

In collaboration with a recent medicinal chemistry program, it became necessary to develop a practical synthesis of diazepinoindolines **1**.[1] This new synthesis is exemplified by the preparation of one of the structures within this series, 1,2,3,4,8,9,10,10a-octahydro-7b*H*-cyclopenta[*b*][1,4]diazepino[6,7,1-*hi*]indole **2** (Fig. 1).

Compounds in this series were originally prepared by the route shown in Scheme 1.[1a,2] The process begins with a condensation of glycine with isatoic anhydride to provide the diazepinedione. The amides are then reduced with lithium aluminum hydride, followed by selective acetylation of the benzylic amine. The aniline is

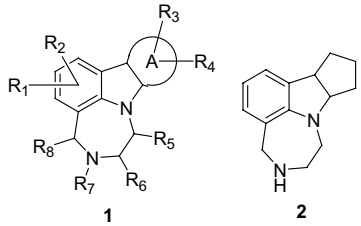
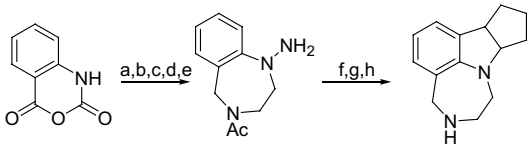


Figure 1. Structures of target compounds **1** and representative example **2**.



Scheme 1. Reagents and conditions: (a) glycine, Et_3N, EtOH, reflux; then HCl, EtOH, reflux; (b) $LiAlH_4$, THF, reflux; (c) Ac_2O, Et_3N, Et_2O, reflux; (d) $NaNO_2$, HCl, H_2O, 0 °C; (e) Zn, HOAc, <30 °C; (f) cyclopentanone, AcOH, reflux; (g) H_2, 5% Pd–C, TFA, EtOH; (h) NaOH, MeOH, reflux.

then converted to the hydrazine by standard methods. The hydrazine is subjected to Fisher indole conditions with cyclopentanone to produce the tricyclic indole. Reduction of the indole to the indoline followed by cleavage of the acetamide ultimately provides the desired compound.

In an effort to discover alternative synthetic pathways to these substrates, we chose to investigate a new synthesis involving the preparation of the indoline first and then subsequent cyclization to form the diazepino moiety (Fig. 2). By developing this new synthetic procedure, the synthesis could begin with commercially-available phenyl hydrazines, eliminating the need of preparing the hydrazine at a later stage. Additionally, this alternate route could lead to new analogs synthetically inaccessible by the original route.

Ideally, the benzodiazepine could be formed directly from an appropriately substituted substrate. In 1957,

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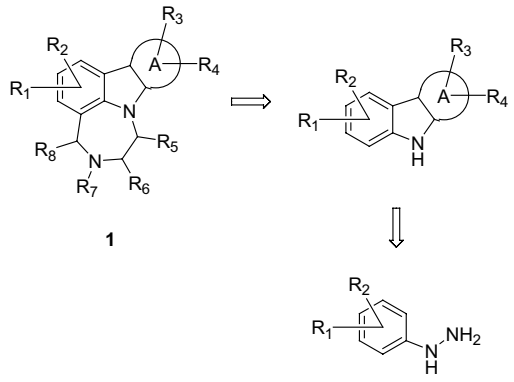


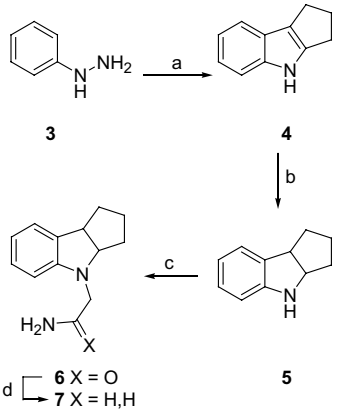
Figure 2. Retrosynthetic analysis.

Archer et al.[3] described the unexpected preparation of 1-ethyl-4-(3-tropanyl)-tetrahydro-1*H*-1,4-benzodiazepine from the treatment of *N*-ethyl-*N*-phenyl-*N*′-(3-tropanyl)-ethylenediamine under Eschweiler–Clark methylation conditions. In 1995, Zhang et al.[4] demonstrated the preparation of pyridoindolo-benzodiazepine utilizing Pictet–Spengler conditions in trifluoroacetic acid. In 1996, Stokker[5] reported the preparation of 1,4-bis(trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-1,4-benzodiazepine in 50% yield from the treatment of 2,2,2-trifluoro-*N*-phenyl-*N*-2-[(trifluoroacetyl)amino]ethylacetamide with *para*-formaldehyde in H_2SO_4/AcOH.

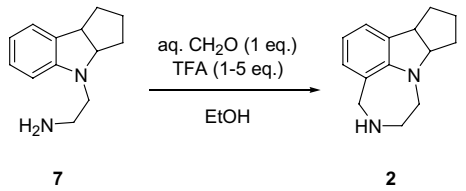
While these literature precedents illustrate the preparation of a benzodiazepine from an aliphatic, secondary amine,[2] from an aniline,[3] and from an amide,[4] none of these examples are directly applicable to our desired synthetic procedure.

2. Results

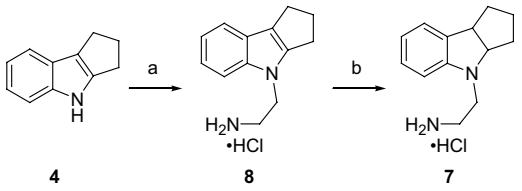
Our synthetic route began with a standard Fisher indole cyclization of phenylhydrazine (**3**) with cyclopentanone to provide 1,2,3,4-tetrahydrocyclopenta[*b*]indole (**4**) (Scheme 2). The indole **4** was hydrogenated under acidic conditions to provide indoline **5**. Initially, indoline **5** was coupled with *N*-protected glycine to provide the amide;



Scheme 2. Reagents and conditions: (a) cyclopentanone, concd H_2SO_4, H_2O; (b) H_2 (45 psi), 5% Pd–C, concd HCl, EtOH; (c) 2-chloroacetamide, EtN(*i*-Pr)$_2$, DMF, 100 °C; (d) BH_3THF, reflux.



Scheme 3.



Scheme 4. Reagents and conditions: (a) NaOH, CH_3CN, 30 min, rt; 2-chloroethylamine hydrochloride, tetrabutylammonium hydrogensulfate, reflux, overnight; (b) H_2, 5% Pd–C, EtOH.

however, all attempts to prepare the benzodiazepine skeleton from this amide either failed or provided very limited success. Indoline **5** was then coupled with 2-chloroacetamide to generate the primary amide **6**. Again, all attempts to cyclize amide **6** directly to the benzodiazepine were unsuccessful. Amide **6** was then reduced to primary amine **7** under standard conditions.

When primary amine **7** was treated with 1 equiv of aqueous formaldehyde in the presence of trifluoroacetic acid in ethanol, the desired benzodiazepine **2** was obtained in good yield (Scheme 3).

Utilizing 1 equiv of formaldehyde maximizes the yield while minimizing any undesired byproducts. Initially, we employed only 1 equiv of trifluoroacetic acid; however, this is not critical. Up to 5 equiv of trifluoroacetic acid have been utilized with success.

The overall synthesis can be further shortened by preparing amine **7** in two steps from indole **4** (Scheme 4). Following the procedure of Cuadro et al.,[6] alkylation of indole **4** with 2-chloroethylamine afforded aminoethylindole **8**, which was isolated as the hydrochloride salt. Hydrogenation of this salt provided aminoethylindoline **7**.

In summary, we have developed a new route for the preparation of benzodiazepines by the cyclization of phenylethylenediamines with formaldehyde in the presence of trifluoroacetic acid. Utilizing this key cyclization step, the synthesis of 1,2,3,4,8,9,10,10a-octahydro-7b*H*-cyclopenta[*b*][1,4]diazepino[6,7,1-*hi*]indole (**2**) was accomplished in four linear steps from readily-available starting materials. To our knowledge, this is the first example of this type of cyclization employing a primary, aliphatic amine to prepare a benzodiazepine.

3. Experimental

All reagents and solvents were obtained from commercial suppliers and used without further purification.

3.1. 1,2,3,4-Tetrahydrocyclopenta[*b*]indole (4)

Concentrated sulfuric acid (~18 M, 35 mL) was added dropwise to a mixture of phenyl hydrazine (510 mmol, 50 mL) and cyclopentanone (45 mL, 510 mmol) in water (250 mL). The resulting mixture was heated to reflux for 30 min and then allowed to cool to room temperature. The liquid was decanted from the reaction mixture leaving a red, gummy solid. A mixture of hexanes (500–600 mL) was added to the flask and the mixture was heated to reflux. The yellow hexane solution was decanted while hot from the mixture and placed in the freezer (crystallization begins immediately). A mixture of hexanes was again added to the flask and the procedure repeated two more times using a total volume of 1500 mL of hexanes. After 1 h in the freezer, the solid was collected from the flasks and dried providing the known indole[7] (410 mmol, 65 g, 80%). Anal. Calcd for $C_{11}H_{11}N$: C, 84.04; H, 7.05; N, 8.91. Found: C, 83.92; H, 7.12; N, 8.85.

3.2. 1,2,3,3a,4,8b-Hexahydrocyclopenta[*b*]indole (5)

A mixture of 1,2,3,4-tetrahydrocyclopenta[*b*]indole (11 mmol, 1.8 g), 5% Pd/C (0.5 g), and concentrated hydrochloric acid (1.2 mL) in EtOH (20 mL) was hydrogenated at 45 psi on a Parr shaker. After 3 h, the mixture was removed from the shaker and filtered through Celite. The solid bed was washed with methanol. The filtrate was concentrated. The crude oil was dissolved in 1 N HCl and washed with ether. The aqueous phase was treated with 2.5 N NaOH to pH >10 and then extracted with chloroform. The combined chloroform extracts were dried over $MgSO_4$, filtered and concentrated to give the crude indoline. The material was purified by flash column chromatography through silica gel (Biotage, elution with 10% ethyl acetate–hexanes) to give the known indoline[8] (7.6 mmol, 1.2 g, 69%) as a clear oil. Anal. Calcd for $C_{11}H_{13}N$: C, 82.97; H, 8.23; N, 8.80. Found: C, 82.61; H, 8.35; N, 8.72.

3.3. 2-(2,3,3a,8b-Tetrahydrocyclopenta[*b*]indol-4(1*H*)-yl)-acetamide (6)

To a stirred solution of 1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole (130 mmol, 21 g) in DMF (50 mL) was added diisopropylethylamine (400 mmol, 70 mL) followed by 2-chloroacetamide (270 mmol, 25 g). The reaction mixture was heated to 100 °C for 18 h. The reaction was concentrated and then diluted with ethyl acetate and water. The phases were separated and the organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude material was purified by flash column chromatography through silica gel (elution with 60% ethyl acetate–hexanes) to afford a yellow solid (90 mmol, 20 g, 69%). Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.45; H, 7.57; N, 12.64. MS ((+)APCI, *m/e* (%)) 217 (100, $[M+H]^+$). IR (solid ATR, cm^{-1}) 3450, 2930, 2870, 1680, 1480, 1150, 740. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.20 (s, 1H), 7.05 (s, 1H), 6.90 (m, 2H), 6.48 (dt, $J = 7.3$, 0.7 Hz, 1H), 6.18 (d, $J = 7.8$ Hz, 1H), 4.22 (m, 1H), 3.70, 3.58 (ABq, $J_{AB} = 17.1$ Hz, 2H), 3.64 (m, 1H), 1.90 (m, 1H), 1.78 (m, 1H), 1.56 (m, 3H), 1.40 (m, 1H).

3.4. 2-(2,3,3a,8b-Tetrahydrocyclopenta[*b*]indol-4(1*H*)-yl)-ethylamine (7)

3.4.1. From acetamide 6. 2-(2,3,3a,8b-Tetrahydrocyclopenta[*b*]indol-4(1*H*)-yl)acetamide (90 mmol, 20 g) was dissolved in 1 M BH_3·THF (200 mL) and heated to reflux for 18 h. The reaction mixture was allowed to cool to room temperature and then quenched slowly with methanol. The solution was concentrated, dissolved in methanol, and again concentrated. The resulting oil was diluted with ether and extracted twice with 1 N HCl. The aqueous phase was treated with 2.5 N NaOH to pH >10 and extracted with chloroform. The combined chloroform extracts were dried over $MgSO_4$, filtered, and concentrated to provide a yellow oil.

3.4.2. From aminoethylindole 8. A mixture of 2-(2,3-dihydro-1*H*-cyclopenta[*b*]indol-4-yl)ethylamine hydrochloride (5.1 mmol, 1.2 g) and 5% Pd/C (0.5 g) in EtOH (20 mL) was hydrogenated at 45 psi on a Parr shaker overnight. The mixture was removed from the shaker and filtered through Celite. The solid bed was washed thoroughly with ethanol. The filtrate was concentrated and the crude solid was purified by trituration from chloroform with hexanes to afford 1.0 g (83%) of the desired hydrochloride salt.

Anal. Calcd for $C_{13}H_{18}N_2$·HCl·0.1 mol H_2O: C, 64.91; H, 8.04; N, 11.65. Found: C, 64.78; H, 8.21; N, 11.48. MS (ES+, m/e (%)) 203.2 (100, $[M+H]^+$). HRESIMS m/z 203.1539 $(M+H)^+$ (calcd for $C_{13}H_{19}N_2$, 203.1543). IR (film ATR, cm^{-1}) 2901, 1602, 1490, 1326, 1258, 1023, 741. ^1H NMR (DMSO-d_6, 400 MHz) δ d 8.13 (s, 3H), 6.97–6.94 (m, 2H), 6.53 (dt, $J = 7.3$, 0.8 Hz, 1H), 6.45(d, $J = 7.8$ Hz, 1H), 4.17 (m, 1H), 3.68 (dt, $J = 8.8$, 1.5 Hz, 1H), 3.41 (m, 2H), 2.95 (m, 2H), 1.96 (m, 1H), 1.72 (m, 1H), 1.61 (m, 3H), 1.40 (m, 1H).

3.5. 2-(2,3-Dihydro-1*H*-cyclopenta[*b*]indol-4-yl)ethylamine (8)

Sodium hydroxide (80 mmol, 3.2 g) was added to a solution of indole **3** (22 mmol, 3.2 g) in 100 mL of CH_3CN. The resulting mixture was stirred at ambient temperature for 30 min and then 2-chloroethylamine hydrochloride (24 mmol, 2.8 g) and tetrabutylammonium hydrogensulfate (0.25 g, 0.74 mmol) were introduced. The resulting mixture was heated to reflux overnight. After cooling to rt, the mixture was concentrated. The crude product was diluted with ether and 2 N HCl. The phases were separated. The aqueous phase was treated with 2.5 N NaOH until basic and then extracted with chloroform. The extract was dried over Na_2SO_4, filtered, and concentrated. The crude indole was dissolved in a 1:1 ethanol–ether solution and then treated with 4 N HCl in dioxane. The precipitate was

collected by filtration and dried to afford the desired indole ethylamine (3.6 g, 68%) as its hydrochloride salt.

Anal. Calcd for $C_{13}H_{16}N_2$·HCl: C, 65.95; H, 7.24; N, 11.83. Found: C, 65.98; H, 7.14; N, 11.76. MS (ES+, *m/e* (%)) 201 (100, $[M+H]^+$). IR (film ATR, cm^{-1}) 2897, 2849, 1602, 1565, 1517, 1457, 1375, 1293, 1143, 942, 734. ^1H NMR (DMSO-d_6, 400 MHz) δ d 8.29 (br s, 3H), 7.49 (d, $J = 8.0$ Hz, 1H), 7.34 (d, $J = 7.4$ Hz, 1H), 7.06 (dt, $J = 7.4$, 1.2 Hz, 1H), 7.00 (dt, $J = 8.0$, 1.0 Hz, 1H), 4.36 (t, $J = 7.0$ Hz, 2H), 3.10 (t, $J = 7.0$ Hz, 2H), 2.88 (t, $J = 7.1$ Hz, 2H), 2.75 (t, $J = 7.0$ Hz, 2H), 2.48 (m, 2H).

3.6. 1,2,3,4,8,9,10,10a-Octahydro-7b*H*-cyclopenta[*b*][1,4]-diazepino[6,7,1-*hi*]indole (2)

A solution of 2-(2,3,3a,8b-tetrahydrocyclopenta[*b*]indol-4(1*H*)-yl)ethylamine (1.5 mmol, 0.30 g) was dissolved in ethanol (20 mL) at room temperature and trifluoroacetic acid (1.6 mmol, 0.12 mL) was added, followed by aqueous formaldehyde (1.5 mmol, 37%, 0.11 mL). The resulting solution was stirred overnight at ambient temperature. The solvent was then removed in vacuo. The resulting oil was dissolved in EtOAc and washed with satd aq $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated in vacuo to yield a light yellow oil. The crude product was dissolved in ether and treated with 1 equiv of 4 N HCl in dioxane. The solid was collected and dried to provide 0.31 g (84%) of the desired product as its monohydrochloride salt. Anal. Calcd for $C_{14}H_{18}N_2$·HCl: C, 67.05; H, 7.64; N, 11.17. Found: C, 67.02; H, 7.74; N, 10.85. MS (ES+, *m/e* (%)) 215.2 (100, $[M+H]^+$). IR (solid ATR, cm^{-1}) 2951, 2797, 2664, 2552, 1592, 1449, 1317, 1200, 1032, 745. ^1H NMR (DMSO-d_6, 400 MHz) δ d 9.58 (br s, 2H), 7.05 (d, $J = 7.2$ Hz, 1H), 7.00 (d, $J = 7.3$ Hz, 1H), 6.70 (dd, $J = 7.5$, 7.2 Hz, 1H), 4.28, 3.94 (ABq, $J_{AB} = 14.8$ Hz, 2H), 3.99 (m, 1H), 3.77 (dt, $J = 8.9$, 2.3 Hz, 1H), 3.50 (m, 1H), 3.40 (m, 1H), 3.10 (m, 2H), 1.95 (m, 1H), 1.80 (m, 1H), 1.70–1.52 (m, 3H), 1.42 (m, 1H).

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