Intramolecular Cyclization of 4-Aryl-1,4-dihydropyridine Acetals

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The synthesis of 4-aryl-1,4-dihydropyridines possessing a protected aldehyde functionality at the *ortho* position is described. These compounds undergo iminium ion mediated cyclization when treated with titanium tetrachloride or gaseous hydrogen chloride. Mechanistically, cyclization utilizes attack of C-3 of the dihydropyridine on the electrophilic species generated from complexation of the acetal. This methodology highlights opportunities for the construction of novel conformationally constrained dihydropyridine analogs.

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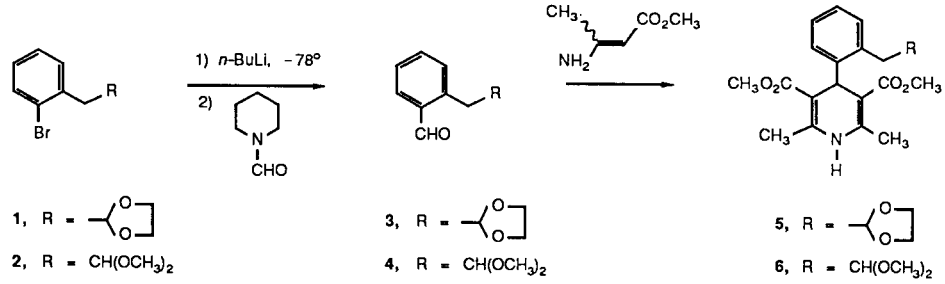
The recent resurgence in the chemistry of 4-aryl-1,4-dihydropyridines has been largely due to the remarkable therapeutic utility of this class of compounds in cardiovascular disease [1,2]. Thus, although the Hantzsch dihydropyridine synthesis [3] was reported over 100 years ago and still continues to be an efficient way of preparing compounds, significant development in both the synthesis and reactions of 1,4-dihydropyridines is apparent [4-8].

Most recently, advances in the chemistry of 4-aryl-1,4-dihydropyridines have involved the preparation of conformationally constrained analogs *via* intramolecular reactions that are mediated by iminium ions [9-13]. Of particular interest has been the observation that the 1,4-dihydropyridine ring can function as either a nucleophile or electrophile under Lewis acid conditions and that this polarity is determined by the 4-aryl substituent [11,12]. Fundamental to the intramolecular cycloaddition behavior seen with this nucleus is the reactivity of the aminocrotonate unit toward suitably positioned electrophiles. This concept had been previously identified and utilized by Aritomi [14] in preparing cyclization products from nucleophilic attack on Mannich reagents. Therefore, our specific goal in this effort was to investigate the ability of the 1,4-dihydropyridine system to express nucleophilic reactivity toward electrophiles derived from substituents on the aryl ring, as a method of synthesizing novel, bridged dihydropyridine analogs.

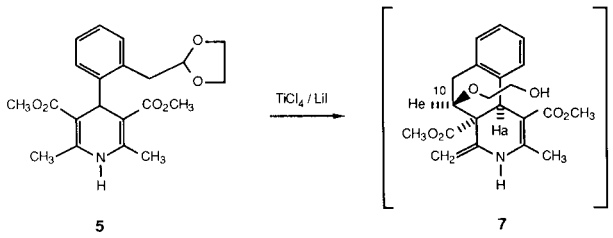
With the intent of generating electrophiles under very mild conditions, we decided to utilize intermediates derived from acid catalyzed acetal cleavage. We therefore prepared compounds **5** and **6** as shown in Scheme I. They were chosen since cyclization in the desired sense would invoke a six membered transition state between the electrophilic center and the nucleophilic C-3 of the parent. The synthesis of **6** is in direct analogy to that of **5** which is previously reported [10].

Treatment of **5** with titanium tetrachloride and lithium iodide gives **7** as previously described [10]. In similar fashion treatment of **6** with titanium chloride in methylene chloride at room temperature resulted in a rapid reaction with disappearance of starting material over 4 hours to afford the tautomeric mixture **8a/8b** in 83% yield (Scheme III). This mixture was characterized by its 360 MHz ^{1}H nmr and mass spectra. Reduction of this mixture with sodium borohydride in acetic acid provided a single product **9**, which had the configuration shown based on single crystal X-ray analysis. The methoxy group at C-10 was anti

Scheme I



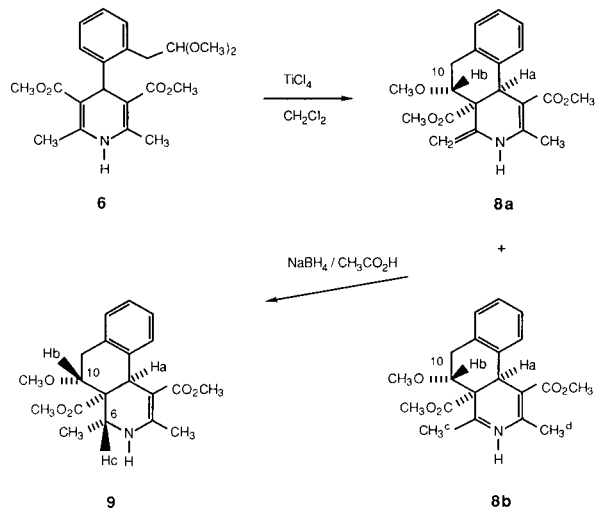
Scheme II



5 7

to the tetrahydropyridine ring and the methyl group at C-6 was α from attack by hydride from the β-face of **8a/8b**.

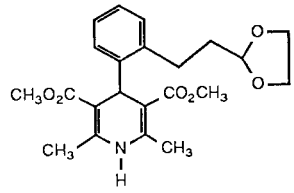
Scheme III



6 8a 9 8b

Mechanistically, cyclization of both **5** and **6** is thought to involve Lewis acid coordination on an acetal oxygen followed by intramolecular attack by C-3 of the dihydropyridine on the acetal carbon. Interestingly, cyclization of **5** and **6** provides ethers **7** and **8**, respectively, which differ in absolute configuration at C-10. The precise nature of this stereoselection is not known at present, however molecular models demonstrate that the hydroxyethyl side chain of **7** probably occupies an equatorial position while the less sterically demanding methoxy group of **8** is axially oriented.

Gratifyingly, cyclization products from **5** and **6** are formed stereoselectively and in high yield, indicating the scope of this methodology for the rational construction of complex intermediates. We anticipate that this type of cyclization will have broad utility for the preparation of dihydropyridine analogs; however, we have found a limitation in that ether **10**, which would require a 7-membered transition state for cyclization in the sense described, does not react under the normal acid conditions employed.



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EXPERIMENTAL

Melting points were determined in air employing a Thomas Hoover apparatus and are uncorrected. Proton NMR spectra were obtained using a Varian T-60, an EM-390, or a Nicolet NT-360 spectrometer with TMS as an internal standard. Mass spectra were obtained on an LKB-9000S mass spectrometer at 70 eV by Dr. H. Ramjit and his staff. The elemental analyses were performed by Dr. W. C. Randall and his staff. *N*-Formylpiperidine, methyl acetoacetate, and methyl 3-aminocrotonate were purchased from Aldrich and were used without purification.

Dimethyl 3,4,4a,5,6,10b-Hexahydro-5β-(hydroxyethoxy)-2-methyl-4-methylidenebenzo[*f*]-isoquinoline-1,4a-dicarboxylate (**7**).

To a solution of 1.94 g (5.0 mmoles) **5** [10] in 80 ml of chloroform was added 1.90 g (10.0 mmoles) titanium tetrachloride under nitrogen. A gumball formed which dissolved over 15 minutes. After 2 hours the reaction was quenched by addition of water, neutralized with saturated sodium bicarbonate solution and the layers were separated. The aqueous layer was extracted with 2 x 50 ml chloroform. The combined extract was washed with brine, dried over sodium sulfate, and concentrated *in vacuo* to give 2.43 g of a glassy solid. The solid was flash chromatographed on a column of E. Merck silica gel eluted with 1% methanol/chloroform to give 1.45 g (75%) product as a yellow, glassy solid which decomposed on standing or on attempted recrystallization; ^{1}H nmr (deuteriochloroform): 360 MHz δ 2.34 (3 H, s), 3.11 (1 H, d of dd, J = 18.5, 3 Hz), 3.43 (1 H, d of d, J = 18, 5 Hz), 3.70 (4 H, m), 3.78 (3 H, s), 3.84 (3 H, s), 4.40 (1 H, d of d, J = 5, 3 Hz, H_e), 4.40 (1 H, d, J = 24 Hz), 4.41 (1 H, d, J = 24 Hz), 4.82 (1 H, s, H_a), 5.88 (1 H, br s), 7.20 (4 H, m); ms: m/e 387 (M^+).

2-(2,2-Dimethoxyethyl)benzaldehyde (**4**).

To 1.0 g (0.0041 mole) of **2** in 25 ml of dry tetrahydrofuran cooled to -78° under nitrogen was added dropwise 0.0041 mole of *n*-butyllithium (in hexane) at such a rate that the internal temperature was kept <-70°. After this yellow-brownish suspension was stirred at -78° for 1 hour, a solution of 0.46 g (0.0041 mole) of *N*-formylpiperidine (Aldrich) in 5 ml of tetrahydrofuran was added dropwise. The resulting solution was allowed to gradually warm to room temperature over 12 hours. The cooled reaction mixture was quenched with 20 ml of saturated ammonium chloride solution and after 30 ml of ether was added, the phases were separated. The organic phase was washed with brine, dried over anhydrous sodium sulfate and stripped to give **4** as a clear oil, 0.40 g (51%) with R_f 0.6 on silica gel eluted with hexane/ether (1/1); ^{1}H nmr (deuteriochloroform): δ 3.37 (2 H, d), 3.65 (4 H, m), 5.05 (1 H, t), 7.1-7.7 (4 H, m), 10.26 (1 H, s, CHO); ms: m/e 192.

Dimethyl 2,6-Dimethyl-4-[2-(2,2-dimethoxyethyl)]phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**6**).

To 2.5 g (0.013 mole) of **4** dissolved in 25 ml of dry methanol was added 1.48 g (0.013 mole) of methyl 3-aminocrotonate and 1.49 g (0 .013 mole) of methyl acetoacetate and the resulting mixture was heated at reflux for 3 days. The solvent was removed on the rotary evaporator and the residue purified by flash chromatography on silica gel (250-400 mesh) eluted with 2% methanol/chloroform to give **6** (R_f 0.3) as a white solid, 2.11 g (42%), mp 113-114°; ^{1}H nmr (deuteriochloroform): δ 2.23 (6 H, s), 3.27 (2 H, d), 3.56 (6 H, s), 3.95 (4 H, m), 5.03 (1 H, t), 5.18 (1 H, s), 5.73 (1 H, bs, NH), 7.00-7.42 (4 H, m, aromatic); ms: m/e 3.86.

Anal. Calcd. for $C_{21}H_{24}NO_6$: C, 65.27; H, 6.26; N, 3.62. Found: C, 65.12; H, 6.62; N, 3.31.

Mixture of Dimethyl 3,4,4a,5,6,10bα-Hexahydro-5α-methoxy-2-methyl-4-methylidinebenzo[*f*]isoquinoline-1,4aα-dicarboxylate (**8a**) and Dimethyl 4a,5,6,10bα-Tetrahydro-5α-methoxy-2,4-dimethylbenzo[*f*]isoquinoline-1,4aα-dicarboxylate (**8b**).

Into a solution of dimethyl 2,6-dimethyl-4-[2-(2,2-dimethoxyethyl)]-phenyl-1,4-dihydropyridine-3,5-dicarboxylate **6** (0.78 g, 2.0 moles) in dichloromethane (20 ml) was bubbled hydrogen chloride for 15 minutes. The solution was stirred 2 hours and then neutralized with saturated sodium bicarbonate. The mixture was diluted with water, the layers separated, and the aqueous layer extracted with 2 x 50 ml of dichloromethane. The combined extract was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 0.87 g of a glassy solid. The solid was dissolved in ether (5 ml) and allowed to stand overnight depositing crystals. The crystals were filtered off to give 0.43 (60%) of a mixture of **8a** and **8b** which discolored on standing. The crystals were taken up in hot cyclohexane, cooled, and filtered. The filtrate was concentrated to dryness and the residue was dissolved in ether and allowed to stand. The resulting crystals were filtered off to give 0.21 g (29%) of a 3 to 1 mixture (by nmr) of **8a/8b**, mp 178-180°. From the ^{1}H nmr (deuteriochloroform) 360 MHz, of the mixture the following assignments were made: **8a**, δ 2.29 (s, 3H), 3.09 (d of d, 1 H, J = 18, 3 Hz), 3.32 (d of d, 1 H, J = 18, 4 Hz), 3.40 (s, 3 H), 3.73 (s, 3 H), 3.77 (s, 3 H), 4.19 (d of d, 1 H, J = 4, 3 Hz, H_b), 4.35 (d of d, 2 H, J = 18, 2 Hz), 4.75 (s, 1 H, H_a), 7.1 (m, 4 H); **8b**, δ2.26 (s, 3 H, CH_3[d]), 2.41 (s, 3 H, CH_3[c]), 3.19 (d, 2 H, J = 5 Hz), 3.45 (s, 3 H), 3.73 (s, 3 H), 3.80 (s, 3 H), 4.03 (t, 1 H, J = 6 Hz, H_b), 4.69 (s, 1 H, H_a), 7.1 (m, 4 H).

Anal. Calcd. for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.22; H, 6.88; N, 3.82.

Dimethyl 3,4,4a,5,6,8b-Hexahydro-5α-methoxy-2,4β-dimethylbenzo[*f*]-isoquinoline-1,4aα-dicarboxylate (**9**).

Sodium borohydride (0.040 g, 1.0 mmole) was added carefully to acetic acid (2.1 ml) with stirring. After 5 minutes the mixture of **8a/8b** (0.125 g, 0.35 mmole) was added. A precipitate formed after 30 minutes and the mixture was stirred overnight. The mixture was then poured into ice-water (10 ml), neutralized with saturated sodium bicarbonate solution and filtered. The yellow solid collected was washed with water, dried, triturated with ether, and allowed to stand overnight under ether. The solid was filtered off to give 0.040 g (32%) **9**, as the hemihydrate, mp 212-214°. ^{1}H nmr (deuteriochloroform): 360 MHz δ 1.40 (d, 3 H, J = 7 Hz), 1.58 (bs, water), 2.31 (s, 3 H), 2.87 (broad d of d, 1 H, J = 14, 6 Hz, H_c), 2.99 (d of d, 1 H, J = 15, 4 Hz), 3.10 (d of d, 1 H, J = 15, 8 Hz), 3.25 (m, 1 H, H_b), 3.41 (s, 3H), 3.62 (s, 3 H), 3.70 (s, 3 H), 4.06 (bs, 1 H), 4.71 (s, 1 H, H_a), 7.1 (m, 4 H).

Anal. Calcd. for $C_{20}H_{25}NO_5 \cdot 0.5\ H_2O$: C, 65.20; H, 7.11; N, 3.80. Found: C, 65.01; H, 7.04; N, 3.88.

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