A New and Unexpected Aminoisoquinoline Formed Under Bischler-Napieralski Reaction Conditions Provides For A New Synthesis of 3-Aminoisoquinolines

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Treatment of an amide, **1**, of a substituted 2-phenethylamine using Bischler-Napieralski reaction conditions with acetonitrile as a solvent, gave the desired dihydroisoquinoline **2** as well as an unexpected 3-aminoisoquinoline product **3**. The applicability of this finding as a method of synthesizing 3-aminoisoquinoline derivatives was examined.

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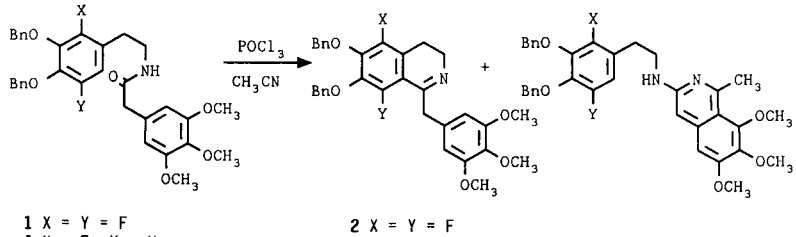
The Bischler-Napieralski reaction is one of the most effective methods of preparing isoquinoline derivatives [1]. This reaction has been used in the synthesis of a variety of tetrahydroisoquinoline analogs of pharmacological interest [2,3,4]. It involves the cyclodehydration, *via* phosphorus oxychloride or other Lewis acids, of an amide, formed from the appropriately substituted phenethylamine, to afford the desired dihydroisoquinoline derivative. The mechanism of the Bischler-Napieralski reaction has been shown by Fodor and Nagubandi to undergo dehydration before cyclization *via* the formation of a nitrilium salt [5,6]. It is through this intermediate nitrilium salt that many side products of the Bischler-Napieralski reaction have been reported [7,8,9].

Using the Bischler-Napieralski reaction in the synthesis of fluorine and trifluoromethyl analogs of trimetoquinol, a potent bronchial relaxant, we observed an unexpected aminoisoquinoline side product which has not been previously reported in the literature. A mixture of amide **1** and a three molar equivalent of phosphorus oxychloride in dry acetonitrile was refluxed for 15 hours under an argon atmosphere. The resulting mixture after work up was passed through a silica gel column (25% ether in dichloromethane) to give the dihydroisoquinoline **2** (51% yield) and the aminoisoquinoline **3** (15% yield). Compound **3** was converted to a hydrochloride salt which was recrystallized from ether/ethanol to afford light yellow crystals mp 118-120°. Acetonitrile appeared to be involved in the reaction that gave rise to **3**. To test this idea, we ran the Bischler-Napieralski reaction of **1** in benzene and this completely eliminated the formation of **3**. We propose the 3-aminoisoquinoline side product to be the result of acetonitrile reacting with the intermediate nitrilium salt as shown in Scheme 2. The above reaction conditions were optimized to achieve a 34% yield of the aminoisoquinoline **3**. To investigate the importance of fluorine substitution we carried out a study of closely related analogs of **1** and found that with the use of acetonitrile in the Bischler-Napieralski reaction of **4** an 10% yield of **6** was formed as well as a 58% yield of the expected **5**. Using these same conditions, only the dihydroisoquinolines **8** and **10** were isolated when the amides **7** and **9** respectively were used as starting materials. We next examined the influence of trifluoromethyl substitution. Refluxing amide **11** in five molar equivalents of phosphorus oxychloride in dry acetonitrile for 5 hours under an argon atmosphere gave the intermediate dihydroisoquinoline **12** which without purification was reduced with sodium borohydride and isolated as the tetrahydroisoquinoline in 37% yield. In this case, none of the aminoisoquinoline was formed. Use of acetonitrile in the reaction of amide **13** resulted in a 11% yield of **14** only, none of the corresponding dihydroisoquinoline was

Scheme 1

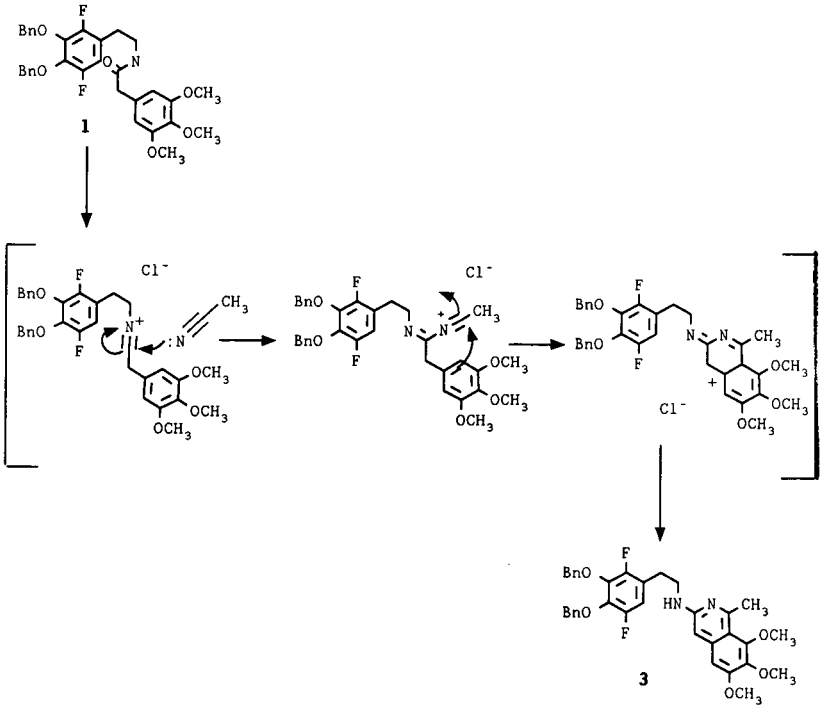


1 X = Y = F
4 X = F, Y = H
7 X = H, Y = F
9 X = Y = H
11 X = CF_3, Y = H
13 X = H, Y = CF_3

2 X = Y = F
5 X = F, Y = H
8 X = H, Y = F
10 X = Y = H
12 X = CF_3, Y = H

3 X = Y = F
6 X = F, Y = H
14 X = H, Y = CF_3

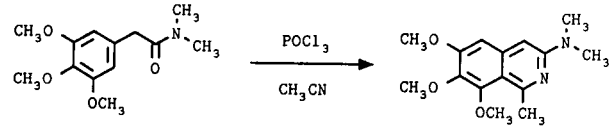
Scheme 2



isolated. Performing the Bischler-Napieralski reaction of **13** in toluene or benzene, again completely eliminated the presence of the aminoisoquinoline side product **14**; however, the corresponding dihydroisoquinoline compound could not be isolated from the mixture.

It is of interest to note that when X = F, an *ortho-para* director, as in amide **4**, the Bischler-Napieralski ring closure must take place at the undesired *meta* position and it is in this situation that the aminoisoquinoline side product is formed. However, the side product is not formed when Y = F, as in amide **7**, where the Bischler-Napieralski ring closure will take place at the desired position *ortho* to the fluorine. The same trend is found with the trifluoromethyl analogs. When Y = CF_3, a *meta* director, as in amide **13**, the ring closure must take place at the positions *ortho* or *para* to the trifluoromethyl group. In this situation, the aminoisoquinoline side product is formed. However, when X = CF_3 as in amide **11**, the ring closure should take place at the desired position *meta* to the trifluoromethyl group and in this case the side product is not formed. To further examine the potential use of Bischler-Napieralski conditions in the synthesis of 3-aminoisoquinoline analogs we carried out the reaction using the simple amide **15** (Scheme 3). This proved to be quite successful, affording 3-dimethylaminoisoquinoline **16** in 75% yield. The above observations present a new method of synthesizing other appropriately substituted aminoisoquinoline analogs.

Scheme 3



EXPERIMENTAL

Melting points (uncorrected) were determined on a Thomas-Hoover melting point apparatus. The ^1H nmr spectra were obtained on an IBM AF-250 spectrometer and reported in parts per million. Mass spectra were obtained at the Ohio State University Chemical Instrumentation Center, by use of a VG 70-250S (or Kratos MS-30) mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, and were within ±0.4% of the theoretical values for the elements indicated.

3-[2-(2,5-Difluoro-3,4-dibenzyloxyphenyl)ethyl]amino-1-methyl-6,7,8-trimethoxyisoquinoline Hydrochloride (**3**).

To a solution of amide **1** (12.0 g, 20.8 mmoles) in dry acetonitrile (100 ml) was added phosphorus oxychloride (4 ml, 43.0 mmoles) and allowed to reflux for 3 hours. The solution was cooled and poured into cold 10% ammonium hydroxide solution. The organic layer was separated, dried (sodium sulfate) and concentrated. The residue was passed through a flash silica column using 10% ether/90% dichloromethane as the solvent. The hydrochloride salt was made with hydrogen chloride gas and recrys-

tallized from ether/dichloromethane to give **3** (4.5 g, 34%), mp 118-120°; FABms: $(M+H)^+$ = 601.31; ^{1}H nmr (deuteriochloroform): 7.85 (br t, 1H, NH), 7.33-7.44 (m, 10H), 6.80 (dd, 1H, J = 6.6 and 10.6 Hz), 6.56 (s, 1H), 6.43 (s, 1H), 5.10 (s, 2H), 5.07 (s, 2H), 4.02 (s, 3H), 3.98 (s, 3H), 3.87 (s, 3H), 3.43 (br q, 2H), 3.14 (s, 3H) and 2.96 (br t, 2H).

Anal. Calcd. for $C_{35}H_{35}ClF_2N_2O_5$: C, 65.98; H, 5.54; N, 4.40. Found: C, 66.16; H, 5.46; N, 4.25.

3-[2-(2-Fluoro-3,4-dibenzyloxyphenyl)ethyl]amino-1-methyl-6,7,8-trimethoxyisoquinoline Hydrochloride (**6**).

To a solution of amide **4** (3.0 g, 5.4 mmoles) in dry acetonitrile (25 ml) was added phosphorus oxychloride (1 ml, 10.7 mmoles) and allowed to reflux for 2 hours. The solution was cooled with ice, diluted with acetonitrile (25 ml) and ether (25 ml) and to it was added cold 10% ammonium hydroxide solution. The organic layer was separated, dried (sodium sulfate) and concentrated. The residue was passed through flash column chromatography using 20% ether/80% dichloromethane as the solvent. The hydrochloride salt was made with hydrogen chloride gas and recrystallized from ether/dichloromethane to give yellow crystals of **6** (0.33 g, 9.9%), mp 146-148°; FABms: $(M+H)^+$ = 583.42; ^{1}H nmr (deuteriochloroform): 7.71 (dd, 1H, J = 5.7 and 3.2 Hz), 7.53 (dd, 1H, J = 5.7 and 3.3 Hz), 7.45-7.24 (m, 10H), 6.56 (s, 1H), 6.44 (s, 1H), 5.10 (s, 2H), 5.08 (s, 2H), 4.02 (s, 3H), 3.99 (s, 3H), 3.98 (s, 3H), 3.42 (br t, 2H), 3.13 (s, 3H) and 2.96 (br t, 2H).

Anal. Calcd. for $C_{35}H_{36}ClFN_2O_5$: C, 67.90; H, 5.86; N, 4.52. Found: C, 67.59; H, 5.78; N, 4.20.

3-[2-(3,4-Dibenzyloxy-5-trifluoromethylphenyl)ethyl]amino-1-methyl-6,7,8-trimethoxyisoquinoline Hydrochloride (**14**).

To a solution of amide **13** (1.00 g, 1.64 mmoles) in dry acetonitrile (30 ml) under an argon atmosphere was added phosphorus oxychloride (0.77 ml, 8.20 mmoles) and heated to reflux. After 5 hours, the solution was cooled and concentrated under reduced pressure. The residue was taken up into ethyl acetate (50 ml) and washed with 10% sodium hydroxide solution (2 × 50 ml), water (1 × 50 ml), brine (1 × 50 ml), dried (magnesium sulfate) and concentrated to a yellow oil. The oil was passed through a gravity silica column using 30% ethyl acetate/70% hexane as the solvent. The hydrochloride salt was made with 3*N* methanolic hydrogen chloride and recrystallized from dichloromethane/ether to afford yellow crystals of **14** (121 mg, 11%), mp 138-140°; ms: 261.13, 248.12, 91.06; ^{1}H nmr (deuteriochloroform/TMS): 7.89 (br t, 1H, NH), 7.49 (d, 1H, J = 1.59 Hz), 7.38-7.26 (m, 10H), 7.08 (d, 1H, J = 1.59 Hz), 6.51 (s, 1H), 6.26 (s, 1H), 5.26 (s, 2H), 5.00 (s, 2H), 4.00 (s, 3H), 3.96 (s, 3H), 3.85 (s, 3H), 3.49-3.45 (m, 2H), 3.11 (s, 3H), 3.02 (br t, 2H).

Anal. Calcd. for $C_{34}H_{36}ClF_3N_2O_5$: C, 63.30; H, 5.62; N, 4.34. Found: C, 63.32; H, 5.45; N, 4.05.

N,N-Dimethylamino-1-methyl-6,7,8-trimethoxyisoquinoline Hydrochloride (**16**).

To a solution of amide **15** (2.45 g, 10.9 mmoles) in dry acetonitrile (30 ml) under an argon atmosphere was added phosphorus oxychloride (4.0 g, 42.9 mmoles) and refluxed for 5 hours. The solution was cooled, poured into 5% ammonium hydroxide solution (150 ml) cooled with ice and extracted with ethyl acetate (2 × 50 ml). The combined organic layers were dried (sodium sulfate) concentrated and the residue passed through a flash silica column using 20% ethyl acetate/80% hexane as the solvent. The hydrochloride salt was made using 8.8*N* alcoholic hydrogen chloride (3 ml) and recrystallized from dichloromethane/hexane to give **16**, (2.28 g, 75%), mp 153-155°; FABms: $(M+H)^+$ = 277.20; ^{1}H nmr (perdeuteriomethanol): 7.05 (s, 1H), 7.00 (s, 1H), 4.05 (s, 3H), 4.02 (s, 3H), 3.87 (s, 3H), 3.19 (s, 6H), 3.13 (s, 3H).

Anal. Calcd. for $C_{15}H_{21}ClN_2O_3$: C, 57.60; H, 6.77; N, 8.96. Found: C, 57.66; H, 6.89; N, 8.82.

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