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Studies on pyrrolidinones: a reaction of methylene dichloride under Friedel–Crafts conditions. Synthesis of an α-hydroxymethyl ketone in the hexahydrobenzo[*f*]indolizine series

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Abstract—When carried out in methylene dichloride, the Friedel–Crafts cyclization of *N*-arylmethyl pyroglutamates can lead to addition of a CH_2OH group in the position α to the newly formed ketone function.

Friedel–Crafts cyclization of *N*-arylmethylpyroglutamic acids is generally an easy reaction,[1] which sometimes leads to interesting rearrangements or by-products.[2] Some of these reactions are displayed in Figure 1. The choice of solvent was found to be important for yields and purities in these series; dichloroethane sometimes gives good yields[1b,c,2c] while dichloromethane[3] often leads to poor purity.[1]

In the present work cyclization of acids **1a**,**b** was studied. The trimethoxybenzyl acid **1a** yielded 70% of the pure ketone **2a** easily when boron trifluoride etherate was added at room temperature to a solution of the initially formed mixed anhydride **3a** in dichloroethane. Under the same conditions, the acid **1b** gave a 75% yield of ketone **2b** (Scheme 1). While studying this last reaction in dichloromethane, an unexpected formation of a

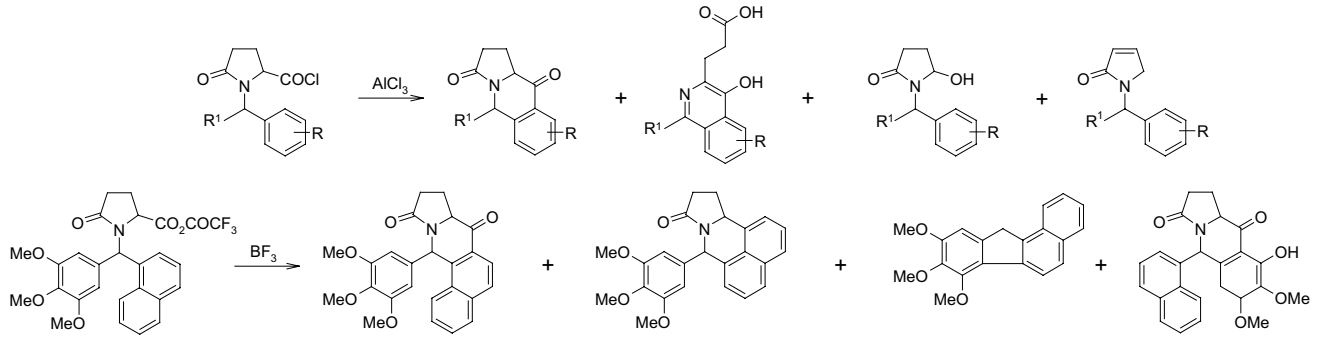

Figure 1. Reactions of *N*-arylmethyl pyroglutamic acids.

Keywords: Dichloromethane; Friedel–Crafts; Pyroglutamic derivatives.
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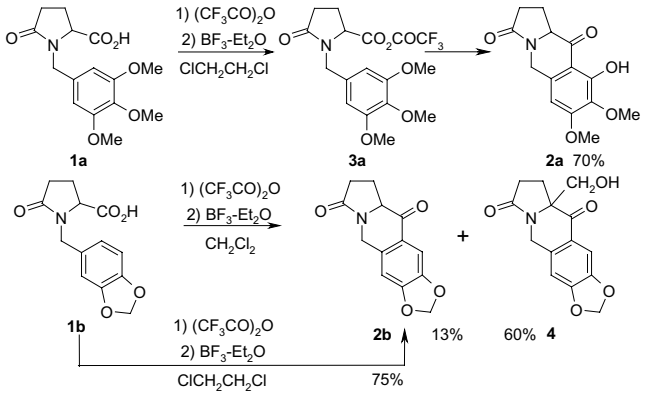
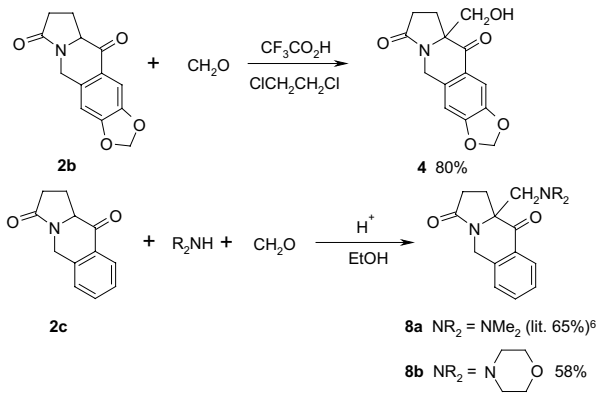


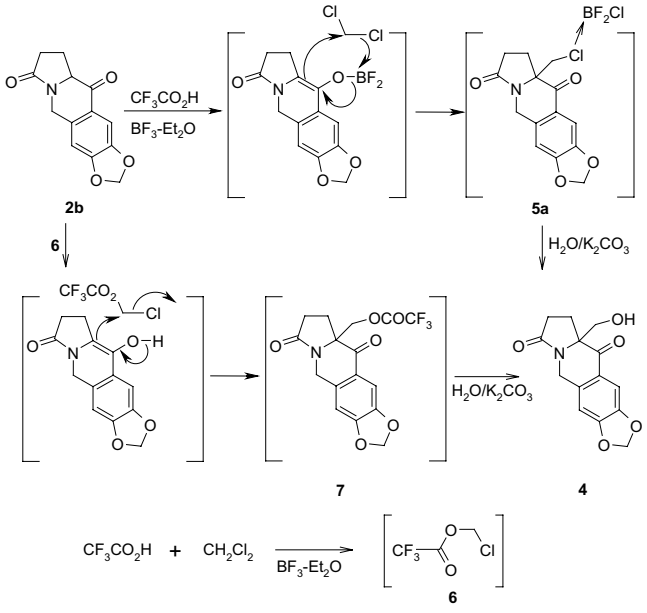
Scheme 1. Friedel–Crafts reaction of acids **1a** and **1b**.



Scheme 3. Mannich reaction of ketones **2**.

small amount of the ketone **4** was observed after an accidental extension of the heating time. After optimization of this new reaction, compound **4** was obtained in 60% yield by heating a mixture of acid **1b** and trifluoroacetic anhydride with boron trifluoride etherate in dichloromethane for 14 h (Scheme 1).

Dimethoxyphenol **2a** was formed by a process similar to other boron trifluoride induced demethylations of *ortho* methoxyaryl ketones.[1c,2c,4] Two different mechanistic hypotheses can account for the formation of the hydroxymethyl ketone **4**. In the first possibility, a boron (or acetyl) enolate could be obtained from the reaction of boron trifluoride with ketone **2b** in the presence of trifluoroacetic acid. Reaction of this enolate with dichloromethane could then give the chloromethyl ketone **5a** whose hydrolysis could produce the hydroxymethyl ketone **4** (Scheme 2). This reaction scheme requires an easy hydrolysis of the chloromethyl compound **5a**, although this product (see later) proved to be rather unreactive towards nucleophiles. According to



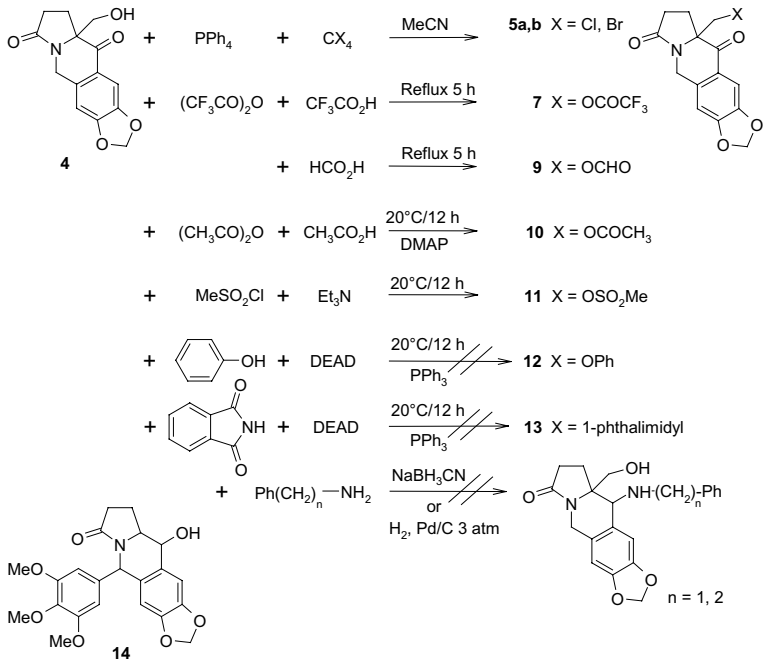
Scheme 2. Mechanistic hypotheses for the formation of compound **4**.

another possible mechanism, reaction of boron trifluoride, trifluoroacetic acid and dichloromethane could produce a transient chloromethyl trifluoroacetate **6**. It is known that chloromethyl esters are very reactive compounds, especially in the presence of Lewis acids.[5] Reaction of **6** with ketone **2b** in a classical Mannich type of reaction would lead to trifluoro ester **7** whose hydrolysis (see later) could give the hydroxymethyl product **4**.

The second mechanistic hypothesis requires an efficient Mannich type of reaction of ketone **2b**. Indeed in these series it proves to be very easy to perform such reactions. Thus the condensation of compound **2b** with polyoxymethylene in trifluoroacetic acid and dichloroethane yields 80% of the hydroxymethyl ketone **4**; furthermore ketone **2c**[1a] reacts with polyoxymethylene and dimethylamine[6] or morpholine to give good yields of aminoketones **8a**,**b** (Scheme 3).

Some aspects of the chemistry of the ketone **4** were then examined. This compound does not react under reductive amination or Mitsunobu conditions (Scheme 4). The use of thionyl chloride leads to chloride **5a** as an impure compound, but 75% yield of pure product **5a** was obtained when hydroxymethyl ketone **4** was reacted with a carbon tetrachloride/triphenylphosphine mixture.[7] Bromomethyl ketone **5b** was obtained in 85% yield by using the same procedure. Esters **7**, **9**, **10**, and mesylate **11** were also easily synthesized (Scheme 4), but **7** and **9** proved to be rather water sensitive and were not isolated. The halides **5** and mesylate **11** do not react with piperidine or morpholine under reflux. It is interesting to compare compounds **4** and **5** with the alcohol **14**,[1c] (Scheme 4) which presents the same CO–N–C–C–X sequence and does not react with nucleophiles directly or under the Mitsunobu conditions. In the same way **4** and **5** proved to be stable when refluxed in dichloromethane or in toluene, with Lewis or Bronsted acids (methanesulfonic acid, trifluoroacetic acid, aluminum chloride, or zinc chloride).

In conclusion we have reported a new unexpected reaction induced by dichloromethane. Reactions of methylene dichloride leading to abnormal Friedel–



Scheme 4. Reactions of compound **4**.

Crafts reactions[8] as well as its susceptibility towards many nucleophiles[9a] or metals or organometallic reagents[9b] have already been reported. It is also to be noted that dichloromethane explodes when mixed with perchloric acid.[9c]

Experimental procedures for compounds **2a**, **2b**, **4**, **5a**, **5b**, **7**, **8b** and **10** are described in Experimental.[10]

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10. *Experimental:* Melting points were determined using an Electrothermal apparatus and are uncorrected. The IR spectra were recorded on a Perkin–Elmer 700 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Gemini 2000 at 200 and 50 MHz, respectively. Microanalyses were performed by the 'Service Central de Microanalyses' of CNRS in Vernaison, France.
9-Hydroxy-7,8-dimethoxy-1,10a-dihydro-2H,5H-pyrrolo-[1,2-b] isoquinoline-3,10-dione **2a**. Trifluoroacetic

anhydride (83 g, 56 mL, 396 mmol) was added to a stirred suspension of acid **1a**[11,12] (82 g, 265 mmol) in dichloroethane (900 mL). The mixture was stirred at room temperature for 15 min, then boron trifluoride etherate (146 g, 130 mL, 1 mol) was added. The mixture was stirred at room temperature for 4 h, then the solvents were evaporated. The residue was stirred in a mixture of methylene dichloride and potassium carbonate in water for 2 h. The organic phase was dried then evaporated leading to ketone **2a**, which was recrystallized from ethyl acetate. Yield 70%, mp 135 °C (ethyl acetate); IR (KBr): ν cm^{-1} 1690, 1630, 1615, 1570, 1510, 1460, 1280; ^{1}H NMR ($CDCl_3$): δ ppm 2.32–2.61 (m, 4H), 3.87 (s, 3H), 3.95 (s, 3H), 4.23 (d, $J = 17$ Hz, 1H), 4.3–4.4 (m, 1H), 5.18 (d, $J = 17$ Hz, 1H), 6.37 (s, 1H), 12.09 (s, 1H, deuterium oxide exchangeable); ^{13}C NMR ($CDCl_3$): δ ppm 20.9, 29.9, 41.3, 56.3, 60.70, 60.71, 101.0, 110.3, 135.1, 136.9, 157.2, 159.4, 173.6, 199.2. Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05; O, 28.85. Found: C, 60.61; H, 5.43; N, 5.20; O, 28.99.

*7,8-Methylenedioxy-1,10a-dihydro-2H,5H-pyrrolo[1,2-*b*]isoquinoline-3,10-dione* **2b**. This compound was synthesized as for ketone **2a**, yield 75%; mp 130–131 °C (ethyl acetate); IR (KBr): ν cm^{-1} 1690, 1620, 1500, 1485, 1030; ^{1}H NMR ($CDCl_3$): δ ppm 2.35–2.62 (m, 4H), 4.18–4.30 (m, 1H), 4.25 (d, $J = 17.5$ Hz, 1H), 5.16 (d, $J = 17.5$ Hz, 1H), 6.06 (s, 2H), 6.70 (s, 1H), 7.45 (s, 1H); ^{13}C NMR ($CDCl_3$): δ ppm 20.7, 29.8, 41.3, 61.1, 101.9, 105.4, 106.0, 124.6, 136.4, 147.4, 152.6, 173.4, 192.2.
Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.46; H, 4.80; N, 5.92.

*10a-Hydroxymethyl-7,8-methylenedioxy-1,10a-dihydro-2H,5H-pyrrolo[1,2-*b*]isoquinoline-3,10-dione* **4** *By Friedel–Crafts reaction:* Trifluoroacetic anhydride (156 g, 105 mL, 743 mmol) was added to a stirred suspension of acid **1b**[13] (168 g, 639 mmol) in dichloromethane (1680 mL). The mixture was refluxed for 12 h then boron trifluoride etherate (367 g, 328 mL, 2.6 mol) was added. The mixture was refluxed for 14 h, then the solvents were evaporated. The residue was dissolved in dichloromethane, then cooled at 0 °C for 2 h, yielding a solid, which was filtered, washed with dichloromethane, ether, and then with a solution of sodium carbonate in water. The solid was washed with water; after drying it was recrystallized from ethyl acetate, yielding 60% of compound **4**, mp 180 °C, IR (KBr): ν cm^{-1} 3290, 1665, 1615, 1505, 1460, 1265; ^{1}H NMR ($CDCl_3$): δ ppm 2.27–2.47 (m, 2H), 2.47–2.74 (m, 2H), 3.74 (d, $J = 11.2$ Hz, 1H), 3.72–3.83 (m, 1H), 3.97 (d, $J = 11.2$ Hz, 1H), 4.4 (d, $J = 17.4$ Hz, 1 H), 5.17 (d, $J = 17.4$ Hz, 1 H), 6.06 (s, 2H), 6.70 (s, 1H), 7.45 (s, 1H); ^{13}C NMR ($CDCl_3$): δ ppm 24.6, 29.5, 39.5, 64.2, 69.7, 101.9, 104.6, 105.6, 124.0, 136.9, 146.8, 152.0, 172.8, 194.2; MS m/z 276.3 (MH^+).
Anal. Calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 61.25; H, 4.69; N, 5.21.
Ketone **2b**, 13% can be isolated from the methylene dichloride solutions.

By Mannich reaction: A stirred mixture of ketone **2b** (31.5 g, 129 mmol), polyoxymethylene (7.7 g, 257 mmol) and trifluoroacetic acid (35.5 g, 24 mL, 312 mmol) in dichloroethane (300 mL) was refluxed for 26 h. The solution was washed with a solution of sodium carbonate in water, then dried and evaporated. The residue was crystallized from ethyl acetate giving an 80% yield of compound **4**.

*10a-Chloromethyl-7,8-methylenedioxy-1,10a-dihydro-2H,5H-pyrrolo[1,2-*b*]isoquinoline-3,10-dione* **5a**. A mixture of alcohol **4** (5 g, 17 mmol), triphenylphosphine (7.1 g, 27 mmol), and carbon tetrachloride (10 mL) in acetonitrile (10 mL) was stirred at room temperature in a closed vessel for 24 h. The solvents were removed, then methylene chloride was added and the solution was washed with water. After drying, the solvents were evaporated and ethyl acetate was added. Filtration of triphenylphosphine oxide gave a solution of impure compound **5**, which crystallized upon evaporation of the solvents. Pure chloride **5** (75%) was obtained by chromatography (SiO_2, dichloromethane/methanol 99/1), mp (ethyl acetate) 170–171 °C; IR (KBr): ν cm^{-1} 1700, 1620, 1505, 1410, 1270; ^{1}H NMR ($CDCl_3$): δ ppm 2.25–2.50 (m, 2H), 2.50–2.80 (m, 2H), 3.66 (d, $J = 11.8$ Hz, 1H), 3.85 (d, $J = 11.8$ Hz, 1H) 4.29 (d, $J = 17.9$ Hz, 1H), 5.23 (d, $J = 17.9$ Hz, 1H), 6.07 (s, 2H), 6.71 (s, 1H), 7.46 (s, 1H) ; ^{13}C NMR ($CDCl_3$): δ ppm 25.7, 29.8, 39.3, 47.2, 68.6, 102.1, 105.5, 106.5, 123.8, 136.3, 147.9, 153.3, 173.9, 192.3. This compound was not analyzed but used directly in the next reactions.

*10a-Bromomethyl-7,8-methylenedioxy-1,10a-dihydro-2H,5H-pyrrolo[1,2-*b*]isoquinoline-3,10-dione* **5b**. Compound **5b** was obtained as for chloride **5a**, by using carbon tetrabromide (20 °C, 48 h). Crystallization of crude **5b** from ethyl acetate led to 85% of pure bromide, mp 165 °C; IR (KBr): ν cm^{-1} 1690, 1615, 1500, 1410, 1260; ^{1}H NMR ($CDCl_3$): δ ppm 2.25–2.50 (m, 2H), 2.50–2.80 (m, 2H), 3.52 (d, $J = 11.6$ Hz, 1H), 3.72 (d, $J = 11.6$ Hz, 1H), 4.24 (d, $J = 17.5$ Hz, 1H), 5.21 (d, $J = 17.5$ Hz, 1H), 6.07 (s, 2H), 6.71 (s, 1H), 7.44 (s, 1H); ^{13}C NMR ($CDCl_3$): δ ppm 26.2, 29.9, 36.1, 39.1, 68.1, 102.2, 105.5, 106.6, 123.6, 136.2, 148.0, 153.4, 173.8, 191.8. This compound was not analyzed but used directly in the next reactions.

*10a-Acetoxymethyl-7,8-methylenedioxy-1,10a-dihydro-2H,5H-pyrrolo[1,2-*b*]isoquinoline-3,10-dione* **10**. A mixture of alcohol **4** (1 g, 3.6 mmol), acetic anhydride (0.76 g, 0.7 mL, 7.4 mmol), dimethylaminopyridine (0.01 g, 0.08 mmol) in acetic acid (20 mL) was stirred at room temperature for 12 h. Methylene dichloride (40 mL) was added and the solution was washed with water, then with a solution of potassium carbonate in water. The organic phase was dried, then evaporated, giving 95% of acetate (**10**), as a yellow oil; ^{1}H NMR ($CDCl_3$): δ ppm 2.02 (s, 3H), 2.29–2.56 (m, 4H), 4.03 (d, $J = 11.8$ Hz, 1H), 4.33 (d, $J = 17.9$ Hz, 1H), 4.60 (d, $J = 11.8$ Hz, 1H), 5.15 (d, $J = 17.9$ Hz, 1H), 6.06 (s, 2H), 6.70 (s, 1H), 7.46 (s, 1H).
Anal. Calcd. for $C_{16}H_{15}NO_6$: C, 60.57; H, 4.77; N, 4.41. Found: C, 60.41; H, 4.82; N, 4.12.

*10a-Trifluoroacetoxymethyl-7,8-methylenedioxy-1,10a-dihydro-2H,5H-pyrrolo[1,2-*b*] isoquinoline-3,10-dione* **7**. This compound was synthesized as for ester **10** (no dimethylaminopyridine, reflux 5 h), and was only characterized by NMR. Yield 95%, ^{1}H NMR ($CDCl_3$): δ ppm 2.33–2.72 (m, 4H), 4.34 (d, $J = 18.2$ Hz, 1H), 4.35 (d, $J = 11.4$ Hz, 1H), 4.84 (d, $J = 11.4$ Hz, 1H), 5.22 (d, $J = 18.2$ Hz, 1H), 6.10 (s, 2H), 6.73 (s, 1H), 7.46 (s, 1H); ^{13}C NMR ($CDCl_3$): δ ppm 25.8, 29.2, 40.1, 67.9, 68.7, 102.4, 105.4, 106.2, 113.7 (q, $J = 283$ Hz), 123.7, 135.9, 148.1, 153.9, 156.3 (9, $J = 43$ Hz), 176.1 (br s), 191.1.

*10a-Morpholinomethyl-1,10a-dihydro-2H,5H-pyrrolo[1,2-*b*]isoquinoline-3,10-dione* **8b**. A stirred mixture of ketone **2c**[1a,13] (5 g, 24.9 mmol), morpholine (1.54 g, 62.2 mmol), paraformaldehyde (5.9 g, 196 mmol), and acetyl chloride (5 drops) in ethanol (50 mL) was refluxed for 26 h. The solvent was removed, methylene dichloride was added, then the solution was washed with water. After drying, the solution was evaporated, and the solid obtained was recrystallized from ether. Yield 58%, mp 114–115 °C; IR (nujol): ν cm^{-1} 1685, 1600; ^{1}H NMR ($CDCl_3$): δ ppm 2.2–2.35 (m, 2H), 2.35–2.50 (m, 5H), 2.5–2.7 (m, 1H), 2.61 (d, $J = 14.6$ Hz, 1H), 2.87 (d, $J = 14.6$ Hz, 1H), 3.34–3.59 (m, 4H), 4.51 (d, $J = 18.1$ Hz, 1H), 5.28 (d, $J = 18.1$ Hz, 1H), 7.28 (d, $J = 7.5$ Hz, 1H), 7.39 (t, $J = 7.3$ Hz, 1H), 7.58 (t, $J = 7.3$ Hz, 1H), 8.06 (d, $J = 7.7$ Hz, 1H).

Anal. calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33; O, 15.98. Found: C, 67.91; H, 6.83; N, 9.68.

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