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On the Cyclization of Acyliminium Salts Derived from Pyroglutamic Acid.

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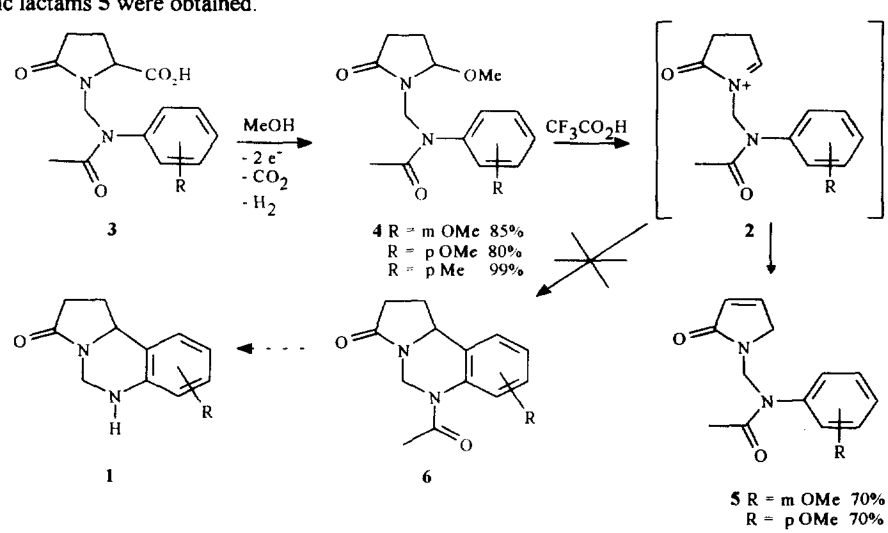
Abstract: The Friedel Crafts reaction of pyroglutamic acid derivative **9** gives an acyliminium salt which cyclize to the condensed N-acylheterocycle **6** thus providing an easy access to the amine **1**.

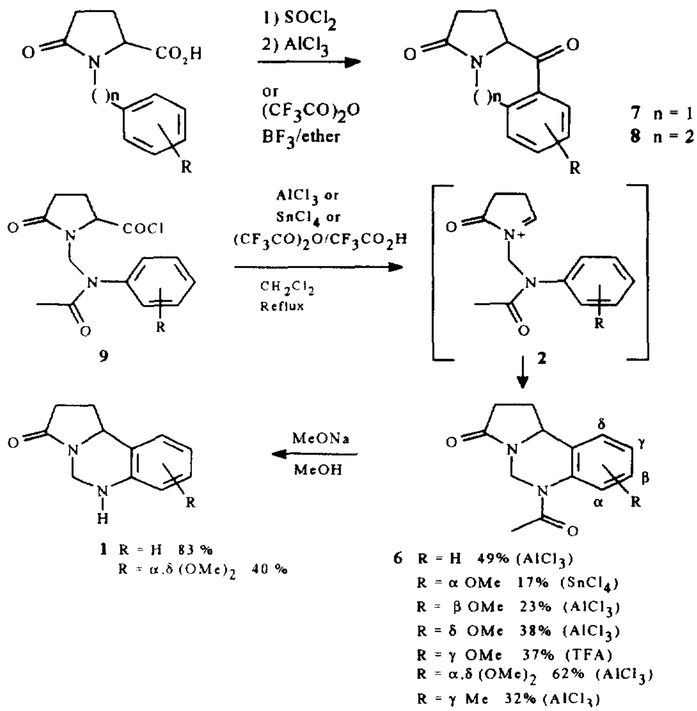
Because of their potential biological properties,[1] the new condensed 5-aryl-2-pyrrolidinones **1** were interesting to synthesize. It could be possible to obtain these compounds from aryl-5-pyrrolidone,[2a] but in a first approach we attempted to cyclize[2b] the iminium salts **2**, obtained after anodic oxidation of the pyroglutamic acids **3**.[3,4] Unfortunately, heating the N-aryl N,O-acetals **4** with acid (PTSA, H_2SO_4) leads to decomposition of the methylene diamide **4** (giving acetanilides) while by heating in trifluoracetic acid, only the ethylenic lactams **5** were obtained.[5]



It is known that the Friedel-Crafts reaction can be used in the pyroglutamic acid series, leading to cyclic ketones such as **7**[6] and **8**.[7]

We found that, under the same conditions, acid chlorides **9** decompose into the acyliminium salts **2** which cyclized to afford the heterocycles **6**. Because of the sensitivity of methylene bis amides **9** and **6** to the acidic media, a retro Mannich reaction occured, giving acetanilides, and the yields of products **6** were moderate. Sodium methylate treatment of compounds **6** gave then amines **1**.

This formation of iminium salts **2** is similar to the one observed when pyroglutamic acids are heated in polyphosphoric acid.[2a] As shown in the schemes, these reactions are quite general, providing moderate to good crude yields of products **4**, **5**, **6** and **1**.[8]



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8. The structure of amide **6** was proven by X-ray cristallography; full details will be reported elsewhere. All the products were identified by ^{1}H and ^{13}C NMR spectral measurements as well as elemental analysis. ^{1}H (200 MHz) NMR for representative compounds ($CDCl_3$): **4 (R = p Me)** δ 1.85 (s, 3H), 1.95–2.15 (m, 2H), 2.2-2.3 (m, 1H), 2.36 (s, 3H), 2.3-2.6 (m, 1H), 3.39 (s, 3H), 5-5.51 (m, 1H), 5.11 (d, J = 13.8 Hz, 1H), 5.33 (d, J = 13.8 Hz, 1H), 7.05 (d, J = 8 Hz, 2H), 7.19 (d, J = 8 Hz, 2H); **5 (R = m OMe)** δ 1.92 (s, 3H), 3.80 (s, 3H), 4.22 (t, J = 1.8 Hz, 2H), 5.34 (s, 2H), 6.09 (dt, J = 5.9; 1.8 Hz, 1H), 6.6-7.0 (m, 3H), 7.14 (dt, J = 5.9; 1.8 Hz, 1H), 7.25-7.35 (m, 1H)); **6 (R = H)** δ 1.85–2.15 (m, 1H), 2.37 (s, 3H), 2.35–2.75 (m, 3H), 4.45 (bd, J = 12.5 Hz, 1H), 4.85-5.05 (m, 1H), 5.85 (d, J = 12.5 Hz, 1H), 7.1-7.8 (m, 4H); **5 (R = α,δ (OMe)$_2$)** δ 1.7-1.90 (m, 1H), 2.3-2.7 (m, 3H), 3.76(s, 3H), 3.78 (s, 3H), 3.8 (bs, deuterium oxide exchangeable, 1H), 4.09 (d, J = 10.9 Hz, 1H), 4.9-5 (m, 1H), 5.23 (d, J = 10.9 Hz, 1H), 6.24 (d, J = 8.7 Hz, 1H=, 6.62 (d, J = 8.7 Hz, 1H).

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