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# STUDIES ON PYRROLIDINONES. A NEW REARRANGEMENT OF PYRROLO[1,2-b]ISOQUINOLINES DERIVATIVES

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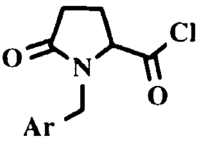
**Abstract** : *New lactones are obtained as by-products during the Friedel-Crafts cyclization of N-arylmethyl pyroglutamoyl chlorides. A mechanism based on N-acyliminium salts is proposed to explain their formation.*

Pyroglutamic acid has been an efficient starting material for the synthesis of many condensed nitrogen heterocycles;[1] for example, Friedel-Crafts reaction of acid chlorides 1 led to ketones such as 2-5 (catalyst : $SnCl_4$).[2]



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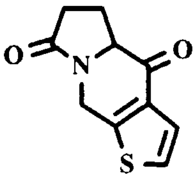

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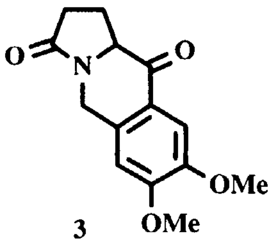

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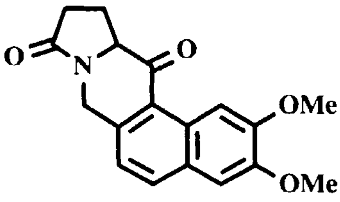

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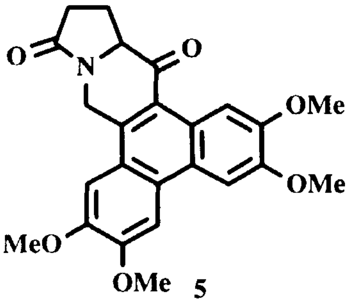

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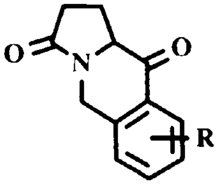
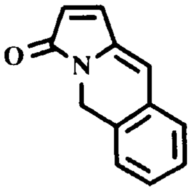
We have recently reported that a PPA treatment of ketone 6c, belonging to this series, gives the unsaturated lactam 7 in good yield,[5] and it has been shown that heating oximes 8 with PPA leads to lactams 9.[4]



6 c R = H



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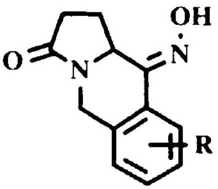

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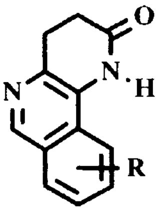

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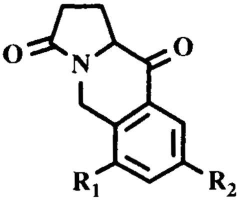
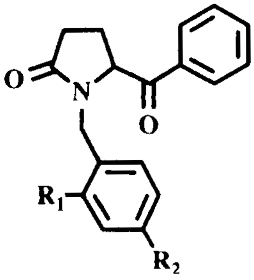
Herein we report that the structure of the by-products 11, 12 obtained during Friedel-Crafts synthesis of ketones 6, gives a supporting evidence for the intermediacy of N-acyliminium salts in these reactions. Indeed, we have reexamined this synthesis, catalyzed by aluminum chloride. According to previous results,[2a] ketones 10 as well as 6 can be obtained when benzene is chosen as solvent. However, in all cases examined (solvent : benzene[2a] or methylene dichloride[4]), small amounts of lactones 11 or their hydrolysis (12b,c) or methanolysis (12d) products (according to the final treatment of the reaction medium), are also formed.

Structural assignments are obtained by spectrometric methods (ir, $^1$H nmr, $^{13}$C nmr, MS) and by chemical methods (refluxing acid 12c with PTSA in toluene gives lactone 11c, and ring opening of lactone 11b yields acid 12b).



**6** **a** *5%* **b** *10%*
**c** *81%* **d** *64%*



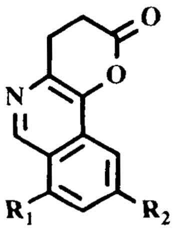
**10** **a** *31%* **b** *14%*

**a** $R_1 = H$ $R_2 = Cl$

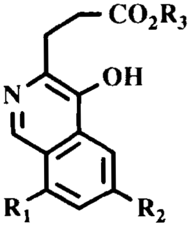
**b** $R_1 = OMe$ $R_2 = H$

**c** $R_1, R_2, R_3 = H$

**d** $R_1, R_3 = Me$ $R_2 = H$

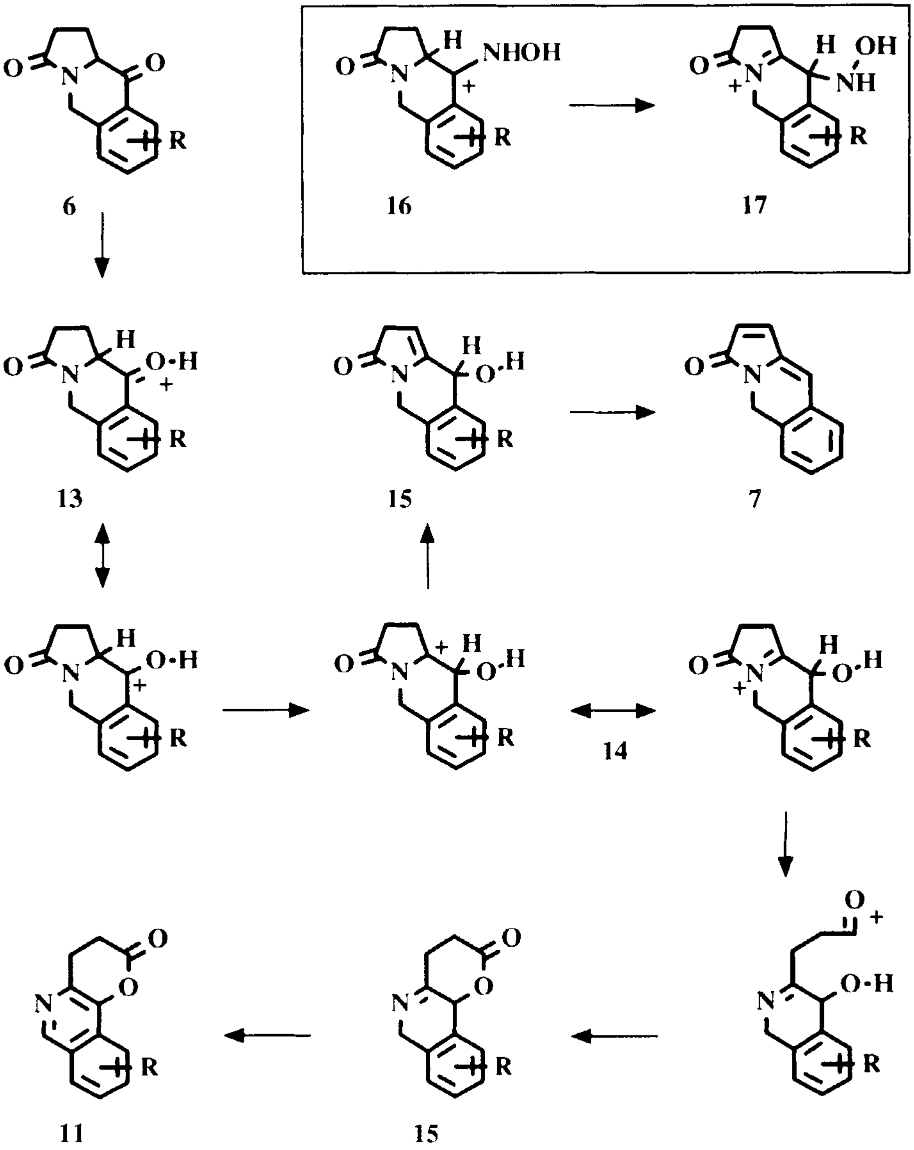


**11** **a** *2%* **b** *16%*



**12** **c** *4%* **d** *0.9%*

A similar mechanism can explain the formation of by-products <u>11</u> and <u>12</u> as well as the formation of lactam <u>7</u> :



A protonation of ketone 6 gives rise to cation 13. It is followed by a hydrogen shift yielding the more stabilized N-acyliminium salt 14. Opening of the lactam ring, recyclization to lactone 15 and air oxidation gives lactones 11. On the other hand, N-acyliminium salts 14 can lead to intermediate enamide 15.[6] The dehydration of this allyl alcohol then produces lactam 7. Similarly, the rearrangement of oxime 8 to lactam 9 can be explained by an initial nitrogen protonation (16) followed by a hydrogen shift giving a more stabilized N-acyliminium salt (17).

It is interesting to note that a related unusual dehydration, associated with a hydride transfer, has already been observed in the series of the acenaphto[5,4-b]furan,[7] acenaphto[5,4-b]thiophene[7] and fluorantheno[1,2-b]thiophene.[8] In these cases too, the driving force giving rise to the hydrogen shift was, in part, an additional stabilization of charge by an heteroatom.

From our results it appears that this rearrangement is quite general, and we believe that mechanisms based on this type of hydrogen shift could help to understand the low stability of some condensed nitrogen heterocycles.

In a typical experiment, $AlCl_3$ (44.7g, 354 mmol) was added in 3 steps to chloride 1 (Ar = 2-$C_6H_5Cl$) (32.1 g, 118 mmol) in benzene (150 ml). The mixture was refluxed during 30 minutes, stirred 2.5 hours at 20°C, then poured on crushed ice. The aqueous phase was extracted

($CH_2Cl_2$) and the organic phases were washed with water, dried and evaporated. The residue was fractionated under vacuum ; ketones 6a (5%, bp 195°C (0.2 mmHg), mp 126-127°C (ether-$CH_2Cl_2$) and 10a (31%, bp 218°C (0.1 mmHg)) were obtained as previously described ;[2a] lactone 7a crystallized by addition of ether and few drops of $CH_2Cl_2$ to the second distillation fraction (bp 179°C (0.2 mmHg)) ; 2% yield, mp 134°C (acetone). $^1H$ NMR ($CDCl_3$, 60 MHz) 2.8-3.7 (sym. m, 4H), 7.1-8.3 (m, 4H), 9.4(bs, 1H).

Anal. calcd for $C_{12}H_8NO_2Cl$ : C, 61.69 ; H, 3.45 ; N, 5.99 ; Cl, 15.17.

Found : C, 61.43 ; H, 3.62 ; N, 5.75 ; Cl, 15.11.

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