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Studies on pyrrolidinones. On the decarboxylation of pyroglutamic acids and *N*-acyl prolines in acidic media

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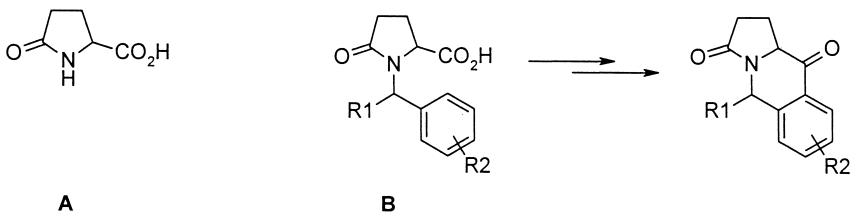
Abstract—During attempted Friedel–Crafts cyclization of some arylmethyl pyroglutamic acids or of *N*-phenacyl prolines, decomposition of the activated form of the acid have been observed, giving new heterocyclic systems. This general decarboxylation occurred when there are difficulties to realize a Friedel–Crafts cyclization and is explained by geometrical or electronic considerations.

1. Introduction

Pyroglutamic acid **A** is an interesting starting block for heterocyclic ketones[1] and we[2] and other authors[3] have already described the cyclization of many *N*-arylmethylpyroglutamic acids **B** (Scheme 1).

Cyclization of acid **1** has been described in 24% yield.[3b] While attempting to repeat this reaction or to cyclize acid **2**, ketones **3** and **4** were obtained in 60 and 33% yields, respectively; surprisingly, a low amount of decarboxylated products **5** (7%) and **6** (17%) were also isolated.

In an attempt to provide supporting evidence for a decarboxylated structure of these products, compound **6** was prepared by an electrochemical synthesis[4] (Scheme 2). In order to suppress the decarbonylation process, some reactions were also tested without success by using aluminum bromide instead of aluminum chloride.[5a]



Scheme 1.

Keywords: decarbonylation; decarboxylation; pyroglutamic acid; *N*-acylproline; lactams; Friedel–Crafts reaction; *N*-acyliminium salts.
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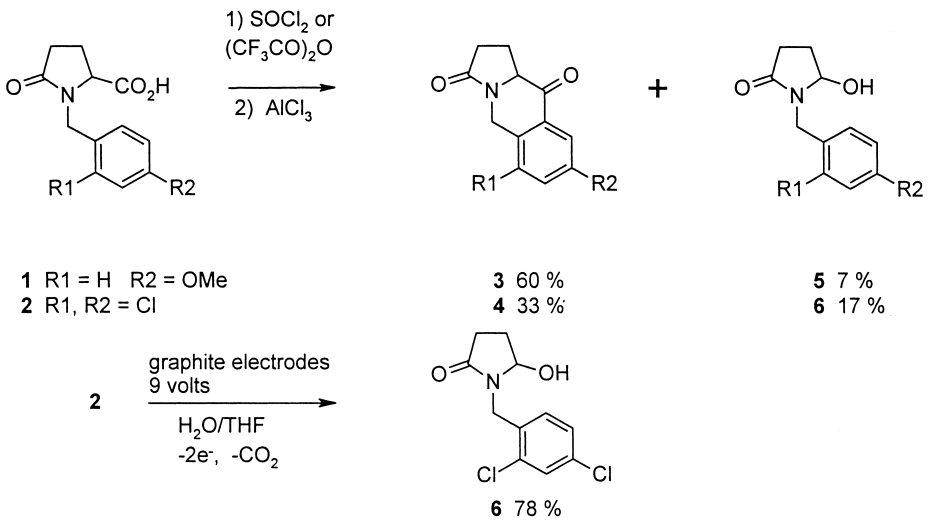
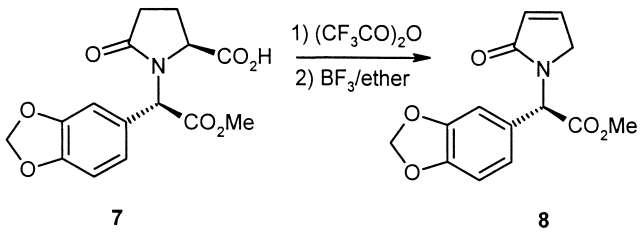


Scheme 2.



Scheme 3.

In another set of reactions, the Friedel–Crafts cyclization of acid **7** could not be achieved: no cyclized product was isolated, and only the unsaturated lactam **8** was obtained in 56% yield (Scheme 3).

2. Results and discussion

Decarboxylations leading to non-cyclic products have to be compared with other reactions that we have previously observed[5b,6,7] or that were reported in literature[3c,8] (Schemes 4 and 5).

For all of these decarboxylations, the initial mechanism is not a tandem radical-oxidation of the compound[9a] but is identical to another decarbonylation described for amino acids:[5,9b] the activated form of the acid decompose by loss of carbon monoxide (Scheme 6). The acyl iminium salt (**20**) then either converts to unsaturated lactam (**8**), or reacts with an aromatic, if present, to give an opened (**10**) or cyclized (**13**, **15**) product. This iminium salt can also be quenched at the end of the reaction, giving products **5**, **6** (Scheme 6); no attempts were made to quench the salt **20** by another nucleophile that water.

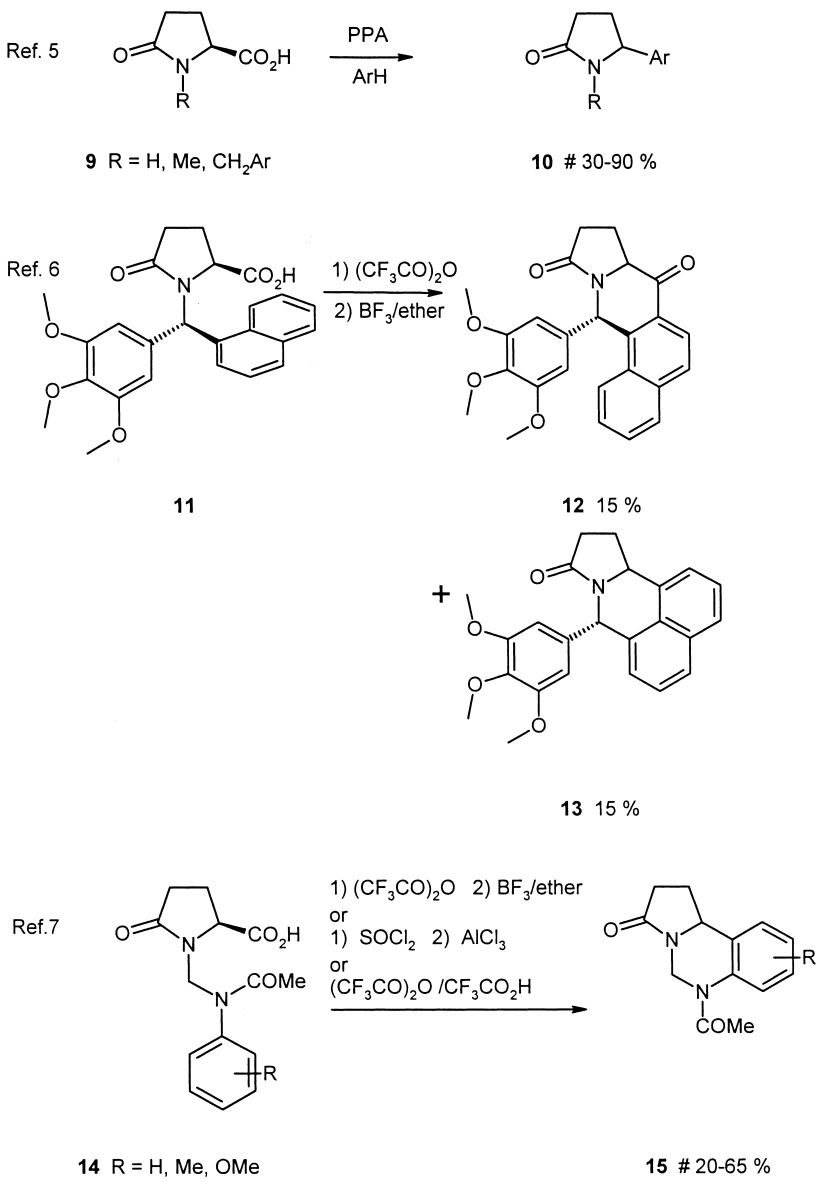
Thus, when an activated form of a pyroglutamic acid is formed (and if necessary subjected to the action of a Lewis acid), there is a competition between two reactions with different kinetics; generally speaking, the fastest process is the reaction of the activated form, to give an aromatic ketone.[2,3] When the aromatic is deactivated (**2**) (Scheme 2) or must be cyclized in the *meta* position of an *ortho*/*para* directing group (**1**) (Scheme 2) the cyclization rate is lower, and loss of carbon monoxide can occur. In other compounds (**7**, **14**) (Schemes 3 and 4), the aromatic nucleus is farther away from the acid carbonyl group, thus decreasing the rate of ketone formation below those of the decarboxylation step. These observations were confirmed by literature reports[3c,8] on the cyclization of acids **16** and **18** (Scheme 5): compound **16**, with electron rich aromatic nucleus gave a seven ring ketone in good yield, while non-electron rich acid **18** gives only a 8% yield of ketone **19**. We postulate that the formation of an iminium salt (**20**) (Scheme 6) can explain this low yield.

In another situation, to obtain ketone **12**, the aromatic ring needs to rotate in order to place a reacting center (α for acid **11**) (Scheme 7) next to the anhydride carbonyl group. By contrast, in the initial conformation (see Fig. 1, the X-ray structure of the methyl ester of acid **11**[6]), another reacting center (β for acid **11**) (Scheme 7) is well situated, below the carbon of the potential iminium salt, thus providing assistance for carbon monoxide evolution (Scheme 7).

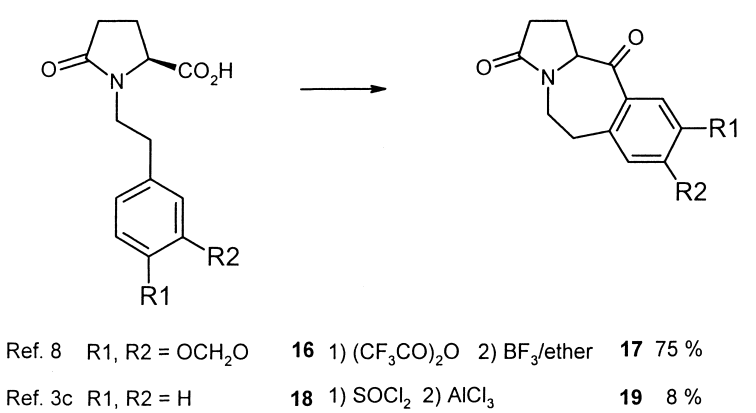
Interestingly, the same decarboxylation reactions can occur in the *N*-acylproline series. Heated in polyphosphoric acid, the acids **21**–**24** yield the seven-membered ring ketones **25**–**28**[10] (Scheme 8). Under the same conditions, decarboxylation of acid **29** lead also to the iminium salt **30** which cyclized, giving the lactam **31**[11] (Scheme 9).

In order to understand these results, geometries of acids **7**, **14**, **16**, **18**, **32** and **33** were optimized by using ab initio DFT calculations (6.31 G^{**}) using JAGUAR 3.5[12a] and SPARTAN 5[12b] to graphically display the results. Among these molecules, **16**, **32** and **33** cyclize easily and with good yields. On the other hand, **7** and **14** do not give a ketone while **18** does it with only a very low yield (Scheme 10).

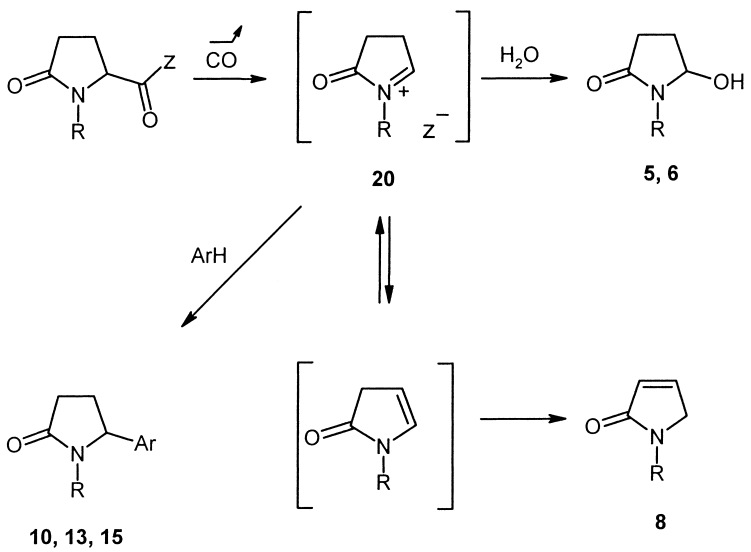
Geometric considerations help to explain why **7** and **14** do not cyclize, but fail to explain the difference in behavior between **16** and **18.**



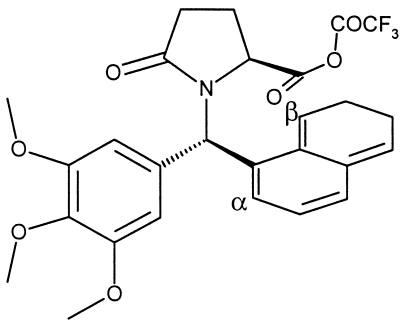
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7. Position α and β of the mixte anhydride of acid **11**.

Energies of the HOMO, LUMO and LUMO(+1) orbitals are reported in Table 1, and it can be seen that these values do not show any significant trend that would allow us to account for the difference in reactivity of these acids. One must note however that the energies of the LUMO and LUMO(+1) are fairly close and in case of **18**, they can be considered as degenerate.

Graphical representation of the first two LUMOs are shown in Fig. 2 for **32**, **33**, **16** and **18**. It is clear that the shape of the LUMO of **32** and **33** give a good indication that a ring closure is likely to take place.

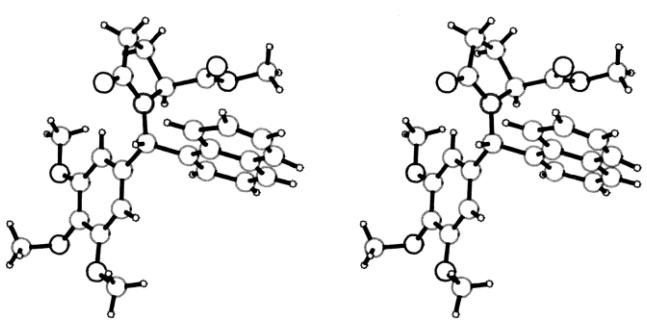
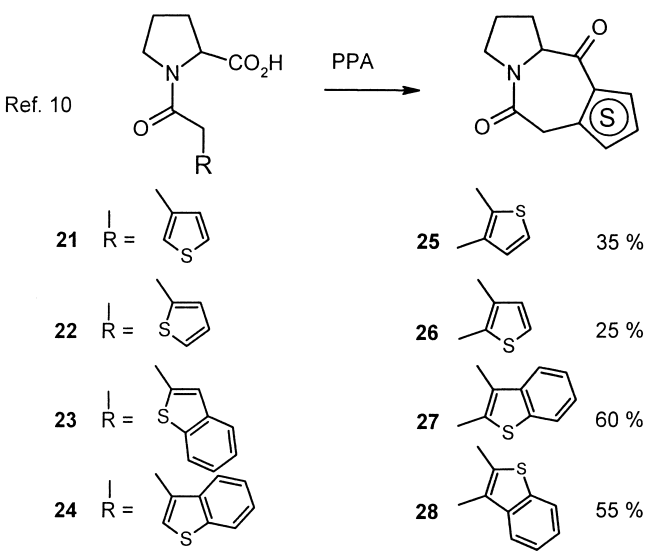


Figure 1. ORTEP diagram of acid **11** methyl ester.

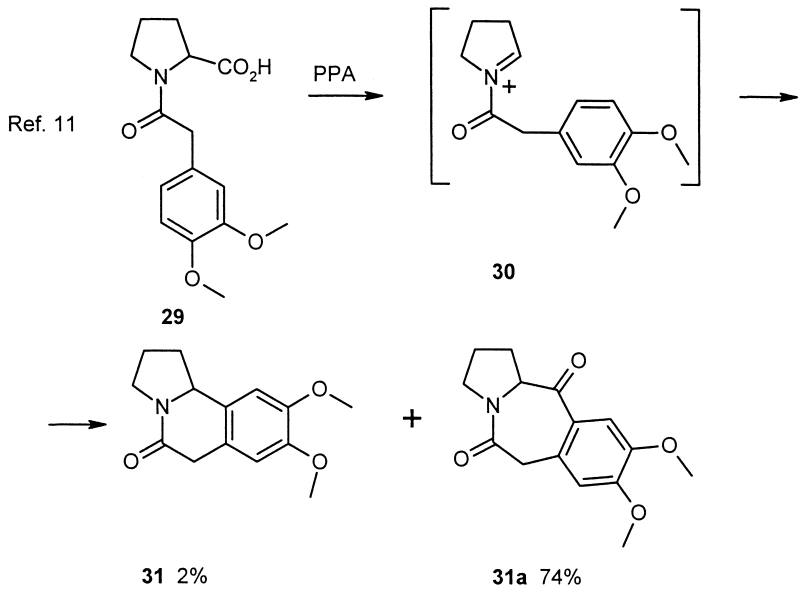
There is no overlap of the LUMO for **16** or **18**, but this is observed for the LUMO(+1) of **16**. In spite of the fact that the energies of LUMO and LUMO(+1) are almost the same in the case of **18**, this overlap is not observed. It would thus seem required that LUMO overlap be required to get cyclization.

3. Synthesis of acids 7 and 2

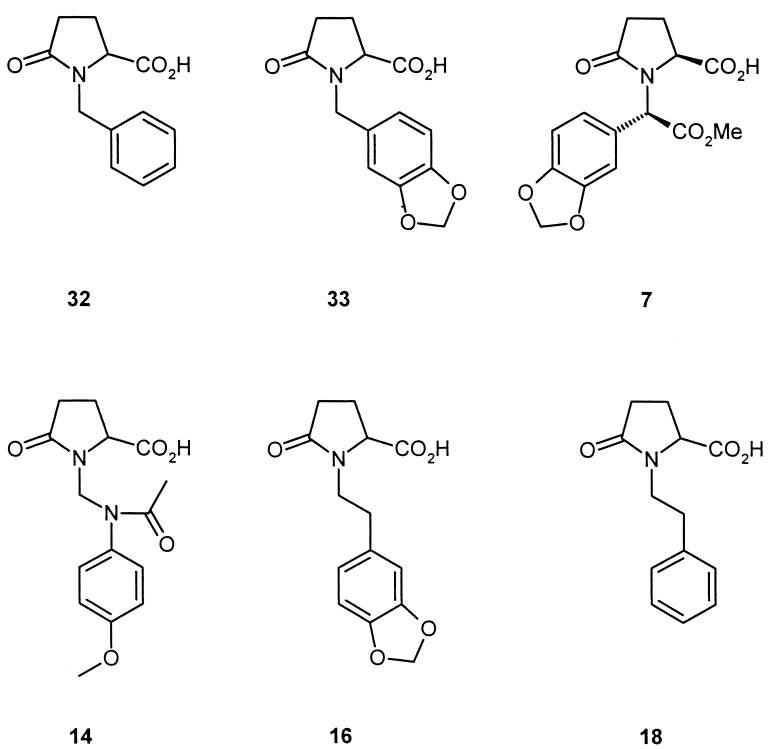
Acid **7** used in the reaction of Scheme 3 was obtained by a modification of a method from Roth:[13] condensation of pyroglutamic acid **A** with the hemiacetal **34** of methyl glyoxylate[14] yields lactam **35** as a 50/50 mixture of diastereoisomers. In acidic medium, iminium salt **36** was formed; steric interactions between the lactam carbonyl group and the ester function of compound **36** explain the formation of a single isomer of the iminium salt. Approach of the benzodioxole is favored on the side opposed to the



Scheme 8.



Scheme 9.



Scheme 10.

Table 1. Energies in kJ of HOMO and LUMOs orbitals obtained by ab initio DFT calculations

Acid	HOMO	LUMO	LUMO(+1)
14	−803	354	403
16	−781	360	408
18	−855	371	380

acid group, giving then acid **7**, also as a single isomer[13] (Scheme 11).

Synthesis of acid **1** used in the reaction of Scheme 2 was already described[15] by saponification of the methyl ester **37** formed by reaction of the sodium salt of methyl pyroglutamate[16] with the corresponding benzyl chloride.[17] Acid **2** was obtained by using a similar reaction pathway (Scheme 12).

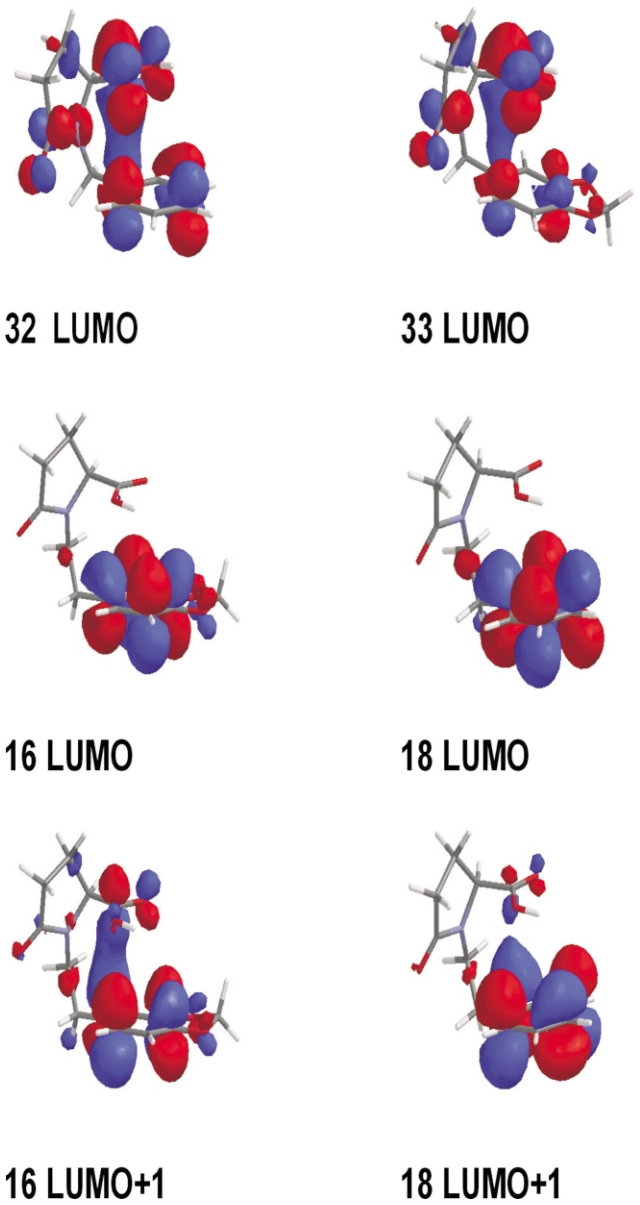


Figure 2. Representation of LUMO orbitals of **16**, **18**, **32** and **33**.

4. Conclusion

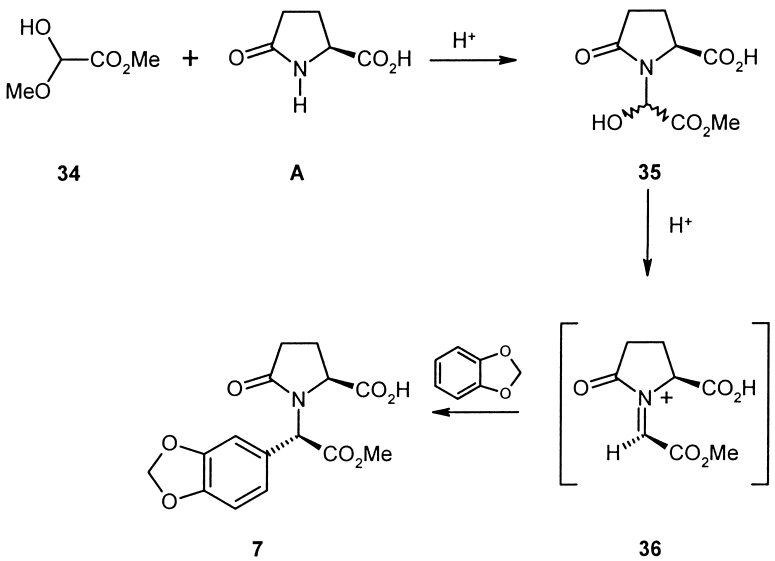
It is thus important to know that the decarboxylation of activated forms of pyroglutamic acids or of *N*-acylprolines is not an 'exceptional' reaction caused solely by reagents such as polyphosphoric acid[5b] or by the ring size of the ketone to be formed,[7] but that a carbon monoxide loss, leading to an acyl iminium salt, can occur in numerous and diverse situations.

5. Experimental

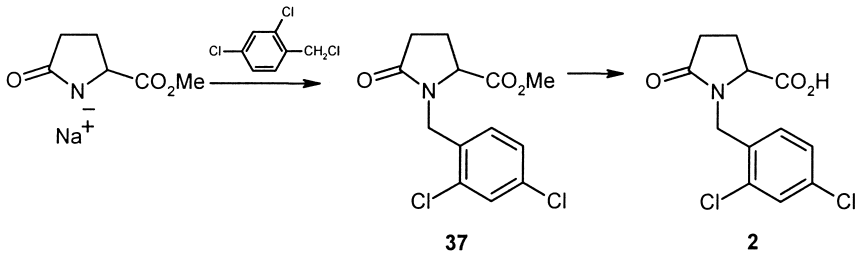
5.1. Materials

Melting points were determined with an Electrothermal® apparatus and are uncorrected. Thin-layer chromatographies were carried out on Merck F-254 silica glass plates. The IR spectra were recorded on a 'Perkin–Elmer' 700 spectrometer and the NMR spectra on a Varian 'Gemini 2000' at 200 MHz for ^{1}H and 50 MHz for ^{13}C, using tetramethylsilane as an internal reference. Elemental analyses were performed by the 'Service Central de Microanalyses' (CNRS, Vernaison, France). Pyroglutamic acids or esters used were racemic.

5.1.1. *N*-(2,4-Dichlorobenzyl)pyroglutamic acid (2). A stirred mixture of methyl *N*-(2,4-dichlorobenzyl)pyroglutamate (60.4 g, 0.20 mol) and sodium hydroxide (12 g, 0.30 mol) in water (400 ml) was refluxed for 2 h. The cooled solution was washed with dichloromethane, solvents were evaporated and the solution was acidified with concentrated hydrochloric acid, giving 91% of acid **2**, mp 161°C (methanol); IR (KBr): ν cm^{-1} 1730, 1640 (C=O), 1590, 1565, 1480 1460 (C=C); ^{1}H NMR ($CDCl_3$): δ ppm 2.1–2.3 (m, 1H), 2.3–2.48 (m, 1H), 2.48–2.75 (m, 2H), 4.17 (dd, J=8.9, 2.9 Hz), 4.28 (d, J=15.3 Hz, 1H), 5.04 (d, J=15.3 Hz, 1H), 7.23 (dd, J=8.3, 1.8 Hz, 1H), 7.30 (d, J=8.3 Hz, 1H), 7.40 (d, J=1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ ppm 23.0, 29.1, 42.9, 59.0, 127.5, 129.4, 131.6, 134.5, 134.6, 174.7, 176.3. Anal. calcd for $C_{12}H_{11}NO_3Cl_2$: C,



Scheme 11.



37 2

Scheme 12.

50.02; H, 3.85; N, 4.86; O, 16.66. Found: C, 50.40, H, 3.92; N, 4.77; O, 16.38.

5.1.2. 7-Methoxy-1,2,3,5,10,10a-hexahydrobenz[*f*]indolizine-3,10-dione (3) and 5-hydroxy-1-(4-methoxybenzyl)-pyrrolidin-2-one (5). A stirred mixture of acid **1** (10 g, 0.04 mol) and thionyl chloride (7.5 ml, 0.1 mol) in dichloroethane (200 ml) was refluxed for 30 min. Solvents were evaporated, dichloroethane (100 ml) was added and the solution was cooled with a water bath at 8°C. Aluminum chloride (21.4 g, 0.16 mol) was added (30 min) and the mixture was stirred at 8°C for 4 h. The mixture was poured in a water/ice mixture and methylene dichloride was added. The organic phase was washed with water until neutralization, then with a potassium carbonate solution. After drying (sodium sulfate), solvents were evaporated and the residue was purified by chromatography (ethyl acetate/heptane, 50/50).

Alcohol **5** was obtained as a white solid, yield 7%, mp 129–130°C (ethyl acetate); IR (KBr): ν cm^{-1} 3175 (OH), 1645 (C=O), 1610, 1590, 1515, 1460 (C=C), ^{1}H NMR ($CDCl_3$): δ ppm 1.73–2.05 (m, 1H), 2.15–2.45 (m, 2H), 2.49–2.73 (m, 1H), 3.02 (bs, 1H, D_2O), 3.79 (s, 3H), 4.16 (d, J=14.7 Hz, 1H), 4.77 (d, J=14.7 Hz, 1H), 5–5.15 (m, 1H), 6.81–6.90 (m, 2H), 7.18–7.26 (m, 2H). Anal. calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33; O, 21.69. Found: C, 65.23; H, 6.78; N, 6.29; O, 21.30.

Ketone **3** was obtained in 60% yield, mp 97–98°C (acetone) (106–107°C[3b]); IR (KBr): ν cm^{-1} 1690 (C=O); ^{1}H NMR ($CDCl_3$): δ ppm 2.28–2.64 (m, 4H), 3.86 (s, 3H), 4.30 (d, J=16.9 Hz, 1H), 4.2–4.4 (m, 1H), 5.22 (d, J=16.9 Hz, 1H), 7.16 (dd, J=8.7, 2.9 Hz, 1H), 7.25 (d, J=8.7 Hz, 1H), 7.54 (d, J=2.9 Hz, 1H). Anal. calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06; O, 20.76. Found: C, 67.59; H, 5.42; N, 5.89; O, 20.83.

5.1.3. 6,8-Dichloro-1,2,3,5,10,10a-hexahydrobenz[*f*](indolizine-3,10-dione (4) and 1-(2,4-dichlorobenzyl)-5-hydroxypyrrolidin-2-one (6). Trifluoroacetic anhydride (7 ml, 0.046 mol) was added to a suspension of acid **2** (11 g, 0.039 mol) in dichloroethane (100 ml) and the solution was refluxed for 1 h, giving the mixed anhydride, ^{1}H NMR ($CDCl_3$): δ ppm 2.1–2.4 (m, 1H), 2.4–2.62 (m, 1H), 2.62–2.8 (m, 2H), 4.29 (dd, J=9.7, 3.2 Hz, 1H), 4.39 (d, J=15 Hz, 1H), 5.06 (d, J=15 Hz, 1H), 7.31 (s, 1H), 7.31 (d, J=1.5 Hz, 1H), 7.45 (d, J=1.5 Hz, 1H). Solvents were evaporated, dichloroethane (100 ml) was added and the solution was cooled with a water bath at 8°C. Aluminum chloride (26 g, 0.195 mol) was added (1 h) and the mixture was stirred at room temperature for 2 days. The mixture was poured in a water/ice mixture and methylene dichloride was added. The organic phase was washed with water until neutralization, then with a potassium carbonate solution. After drying (sodium sulfate) solvents were evaporated. Crystallization of the residue in ethyl acetate gives ketone **4** (33%), mp 137–140°C (ethyl acetate); IR (KBr): ν cm^{-1} 1678, 1630 (C=O); ^{1}H NMR ($CDCl_3$): δ ppm 2.36–2.64 (m, 4H), 4.20 (d, J=18.2 Hz, 1H), 4.26–4.33 (m, 1H), 5.41 (d, J=18.2 Hz, 1H), 7.65 (d, J=2.2 Hz, 1H), 8.0 (d, J=2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ ppm 20.0, 29.5, 39.9, 60.7, 126.1, 132.6, 133.2, 134.2, 134.4, 135.8, 173.9, 191.5. Anal. calcd for $C_{12}H_9NO_2Cl_2$: C, 53.36; H, 3.36; N, 5.19; O, 11.85. Found: C, 53.21; H, 3.36; N, 5.06; O, 12.27.

Chromatography (ethyl acetate/heptane, 50/50) of the residue from crystallization of ketone **4** yields compound **6** (17%), mp 131–133°C (ethyl acetate), IR (KBr): ν cm^{-1} 3175 (OH), 1645 (C=O), 1590, 1570 (C=C); ^{1}H NMR ($CDCl_3$): δ ppm 1.87–2.06 (m, 1H), 2.22–2.51 (m, 2H), 2.53–2.74 (m, 1H), 2.83 (bs, D_2O exchangeable, 1H), 4.42 (d, J=15.5 Hz, 1H), 4.79 (d, J=15.5 Hz, 1H), 5.14 (d, J=5.0 Hz, 1H), 7.22 (dd, J=8.3, 2.1 Hz, 1H), 7.30 (d, J=8.3 Hz, 1H), 7.40 (d, J=2.1 Hz); ^{13}C NMR ($CDCl_3$): δ ppm 27.8, 28.5, 40.6, 82.4, 127.1, 129.0, 130.3, 132.8, 133.5, 133.8, 175.0. Anal. calcd for $C_{11}H_{11}NO_2Cl_2$: C, 50.79; H, 4.26; N, 5.38; O, 12.30. Found: C, 51.07; H, 4.44; N, 5.20; O, 12.68.

5.1.4. Electrochemical synthesis of 1-(2,4-dichlorobenzyl)-5-hydroxypyrrolidin-2-one (6). A mixture of acid **2** (3 g, 0.011 mol) and sodium hydroxide (0.04 g, 0.0011 mol) in water (15 ml) and tetrahydrofuran (15 ml) was stirred into an undivided jacketed beaker equipped with six graphite-rods anodes and six graphite-rods cathodes. The carbon-rods (6.15 mm in diameter), immersed 5 cm into the suspension, were spaced 10 mm apart. The current was adjusted at 175 mA; the initial voltage was 9.3 V. After 5 h, tetrahydrofuran was evaporated, methylene dichloride was added and the organic phases were washed with an hydrogenocarbonate solution. The organic phases were dried (sodium sulfate) then evaporated, giving compound **6** as a white solid, yield 78%, identical to the by-product of the Friedel–Crafts cyclization of acid **2**.

5.1.5. Methyl 2-(1,3-benzodioxol-5-yl)-2-(2-oxoprolin-1-yl)acetate (7). Triflic acid (1 ml, 1.71 g, 0.001 mol) was added via syringe to a mixture of crude acid **35** (97.7 g, 0.45 mol) and benzodioxole (61.1 g, 0.5 mol) in trifluoroacetic acid (150 ml). The solution was stirred at room temperature for three days, solvents were evaporated and

the residue was dissolved in dichloromethane. The solution was extracted with aqueous sodium carbonate, aqueous phases were washed with dichloromethane then acidified with dilute hydrochloric acid. Dichloromethane was added and the organic phases were dried (sodium sulfate) then evaporated giving a yellow oil, 41%, IR (KBr): $\nu\,cm^{-1}$ 3450 (OH), 1750, 1700, 16960 (C=O), 1510 1495, 1450 (C=C); ^1H NMR ($CDCl_3$): δ ppm 2.15–2.32 (m, 2H), 2.32–2.53 (m, 1H), 2.59–2.82 (m, 1H), 3.78 (s, 3H), 4.05–4.15 (m, 1H), 5.88 (s, 1H), 5.99 (s, 2H), 6.72–6.88 (m, 3H), 7.61 (bs, 1H), D_2O exchangeable); ^{13}C NMR (acetone-d6): δ ppm 24.9, 29.3, 52.1, 58.2, 58.7, 101.9, 108.5, 108.8, 122.2, 129.2, 148.3, 148.4, 169.8, 173.3, 175.8. Anal. calcd for $C_{15}H_{15}NO_7$: C, 56.08; H, 4.71; N, 4.36; O, 34.86. Found: C, 56.32; H, 4.49; N, 4.33; O, 34.99.

5.1.6. Methyl 2-(1,3-benzodioxol-5-yl)-2-(2-oxo-2,5-dihydro-1*H*-pyrrol-1-yl)acetate (8). Trifluoroacetic anhydride (1.7 ml, 2.5 g, 0.012 mol) was added to a mixture of crude acid **7** (3.3 g, 0.010 mol) and 1,2-dichloroethane (50 ml). Boron trifluoride etherate (5.2 ml, 5.9 g, 0.042 mol) was added to the solution. After reflux for 3 h, solvents were evaporated, dichloromethane was added, organic phases were washed with sodium carbonate, then dried (sodium sulfate). After evaporation, the residue was refluxed in ethyl acetate for 2 h (acticarbon). After evaporation, the residue was purified by chromatography (ethyl acetate), giving a 56% of compound **8** as a yellow oil, IR (KBr): $\nu\,cm^{-1}$ 1750, 1700 (C=O) 1600, 1510, 1495 (C=C), ^1H NMR ($CDCl_3$): (δ ppm 3.70 (dt, J=19.1, 1.8 Hz, 1H), 3.78 (s, 3H), 4.42 (dt, J=19.1, 1.8 Hz, 1H), 5.98 (s, 3H), 6.22 (dt, J=6, 1.8 Hz, 1H), 7.6–7.8 (m, 3H), 7.14 (dt, J=6, 1.8 Hz, 1H). Anal. calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09; O, 29.06. Found: C, 60.81; H, 4.38; N, 5.41; O, 29.12.

5.1.7. Methyl 2-hydroxy-2-(2-oxoprolin-1-yl) acetate (35). A stirred solution of pyroglutamic acid (15 g, 0.116 mol) and methyl 2-hydroxy-2-methoxy acetate (**22**) (16.7 g, 0.139 mol) in anhydrous acetone (150 ml) was refluxed for 60 h. Solvents were evaporated, dichloromethane (300 ml) was added, and the solution was extracted three times with water (100 ml). The aqueous phases were evaporated, giving a viscous yellow oil which was not analyzed but directly used for the next step (97% yield); IR (KBr): $\nu\,cm^{-1}$ 3400 (OH), 1740, 1700 (C=O), ^1H NMR ($CDCl_3$): δ ppm 2–2.3 (m, 1H), 2.3–2.8 (m, 3H), 3.79 (s, 1.5H), 3.83 (s, 1.5H), 4.28–4.41 (m, 0.5H), 4.43–4.58 (m, 0.5H), 5.73 (s, 0.5H), 5.89 (s, 0.5H), 6.6–7.3 (bs, 1H).

5.1.8. Methyl *N*-(2,4-dichlorobenzyl)pyroglutamate (37). A solution of methyl pyroglutamate (73 g, 0.51 mol) in toluene (400 ml) was added (1 h) to a well-stirred suspension of sodium hydride (13 g, 0.54 mol) in toluene (400 ml). The mixture was refluxed for 1 h, *N*-methylpyrrolidinone (200 ml) was added, then a solution of 2,4-dichlorobenzyl chloride (97.7 g, 0.50 mol) in toluene was added dropwise. The mixture was refluxed for 2 h. After cooling, water was added and the aqueous phases were extracted with dichloromethane. The organic phases were washed with water, dried (sodium sulfate) then evaporated, giving a yield of 75%, mp 67°C (acetone); IR (KBr): $\nu\,cm^{-1}$ 1740, 1700 (C=O), 1590, 1565, 1480 (C=C); ^1H NMR ($CDCl_3$): δ ppm 2.01–2.2 (m, 1H), 2.2–2.40 (m, 1H), 2.40–2.7 (m, 2H), 3.72 (s, 3H), 4.05 (dd, J=8.8, 3.4 Hz), 4.26 (d, J=16 Hz, 1H), 4.97 (d, J=16 Hz, 1H), 7.18–7.30 (m, 2H), 7.39 (s, 1H); ^{13}C NMR ($CDCl_3$): δ ppm 22.4, 28.5, 42.1, 51.8, 58.4, 126.9, 128.7, 130.9, 131.7, 133.5, 133.9, 171.4, 174.5. Anal. calcd for $C_{13}H_{13}NO_3Cl_2$: C, 51.68; H, 4.34; N, 4.64; O, 15.89. Found: C, 51.29, H, 4.42; N, 4.28; O, 15.97.

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