ACADEMIA ROMÂNĂ
Revue Roumaine de Chimie
http://web.icf.ro/rrch/

Rev. Roum. Chim.,
2012, 57(12), 1065-1072

STUDIES ON PYRROLIDINONES. ON THE SYNTHESIS OF 5-ARYL-2-PYRROLIDONES

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Received November 20, 2012

The optimization of the synthesis of 5-aryl-2-pyrrolidinones from decarbonylation of pyroglutamic acid in Eaton's reagent in the presence of aromatic derivatives is described. Four synthesized compounds were evaluated for their antiproliferative activity in the NCI-60 cancer cell lines panel.

INTRODUCTION

2-Pyrrolidinones are important compounds because of their biological significance.[1] Among them, 5-aryl-2-pyrrolidones need to be distinguished; indeed, some of them display high binding affinity towards CCR4 receptor,[2] are sleep inducing agents,[3] are inhibitors of the CB1 cannabinoid receptor,[4] of the tumor necrosis factor alpha-converting enzyme (TACE), tumor necrosis factor alpha (TNF-α), matrix metallo proteinases (MMP), a disintegrin and metalloproteinase (ADAM) and aggrecanase[5] or of the orexin receptor.[6] They are also useful as intermediates in the synthesis of pyrrolines[7] and of various types of drugs,[8] of antimicrobial products[9] or polymers,[10] or of biologically active 2-aryl amines.[11] Many methods[12] have been described for the synthesis of these key compounds, such as the reductive amination of β-aroylpropionic acids,[13] the reaction of aryl lactones with amines,[14] the radical cyclization of *N*-vinyl-phenylsulfanylacetamides,[15] the SmI_2 mediated coupling of β-lactones and electrophiles,[16] the photo reaction of cyanobenzenes with pyrrolidone,[17] the Pd-catalyzed cyclization of *N*-carbamoyl aminoalkynes[18] or amidoalkenes,[19] the oxidative cyclization of tertiary amides[20] or the oxidation of pyrrolidines.[21] However, one of the most utilized method is the reaction of γ-lactam *N*-acyliminium salts with aromatic compounds[22] or potassium aryltrifluoroborates.[23]

However, one of shorter and interesting methods starts from 2-pyrrolidinone-5-carboxylic acid (pyroglutamic acid, **1**) which has been called "the forgotten amino acid"[24] and is an essential biological member of the "chiral pool".[25] Indeed, diacetoxyiodobenzene/I_2,[26a,d] cerium ammonium nitrate[26b] or sodium periodate[26c] are able to decarboxylate pyroglutamic acid **1** or its derivatives to the *N*-acyliminium salt intermediate **2**, which can be further transformed for example into a 5-allyl-2-pyrrolidone, 5-hydroxy-2-pyrrolidone, 5-methoxy-2-pyrrolinone or maleimide. Decarboxylation (*elimination of carbon dioxide*) of pyroglutamic acid **1** is also possible by anodic oxidation. This method leading to the *N*-acyliminium salt **2** was first described in 1979,[27] and we later reported its use in the synthesis of new heterocycles.[28] Interestingly, we also observed the formation of an *N*-acyliminium salt **2** by decarbonylation (*elimination of carbon monoxide*) of pyroglutamic acid derivatives in presence of Eaton's reagent[29] or polyphosphoric acid

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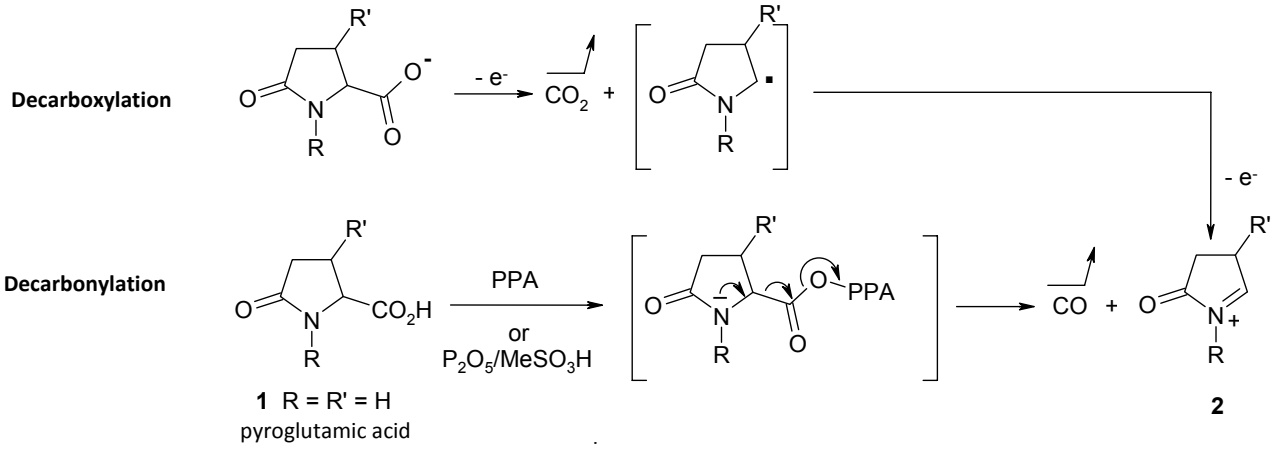
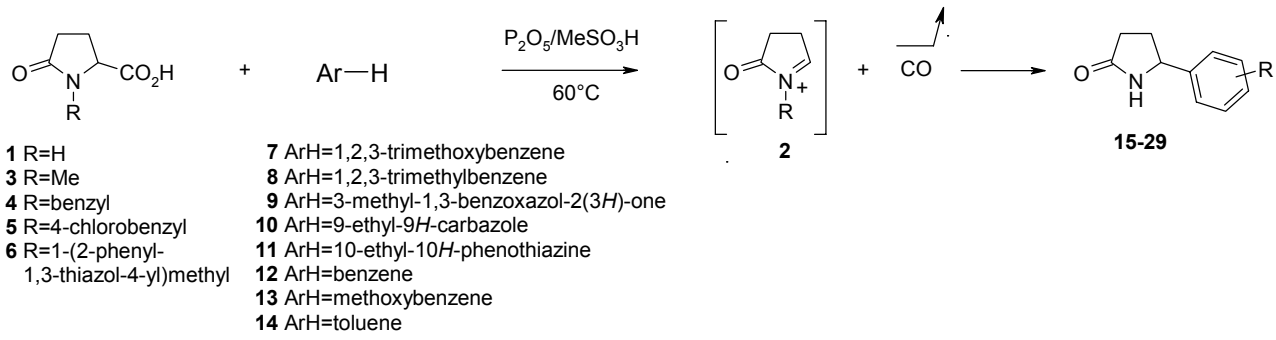
(Scheme 1) - or the corresponding acid chloride with Lewis acids -,[25e,30] which is able to react *in situ* with aromatics to give 5-aryl-2-pyrrolidinones **15-19**, **24**, **26**, and **28** (Scheme 2).[30a,b] This method of obtention of the *N*-acyliminium salt **2** was extended to the use of triflic anhydride as a promoting reagent,[31] and was applied to the synthesis of agonists of sphingosine-1-phosphate receptors.[11]

In the present paper, we describe the result of optimization of the synthesis of 5-aryl-2-pyrrolidinones from decarbonylation of pyroglutamic acid in Eaton's reagent in the presence of aromatic derivatives.



Scheme 1 – Syntheses of *N*-acyliminium salts **2** from pyroglutamic acid **1**.



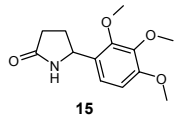
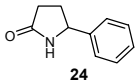
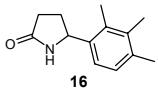
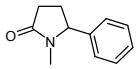
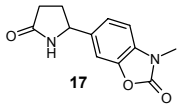
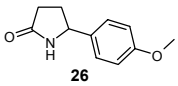
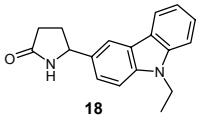
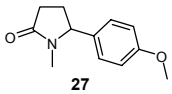
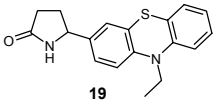
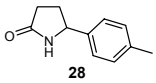
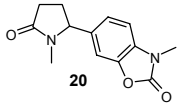
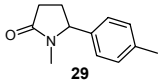
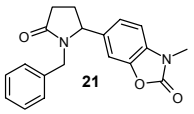
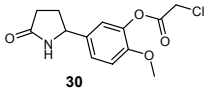
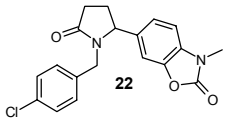
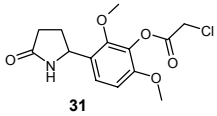
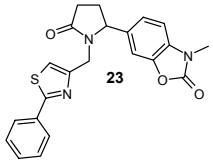
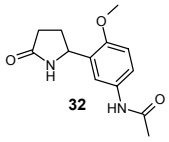
Scheme 2 – Reactions of pyroglutamic acid **1** and analogues **3**-**6** with aromatic derivatives **7**-**14** in Eaton's reagent.[30a,b]

RESULTS AND DISCUSSION

1. Synthesis of 5-aryl-2-pyrrolidinones. Cleavage of the chloroacetic esters 30, 31 in presence of sodium acetate

Eaton's reagent[29a] is a 1:10 solution by weight of phosphorus pentoxide in methanesulfonic acid. Organic compounds often dissolve rapidly[29c] in this mobile liquid, and the solutions obtained can be easily stirred. This condensing agent is often more efficient than polyphosphoric acid (PPA), and is rapidly hydrolyzed at the end of the reaction. According to Eaton,[29a] methanesulfonic anhydride is formed in this mixture, but other species are also present, such as polyphosphoric and mixed anhydrides of polyphosphoric and methanesulfonic acid.[29b] In some reactions, phosphorous pentoxide is mainly used as a drying agent.[29b] Indeed, methanesulfonic acid is a hygroscopic liquid containing 0.5% of water and, in the case of our study of the synthesis of 5-aryl-2-pyrrolidinones **15-32** (Table 1), it was observed that old bottles of methanesulfonic acid often lead to poor results. Previously[30b] a 1/7 ratio of pyroglutamic acid *versus* Eaton's reagent was utilized at temperatures between 65 °C and 100 °C. These conditions were optimized to a 1/4 ratio at 60 °C without lowering the yields,[30a] and the results obtained are described in Table 1.

Table 1
Synthesis of 5-aryl-2-pyrrolidinones[a]

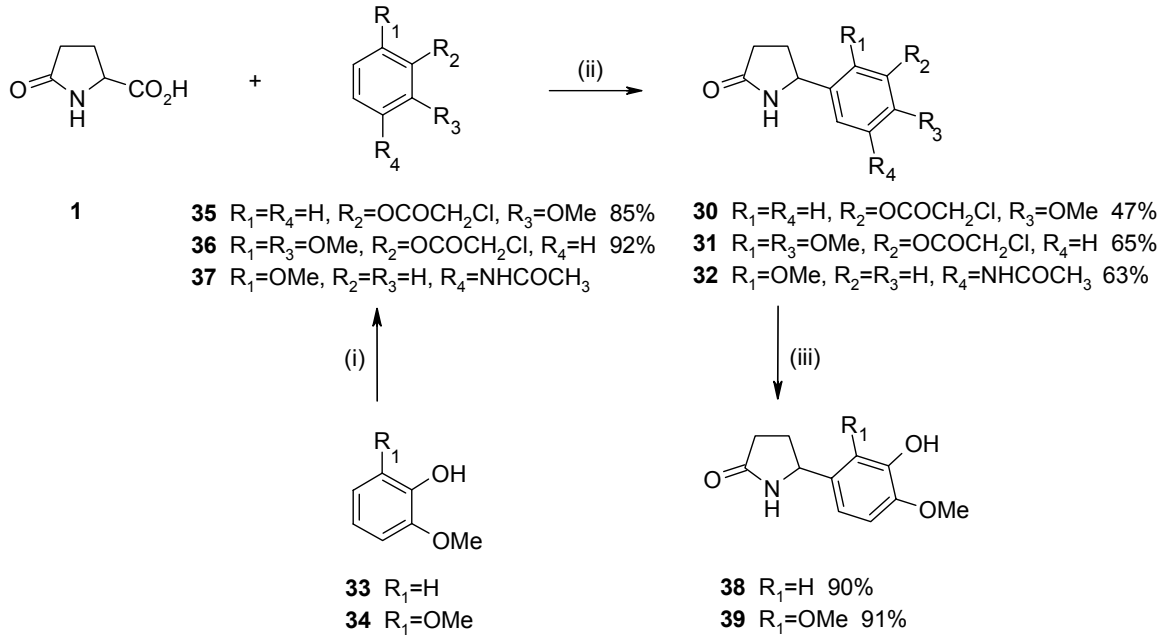
Entry	Product	t (h)	Yield (%)	Entry	Product	t (h)	Yield (%)
1	 **15**	24[b]	53[b]	**10**	 **24**	24	32 (28[c])
2	 **16**	24[b]	61[b]	**11**	 **25**	24	30 (27[c])
3	 **17**	24[b]	63[b] (82[c])	**12**	 **26**	24	80 (77[c])
4	 **18**	43[b]	52[b]	**13**	 **27**	20	88 (90[c])
5	 **19**	24[b]	60[b]	**14**	 **28**	20	73 (68[c])
6	 **20**	20	80 (71[c])	**15**	 **29**	20	72 (76[c])
7	 **21**	24	50 (39[c])	**16**	 **30**	9	47
8	 **22**	19	63 (55[c])	**17**	 **31**	12	65
9	 **23**	16	48 (47[c])	**18**	 **32**	16	63

[a] Reactions carried out at 60 °C;
[b] Ref. 30a;
[c] Ref. 30b.

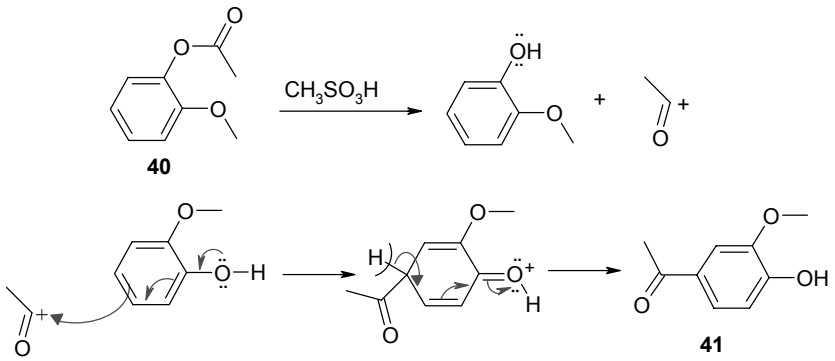
We were also interested in obtaining 5-aryl-2-pyrrolidinones bearing an amide or a phenol group on the aromatic moiety. Thus, compounds **38** and **39** were synthesized by reacting pyroglutamic acid **1** with protected phenols **35** and **36**[32] in Eaton's reagent at 60 °C to give chloroacetic pyrrolidinones **30** and **31** (47 and 65% yield, respectively), followed by removal of the chloroacetyl protection group by using sodium acetate in methanol (90 and 91% yield, respectively). The same condensation sequence in presence of Eaton's reagent applied to *N*-(4-methoxyphenyl)acetamide **37** led to pyrrolidinone **32** (63% yield) (Scheme 3).

The chloroacetyl protecting group has been chosen after an experimental observation when trying to react pyroglutamic acid **1** with 2-methoxyphenyl acetate **40** in the presence of Eaton's reagent. In this case, we obtained as the major reaction product, a Fries rearrangement product **41** (Scheme 4). Aromatic esters, heated with a Lewis acid such as $AlCl_3$, are transposed to afford phenol-ketones.[33] In our case, methanesulfonic acid plays the same role as $AlCl_3$.

Thus, we opted for a protecting group, easily cleavable, but with an electron-withdrawing group, unfavorable to transposition. All phenols described in this paper were therefore protected as chloroacetates.



Scheme 3 – Reagents and conditions: (i) $ClCH_2COCl$ 1.4-1.5 equiv, 135 °C, 7-8 h;[32] (ii) aromatic derivative **35**-**37** 1.15 equiv, Eaton's reagent 4 equiv, 60 °C, 9-16 h; (ii) $AcONa \cdot 3H_2O$ 4.5 equiv, MeOH, reflux, 1-3 h.

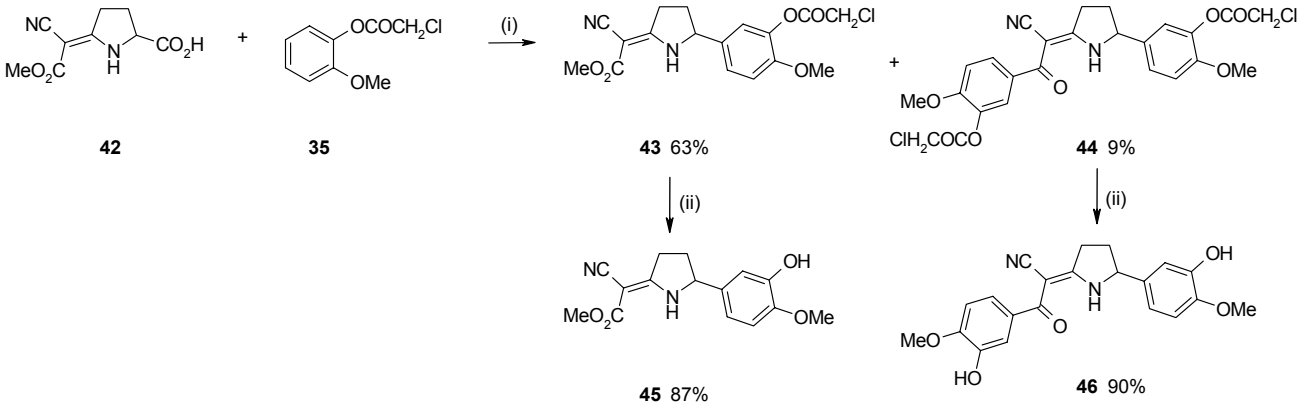


Scheme 4 – Mechanistic pathway for the Fries transposition observed on 2-methoxyphenyl acetate **40**. Reagents and conditions: Eaton's reagent (P_2O_5/CH_3SO_3H 1/10 w/w) 4.5 equiv, 90 °C, 5 h, 67%.

2. Reaction of enaminoester 42, vinylogue of pyroglutamic acid, with aromatic derivative 35. Cleavage of the chloroacetic esters 43, 44 in the presence of sodium acetate

We then decided to study the reactivity of the cyanoenaminoester **42** in Eaton's reagent. However, the desired compound resulting from decarbonylation of acid **42** was obtained along with enaminoketone **44**, isolated in 9% yield (Scheme 5). The cleavage of the protecting groups of compounds **43** and **44** provided the corresponding phenols **45** and **46** in good yields.

Compounds **18**, **19**, **45**, and **46** were selected by NCI (National Cancer Institution, USA) for screening against 60 human tumor cell lines. Molecule **45** showed good cell growth inhibition at a 10 μM concentration on two cell lines (62% inhibition of RPMI-8226 (leukemia), and 60% of NCI-H522 (non-small cell lung cancer)) and very promising inhibition (93%) of the growth of MDA-MB-435 (melanoma)) (Figure 1). The closely related derivative **46** conserved very modest biological potency on leukemia cell lines (only 25% inhibition of RPMI-8226 and 32% inhibition of HL-60(TB)) (Fig. 1). All other tested compounds were inactive.



Scheme 5 – Reagents and conditions: (i) 2-methoxyphenyl chloroacetate **35** 1.15 equiv, Eaton's reagent 4 equiv, 60 °C, 20 h; (ii) $AcONa \cdot 3H_2O$ 4.5 equiv, MeOH, reflux, 1-3 h.

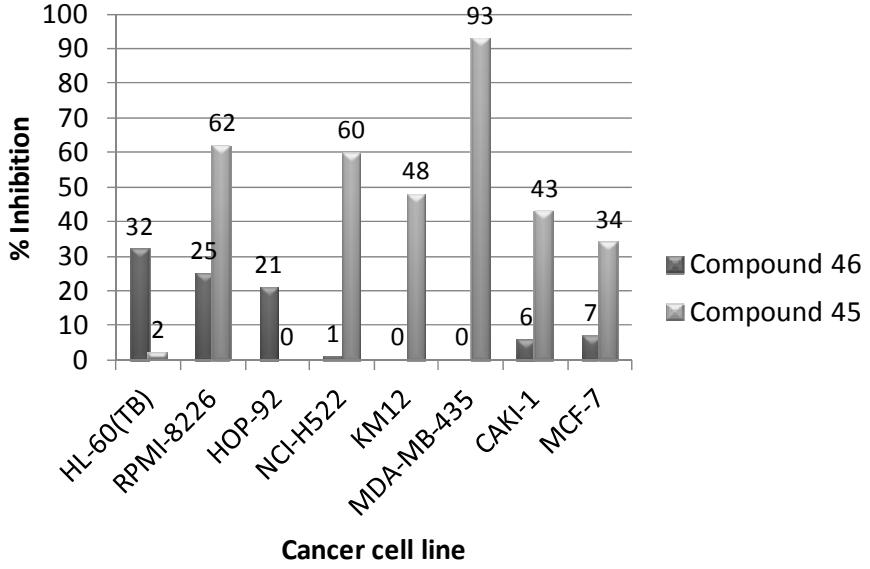


Fig. 1 – Results of the in vitro human cell growth inhibition obtained with compounds **45** and **46** at a 10 μM concentration.

EXPERIMENTAL

1. General

Starting materials were commercially available. Melting points were measured on a MPA 100 OptiMelt® apparatus and are uncorrected. NMR spectra were acquired at 200 MHz for ^{1}H-NMR and 50 MHz for ^{13}C-NMR on a Varian Gemini 2000® spectrometer, or at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR on a Varian 400 MHz Premium Shielded® spectrometer. Chemical shifts (δ) are expressed in ppm relative to TMS as internal standard. IR spectra were recorded on a Varian 640eIR FT-IR Spectrometer. Thin layer chromatographies were realized on Macherey Nagel silica gel plates with a fluorescent indicator and were visualized with UV-lamp at 254 nm and 366 nm. Column chromatographies were performed on silica gel (40-60 μm; Macherey-Nagel). Elemental analyses (C, H, N, S) of new compounds were determined by "Service de Microanalyses", Faculté de Sciences Mirande, Université de Bourgogne, Dijon, France.

2. General procedure A for Friedel-Crafts reactions in the presence of Eaton's reagent

Eaton's reagent was prepared from phosphorus pentoxide (P_2O_5) and methanesulfonic acid (CH_3SO_3H) (weight ratio P_2O_5:CH_3SO_3H 1:10). The mixture was heated at 40 °C under nitrogen atmosphere until complete homogeneity. Carboxylic acid (1.0 equiv) and aromatic derivative (1.1 – 1.5 equiv) were then added to Eaton's reagent. The mixture was heated at 60 °C under inert atmosphere for 9-43 h. After cooling to room temperature, the reaction medium was diluted with dichloromethane and carefully poured into a separatory funnel containing sodium bicarbonate aqueous solution (50% $NaHCO_3$). The aqueous solution was extracted with dichloromethane, and the combined organic layers were dried ($MgSO_4$). Solvent was removed under reduced pressure to give a brownish oil. The crude product was purified by column chromatography on silica gel or recrystallized to afford pure compounds **15**-**32**, **43**, and **44**.

2-Methoxy-5-(5-oxopyrrolidin-2-yl)phenyl chloroacetate **(30)** (Scheme 3 and Table 1). The general procedure A was

followed using L-pyroglutamic acid **1** (4.68 g, 36.25 mmol), 2-methoxyphenyl chloroacetate **35** (8.00 g, 39.88 mmol), and Eaton's reagent (1.70 g P_2O_5 in 11.49 mL CH_3SO_3H). The mixture was heated at 60 °C for 9 h. The final brown oil was purified by column chromatography on silica gel with a gradient EtOAc/*n*-heptane from 50/50 to 100/0 to give pure pyrrolidinone **30** (47%) as a white solid; mp (EtOAc) 124-125 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.87-2.06 (m, 1H, CH_2CH_2CH), 2.36-2.65 (m, 3H, CH_2CH_2CH), 3.84 (s, 3H, OCH_3), 4.35 (s, 2H, $OCOCH_2Cl$), 4.68 (dd, J = 14.2, 6.7 Hz, 1H, CH_2CH_2CH), 5.65 (s, 1H, NH), 6.97 (d, J = 8.3 Hz, 1H, ArH), 7.03 (d, J = 2.1 Hz, 1H, ArH), 7.18 (dd, J = 8.5, 2.1 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 33.1 (CH_2), 31.3 (CH_2), 40.5 (CH_2), 56.0 (CH), 57.2 (CH_3), 112.8 (CH), 119.9 (CH), 124.5 (CH), 135.1 (C), 140.2 (C), 150.5 (C), 161.0 (C), 178.2 (C). IR ν cm^{-1}: 692, 1140, 1316, 1350, 1440, 1512, 1680, 1775, 3184. Calcd for $C_{13}H_{14}O_4NCl$: C, 55.04; H, 4.97; N, 4.94. Found: 55.40; H, 4.75; N, 4.77.

2,6-Dimethoxy-3-(5-oxopyrrolidin-2-yl)phenyl chloroacetate **(31)** (Scheme 3 and Table 1). The general procedure A was followed using L-pyroglutamic acid **1** (2.54 g, 19.67 mmol), 2,6-dimethoxyphenyl chloroacetate **36** (5.00 g, 21.68 mmol), and Eaton's reagent (0.92 g P_2O_5 in 6.24 mL CH_3SO_3H). The mixture was heated at 60 °C for 12 h. The final brown oil was purified by column chromatography on silica gel with a gradient EtOAc/*n*-heptane from 50/50 to 100/0 to give pure pyrrolidinone **31** (65%) as a white solid; mp (EtOAc/*n*-heptane) 92-94 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.85-2.10 (m, 1H, CH_2CH_2CH), 2.40-2.63 (m, 3H, CH_2CH_2CH), 3.83 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.37 (s, 2H, $OCOCH_2Cl$), 5.01 (t, J = 6.8 Hz, 1H, CH_2CH_2CH), 5.90 (s large, 1H, NH), 6.74 (d, J = 8.1 Hz, 1H, ArH), 7.16 (d, J = 8.1 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.9 (CH_2), 30.1 (CH_2), 40.4 (CH_2), 52.4 (CH), 56.2 (CH_3), 61.8 (CH_3), 107.4 (CH), 123.4 (CH), 128.3 (C), 132.6 (C), 150.1 (C), 151.7 (C), 164.9 (C), 178.7 (C). Calcd for $C_{14}H_{16}O_5NCl$: C, 53.60; H, 5.14; N, 4.46. Found: C, 53.20; H, 5.10; N, 4.28.

N-[4-Methoxy-3-(5-oxopyrrolidin-2-yl)phenyl]acetamide **(32)** (Scheme 3 and Table 1). The general procedure A was followed using L-pyroglutamic acid **1** (1.50 g, 7.14 mmol), *N*-(4-methoxyphenyl)acetamide **37** (2.21 g, 13.38 mmol), and Eaton's reagent (0.55 g P_2O_5 in 3.68 mL CH_3SO_3H). The mixture was heated at 60 °C for 16 h. The final brown oil was purified by column chromatography on silica gel with EtOAc/*n*-heptane 4/6 to give pure compound **32** (63%) as a white solid; mp (EtOAc/*n*-heptane) 245-247 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ (ppm) 1.80-2.00 (m, 1H, CH_2CH_2CH), 2.09 (s, 3H, $NHCOCH_3$), 2.30-2.45 (m, 2H, CH_2CH_2CH), 2.50-2.71 (m, 1H, CH_2CH_2CH), 3.84 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.60 (bs, 1H, NH), 5.05 (dd, J = 10.8, 5.2 Hz, 1H, CH_2CH_2CH), 6.94 (d, J = 8.7 Hz, 1H, ArH), 7.34 (d, J = 2.5 Hz, 1H, ArH), 7.48 (dd, J = 8.7, 2.5 Hz, 1H, ArH). IR ν cm^{-1}: 1250, 1450, 1605, 1615, 1660, 1695, 1985, 3310. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.63; H, 6.53; N, 11.36.

Methyl (2Z)-(5-{3-[(chloroacetyl)oxy]-4-methoxyphenyl}pyrrolidin-2-ylidene)(cyano)acetate **(43)** (Scheme 5). The general procedure A was followed using carboxylic acid **42** (1.50 g, 7.14 mmol), 2-methoxyphenyl chloroacetate **35** (1.57 g, 7.83 mmol), and Eaton's reagent (0.55 g P_2O_5 in 3.68 mL CH_3SO_3H). The mixture was heated at 60 °C for 20 h. The final brown oil was purified by column chromatography on silica gel with EtOAc/*n*-heptane 4/6 to give pure compound **43** (63%) as a white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.89-2.10 (m, 1H, CH_2CH_2CH), 2.48-2.63 (m, 1H, CH_2CH_2CH), 2.88-3.21 (m, 2H, CH_2CH_2CH), 3.77 (s, 3H, $COOCH_3$), 3.84 (s, 3H, OCH_3), 4.34 (s, 2H, $OCOCH_2Cl$), 5.01 (t, J = 6.8 Hz, 1H, CH_2CH_2CH), 6.96 (s, 1H, ArH), 6.98 (d, J = 8.6 Hz, 2H, ArH), 7.12 (dd, J = 8.5, 2.0 Hz, 1H, ArH), 9.10 (s, large, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.70 (CH_2), 32.58 (CH_2), 40.21 (CH_2), 53.82 (CH_3), 55.82 (CH_3), 61.56 (CH), 64.01 (C), 113.52 (CH), 114.45 (C), 121.90 (CH), 126.85 (CH), 135.02 (C), 142.3 (C), 150.2 (C), 159.9 (C), 170.4 (C), 175.1 (C). Calcd for $C_{17}H_{17}O_5N_2Cl$: C, 55.97; H, 4.70; N, 7.68. Found: 56.34; H, 4.62; N, 7.08.

5-[(5Z)-5-(2-{3-[(Chloroacetyl)oxy]-4-methoxyphenyl}-1-cyano-2-oxoethylidene)pyrrolidin-2-yl]-2-methoxyphenyl chloroacetate **(44)** (Scheme 5). By-product from the synthesis of compound **43**; white solid; 9% yield; mp (EtOAc/*n*-heptane) 120-123 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.94-2.18 (m, 1H, CH_2CH_2CH), 2.53-2.70 (m, 1H, CH_2CH_2CH), 3.01-3.34 (m, 2H, CH_2CH_2CH), 3.85 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.34 (s, 2H, $OCOCH_2Cl$), 4.35 (s, 2H, $OCOCH_2Cl$), 5.11 (t, J = 7.6 Hz, 1H, CH_2CH_2CH), 6.98 (d, J = 3.6 Hz, 1H, ArH), 7.01 (d, J = 3.0 Hz, 1H, ArH), 7.03 (d, J = 5.4 Hz, 1H, ArH), 7.15 (dd, J = 8.4, 2.2 Hz, 1H, ArH), 7.68 (d, J = 2.2 Hz, 1H, ArH), 7.98 (dd, J = 8.7, 2.2 Hz, 1H, ArH), 10.99 (s, large, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.59 (CH_2), 33.78 (CH_2), 40.48 ($2CH_2$), 56.00 ($2CH_3$), 65.00 (CH), 82.11 (C), 111.34 (CH), 112.81 (CH), 120.08 (CH), 122.75 (CH), 124.89 (CH), 127.97 (CH), 131.13 (C), 132.35 (C), 139.54 (C), 148.70 (C), 150.91 (C), 153.55 (C), 158.90 (C), 164.89 (C), 165.01 (C), 169.92 (C), 175.38 (C). IR ν cm^{-1}: 696, 1142, 1247, 1440, 1628, 1714, 2208, 3264. Calcd for $C_{25}H_{22}O_7N_2Cl_2$: C, 55.97; H, 4.70; N, 7.68. Found: 56.34; H, 4.62; N, 7.08.

Compounds **15-29** presented the same physico-chemical properties as described in the literature by our research group.[30a,b]

3. General procedure B for the synthesis of phenols from chloroacetic esters

Monochloroacetic ester **30**, **31**, **43**, and **44** (1 equiv) and sodium acetate (4.5 equiv) were dissolved in methanol. The solution was refluxed for 1–3 h. After cooling at rt, the mixture was concentrated under reduced pressure. The residue was taken into distilled water. The resulting precipitate was filtered, washed with water several times to remove remaining sodium acetate. The solid was recrystallized from ethanol to provide pure phenols **38**, **39**, **45**, and **46**.

5-(3-Hydroxy-4-methoxyphenyl)pyrrolidin-2-one **(38)** (Scheme 3). The general procedure B was followed using chloroacetate **30** (0.60 g, 2.12 mmol) and sodium acetate ($AcONa{\cdot}3H_2O$) (1.30 g, 9.55 mol) in MeOH (15 mL). The reaction mixture was refluxed for 1 h. The formed solid was collected by filtration and recrystallized from EtOH to obtain phenol **38** (90%) as a white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.83-2.03 (m, 1H, CH_2CH_2CH), 2.34-2.55 (m, 3H, CH_2CH_2CH), 3.87 (s, 3H, OCH_3), 4.64 (t, J = 6.6 Hz, 1H, CH_2CH_2CH), 6.65 (s, 1H, OH), 6.74 (dd, J = 8.2, 1.9 Hz, 1H, ArH), 6.83 (d, J = 8.6 Hz, 1H, ArH), 6.85 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.81 (CH_2), 32.21 (CH_2), 53.30 (CH), 56.22 (CH_3), 109.53 (CH), 114.60 (CH), 117.92 (CH), 136.50 (C), 145.11 (C), 147.82 (C), 179.44 (C). Calcd for $C_{11}H_{13}O_3N$: C, 63.76; H, 6.32; N, 6.76. Found: 63.62; H, 6.30; N, 6.60.

5-(3-Hydroxy-2,4-dimethoxyphenyl)pyrrolidin-2-one **(39)** (Scheme 3). The general procedure B was followed using chloroacetate **31** (0.80 g, 2.55 mmol) and sodium acetate ($AcONa{\cdot}3H_2O$) (1.56 g, 11.46 mol) in MeOH (15 mL). The reaction mixture was refluxed for 2 h. The formed solid was collected by filtration and recrystallized from EtOH to obtain phenol **39** (91%) as a white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.88-2.09 (m, 1H, CH_2CH_2CH), 2.37-2.69 (m, 3H, CH_2CH_2CH), 3.90 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 5.01 (t, J = 7.0 Hz, 1H, CH_2CH_2CH), 5.74 (s, 1H, ArO*H*), 6.64 (d, J = 9.0 Hz, 1H, Ar*H*), 6.76 (d, J = 9.0 Hz, 1H, Ar*H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 29.8 (CH_2), 30.1 (CH_2), 52.6 (CH), 56.3 (CH_3), 60.7 (CH_3), 106.1 (CH), 115.4 (CH), 128.3 (2H), 138.7 (C), 144.5 (C), 147.5 (C), 178.6 (C). Calcd for $C_{12}H_{15}O_4N$: C, 60.75; H, 6.37; N, 5.90. Found: 60.38; H, 6.16; N, 5.59.

Methyl (2Z)-cyano[5-(3-hydroxy-4-methoxyphenyl)pyrrolidin-2-ylidene]acetate **(45)** (Scheme 5). The general procedure B was followed using chloroacetate **43** (0.15 g, 0.41 mmol) and sodium acetate ($AcONa{\cdot}3H_2O$) (0.25 g, 1.84 mol) in MeOH (8 mL). The reaction mixture was refluxed for 1 h. The formed solid was collected by filtration and recrystallized from EtOH to obtain phenol **45** (87%) as a white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.85-2.07 (m, 1H, CH_2CH_2CH), 2.43-2.64 (m, 1H, CH_2CH_2CH), 2.85-3.22 (m, 2H, CH_2CH_2CH), 3.77 (s, 3H, $COOCH_3$), 3.90 (s, 3H, OCH_3), 4.95 (t, J = 6.9 Hz, 1H, CH_2CH_2CH), 5.68 (s, 1H, ArO*H*), 6.65-6.86 (m, 2H, Ar*H*), 6.79 (s, 1H, Ar*H*), 9.11 (s, large, 1H, N*H*). Calcd for $C_{15}H_{16}O_4N_2$: C, 62.49; H, 5.59; N, 9.72. Found: 62.65; H, 5.51; N, 10.01.

(2Z)-3-(3-Hydroxy-4-methoxyphenyl)-2-[5-(3-hydroxy-4-methoxyphenyl)pyrrolidin-2-ylidene]-3-oxopropanenitrile **(46)** (Scheme 5). The general procedure B was followed using chloroacetate **44** (0.05 g, 0.09 mmol) and sodium acetate ($AcONa{\cdot}3H_2O$) (0.05 g, 0.37 mol) in MeOH (5 mL). The reaction mixture was refluxed for 3 h. The formed solid was collected by filtration and recrystallized from EtOH to obtain phenol **46** (90%) as a white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 1.89-2.08 (m, 1H, CH_2CH_2CH), 2.41-2.75 (m, 1H, CH_2CH_2CH), 2.97-3.38 (m, 2H, CH_2CH_2CH), 3.91 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 5.04 (t, J = 7.7 Hz, 1H, CH_2CH_2CH), 5.64 (s, 1H, ArO*H*), 5.68 (s, 1H, ArO*H*), 6.70-6.93 (m, 4H, Ar*H*), 7.43 (s, 1H, Ar*H*), 7.56 (d, J = 8.9 Hz, 1H, Ar*H*), 10.96 (s large, 1H, N*H*). Calcd for $C_{21}H_{20}O_5N_2$: C, 55.04; H, 4.97; N, 4.94. Found: 55.40; H, 4.75; N, 4.77.

1-(4-Hydroxy-3-methoxyphenyl)ethanone **(41)**[32] (Scheme 4). A mixture of 2-methoxyphenyl acetate **40** (7.08 g, 42.6 mmol) and Eaton's reagent (3.18 g P_2O_5 in 21.48 mL CH_3SO_3H) was stirred vigorously at 90 °C for 5 h. The reaction mixture was diluted with water, neutralized with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, and concentrated to leave a brown oil. Further purification by silica chromatography (CH_2Cl_2/MeOH 95/5) gave transposition product **41** (4.74 g, 67%) as an off-white solid; mp (CH_2Cl_2/MeOH) 114-115 °C (lit. 114-116 °C);[44] ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm) 2.57 (s, 3H, $COCH_3$), 3.96 (s, 3H, OCH_3), 6.11 (s, 1H, ArO*H*), 3.98 (s, 3H, OCH_3), 6.95 (d, J = 8.2 Hz, 1H, Ar*H*), 7.51-7.55 (m, 2H, Ar*H*).

CONCLUSIONS

In conclusion, we have realized an extension of our previous work and showed that 5-aryl-2-pyrrolidinones bearing a phenol group on the aromatic moiety can be easily obtained by condensation in presence of Eaton's reagent followed by simple cleavage of the chloroacetyl protecting group. The enaminoester **42**, vinylogue of pyroglutamic acid, was subject to decarbonylation in the same way as the parent acid for which this condensation was optimized. However, a by-product was also formed in this reaction. The possibility for enaminoesters to react with aromatics in bimolecular reaction to give enaminoketones needs also to be noted.

Acknowledgements: The authors gratefully acknowledge the PRES (Pôle de Recherche et d'Enseignement Supérieur, Université Lille Nord de France) for financial support and the NCI (National Cancer Institute, USA) for the biological evaluation of compounds on their 60-cell panel.

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