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Studies on pyrrolidinones. Reaction of pyroglutamic acid and vinylogues with aromatics in Eaton's reagent

Alina Ghinet [a,b,*,†], Nathalie Van Hijfte [b,c,†], Philippe Gautret [a,b], Benoît Rigo [a,b], Hassan Oulyadi [d], Jolanta Rousseau [a,b]

[a] Univ Lille Nord de France, F-59000 Lille, France
[b] UCLille, EA GRIIOT (4481), Laboratoire de pharmacochimie, HEI, 13 rue de Toul, F-59046 Lille, France
[c] URCOM, EA 3221, INC3M, FR-CNRS 3038, UFR des Sciences et Techniques de l'Université du Havre, 25 rue Philippe Lebon, F-76058 Le Havre, France
[d] IRCOF-UMR 6014 CNRS, INC3M, FR-CNRS 3038, Place Emile Blondel, Université de Rouen, F-76131 Mt-St-Aignan Cedex, France

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ABSTRACT

The optimization of the synthesis of 5-aryl-2-pyrrolidinones through decarbonylation of pyroglutamic acid in Eaton's reagent, in presence of aromatic derivatives, is described. The utilization of these reaction conditions in the arylation of enaminoester vinylogues (**17**, **24**) of pyroglutamic acid was also realized, confirming that these derivatives are subject to decarbonylationî in the same way as the parent acid. Depending on the nature of the aromatic derivative (**15**, **21**, **28**, and **32**), two different families of compounds were obtained. Many by-products were also formed, suggesting a utilization of this reaction for compounds more stable than the enaminoesters and enaminonitriles used in this study. The possibility of enaminoesters reacting with aromatics in bimolecular reactions to give enaminoketones should also be noted. Five synthesized compounds were evaluated for their antiproliferative activity on the NCI-60 cancer cell lines panel.

1. Introduction

The 2-pyrrolidinone ring system is common to many molecules of great value in medicinal chemistry.[1] In particular, 2-pyrrolidinone-5-carboxylic acid (pyroglutamic acid, **1**), which has been called 'the forgotten amino acid'[2] is an essential biological member of the 'chiral pool'.[3] In addition, *N*-acyliminium salts[4] are very important in organic synthesis since they are reactive intermediates involved in the preparation of many compounds with interesting biological properties. Nucleophilic addition to *N*-acyliminium salts has been used as a key method for the synthesis of α-functionalized amino compounds and many biologically active nitrogen heterocycles.[5,6] Many classes of nucleophiles can react with *N*-acyliminium ions, including allylsilanes,[7] TMSCN,[8] isonitriles,[9] organotrifluoroborates,[5] enol derivatives,[10] and aromatics.[11]

Diacetoxyiodobenzene/I_2,[12a,d] CAN[12b] or $NaIO_4$[12c] 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,[13] and we later reported its use in the synthesis of new heterocycles.[14] We also showed that enaminoesters issued from pyroglutamic acid (**1**), in which the lactamic carbonyl group is exchanged with an isosteric enaminoester functionality, contain an N–C–CO_2H group, displaying similar behavior under anodic oxidation conditions. Indeed, decarboxylation leads to the formation of vinylogues of *N*-acyliminium salts, which either can add (silyl)nucleophiles[15] or evolve into pyrroles.[16]

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[17] or polyphosphoric acid (Scheme 1) (or the corresponding acid chloride with Lewis acids[3e,18–20]), which is able to react in situ with aromatics to give 5-aryl-2-pyrrolidinones **3** (Scheme 2).[18] This method of obtention of the *N*-acyliminium salt **2** was extended to the use of triflic anhydride as a promoting reagent,[21] and was applied to the synthesis of agonists of sphingosine-1-phosphate receptors.[22]

In the present paper, we describe the results in optimization of the synthesis of 5-aryl-2-pyrrolidinones through decarbonylation of pyroglutamic acid in Eaton's reagent, in the presence of aromatic derivatives. We also studied, because of our interest in these compounds as starting building blocks in heterocyclic synthesis,[23] particularly in the field of DNA ligands,[24] the utilization of these reaction conditions in the arylation of enaminoester vinylogues of pyroglutamic acid.

* Corresponding author. Tel.: +33 328384858; e-mail address: alina.ghinet@hei.fr (A. Ghinet).
† Both authors contributed equally to this work.

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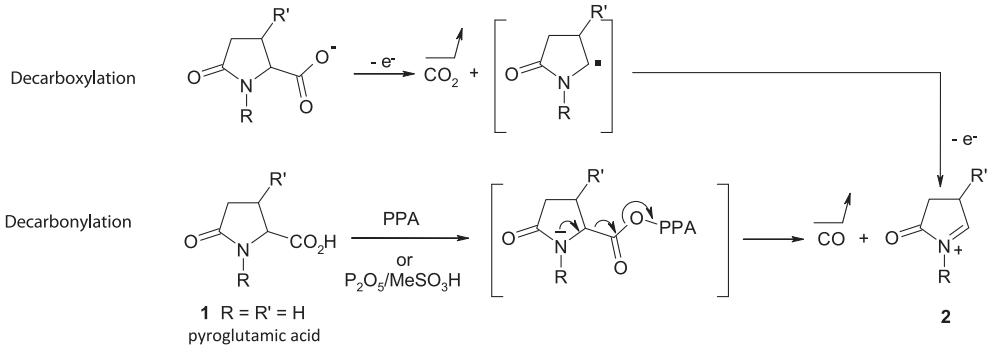
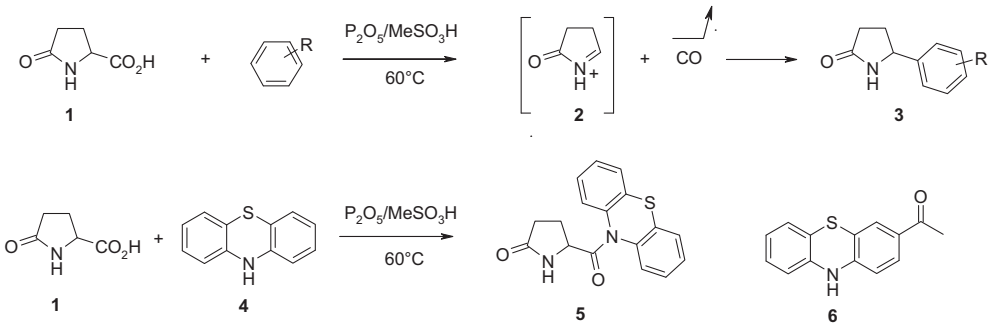


Scheme 1. Syntheses of *N*-acyliminium salts from pyroglutamic acid (**1**).



Scheme 2. Reactions of pyroglutamic acid (**1**) with aromatic derivatives in Eaton's reagent.

2. Results and discussion

2.1. Synthesis of 5-aryl-2-pyrrolidinones

Eaton's reagent[17a] is prepared as a 1:10 solution by weight of phosphorus pentoxide in methanesulfonic acid. Organic compounds often dissolve rapidly[17c] in this mobile liquid, and the solutions obtained are easily stirred. This condensing agent is often more efficient than PPA, and is rapidly hydrolyzed at the end of the reaction. According to Eaton,[17a] methanesulfonic anhydride is formed in this mixture, but other species are also present, such as PPA and mixed anhydrides of PPA and $MeSO_3H$.[17b] In some reactions, P_2O_5 is mainly used as a drying agent.[17b] Indeed, methanesulfonic acid is a hygroscopic liquid containing 0.5% water and, in the case of our study of the synthesis of 5-aryl-2-pyrrolidinones **3** (Scheme 2), it was observed that old bottles of $MeSO_3H$ often lead to poor results. Previously[18] 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 yield. The results obtained are described in Table 1. This preparative synthetic method gave average yields of products **3**, but is more efficient than the other syntheses of 5-aryl-2-pyrrolidones described,[25] as it is much faster, with fewer steps for comparable global yields. In contrast, acid sensitive indole leads to the formation of a complex and inseparable mixture (Table 1, entry 7), and amino heterocycle phenothiazine **4** was acylated by pyroglutamic acid yielding 55% of amide **5** along with side-product **6** (3%) (Scheme 2).

2.2. Reactions of vinylogues of pyroglutamic acid

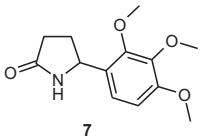
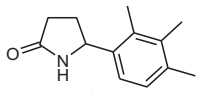
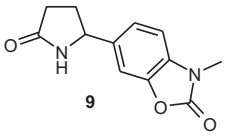
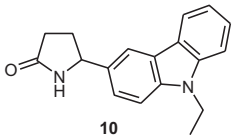
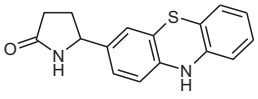
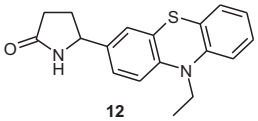
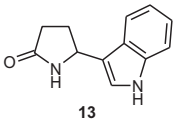
Under the same optimized decarbonylation/arylation conditions established for pyroglutamic acid (**1**), we investigated the reactivity of vinylogues. The first enaminoester considered was the acid **14**,[26] derived from Meldrum's acid. However, the results were rather disappointing, as treatment with 1,2,3-trimethoxybenzene (**15**) gave a very complex mixture from which the aryl product **16** could not be isolated (Scheme 3).

The presence of the Meldrum's group in **14** might explain the poor result as it is a rather unstable group under acidic conditions.[27] We thus decided to study the reactivity of the cyanoenaminoester derivative **17**[26] in Eaton's reagent. However, the desired compound resulting from decarbonylation of acid **17** was not obtained, and enaminoketone **18** was isolated in 51% yield (Scheme 4). Interestingly, the acid group was esterified by the methanol formed during the acylation reaction (nb: proof that the methyl group origin was not the contamination of acid **17** by the corresponding methyl ester is provided in the next section: see Scheme 5). Intramolecular reactions of *N*-arylaminoesters are well documented, often in Eaton's reagent,[28] but to the best of our knowledge the analogue bimolecular reaction had yet to be described.

Two other products were isolated from this reaction; methylsulfonate ester **19** obtained in 7% yield, issued from acid demethylation[29] of trimethoxybenzene (**15**), then reaction of the 1,3-dimethoxyphenol obtained with methanesulfonic anhydride present in Eaton's reagent.[17b] Sulfone **20**, previously obtained using a $P_2O_5/H_3PO_4/H_2SO_4$ mixture,[30] was also isolated as a by-product in 2% yield (Scheme 4).

Acid **17** was also reacted with *N*-methylbenzoxazolone (**21**) and aryl enaminoester **22** was isolated in 38% yield, confirming that Eaton's reagent promoted decarbonylation of pyroglutamic acid vinylogues. Again, esterification of the acid group of **17** occurred, and methyl ester **23** was isolated in 24% yield. In order to rule out contamination of the starting **17** acid by some undetected initial methyl ester, methyl ester **27**[23a,31] was saponified to acid **24** as described for compound **17**,[26] and then **25** was subjected to reaction in Eaton's reagent (Scheme 5). Amides[32] **25** and **26** were obtained in yields similar to those of **22** and **23**, confirming that the acid functionality was esterified by the EtOH/MeOH group of the

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

Entry	Product	*t* (h)	Yield (%)
1	 **7**	24	53
2	 **8**	24	61
3	 **9**	24	63
4	 **10**	43	52
5	 **11**	24	0[b]
6	 **12**	24	60
7	 **13**	19	—[c]

[a] Reactions carried out at 60 °C.
[b] Amide **5** (Scheme 2) was isolated in 55% yield.
[c] Inseparable mixture.

enaminoester of the scaffold and that the nature of the ester moiety has no influence on the mechanism pathway.

Reaction of *N*-ethylcarbazole (**28**) with the acid **24** in Eaton's reagent, similarly, gave identical results to those previous (Scheme 6): ketone **29** was isolated in 40% yield, accompanied by 20% ethyl ester **30**, and 9% amide **26** issuing from hydrolysis of the nitrile group of **30**. The methyl ketone **31** was also obtained in 1% yield. This surprising product is thought to come from acylation of **28**, promoted by methanesulfonic acid traces, during ethyl acetate chromatographic purification of the reaction mixture.

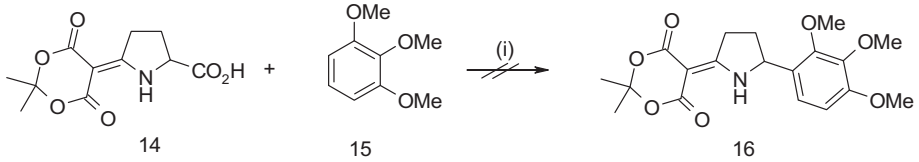
Subsequently, acid **24** was reacted with 1,2,3-trimethylbenzene (**32**) (Scheme 7), and the expected aryl enaminoester **33** was isolated in 21% yield, accompanied, respectively, by amides **34** (12%) and **26** (15%), by 13% of diaryl product **35**, and also by 2% enaminoester **36**, produced by hydrolysis and then decarboxylation of nitrile **33**. It is noteworthy that, 3% of methylsulphone **37** was formed, again underlining the chemical reactivity of Eaton's reagent.

Spectral investigation of compound **34** allowed determination of the exact geometry, using NMR at 600 MHz. A correlation between the methylene group of the ethyl ester and the methylene of the pyrrolidine ring was also visualized (Scheme 8), corresponding to a stronger intramolecular hydrogen bond formed between the pyrrolidine nitrogen and the carbonyl of the amide moiety versus that of the ester group, thus leading to preferential formation of the corresponding isomer (Scheme 8).

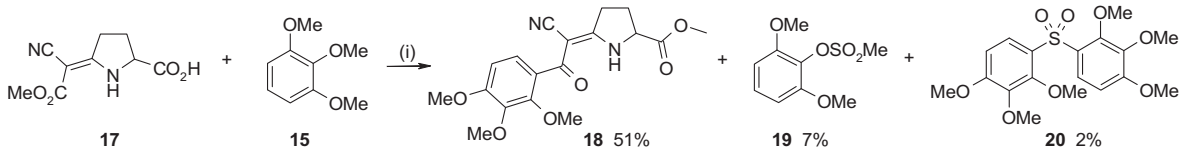
It is interesting to note that the chemical shift of the proton in position 5 of the compounds synthesized in this study was characteristic, facilitating deduction of the structures of the resulting products: when an ester group is placed in this position (**18**, **23**, **26**, **27**, **30**), the chemical shift of the angular proton was between 4.47 and 4.67 ppm, while aryl groups in this position (**22**, **25**, **33**, **34**, **35**, and **36**) result in a downfield shift, leading to values between 5.06 and 5.42 ppm (Table 2).

2.3. Reaction mechanism

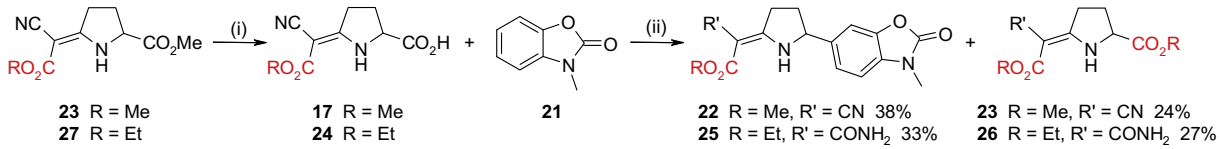
Although we have not carried out any mechanistic study, we suggest that the different reactivities observed during the reaction of the pyroglutamic acid vinylogues (**17** and **24**) with aromatic derivatives (**15**, **21**, **28**, and **32**), could be due to a competition between two reactions: Eaton's reagent lead to a rapid and reversible protonation of the carbonyl group of the ester. This is followed by the attack of a reactive aromatic residue (**15** or **28**) that rapidly leads to acid **39**, and after esterification, to a ketoester (**18** or **29**). When the aromatic moiety is less reactive, this ketone formation doesn't take place; a slow decarbonylation corresponding to the



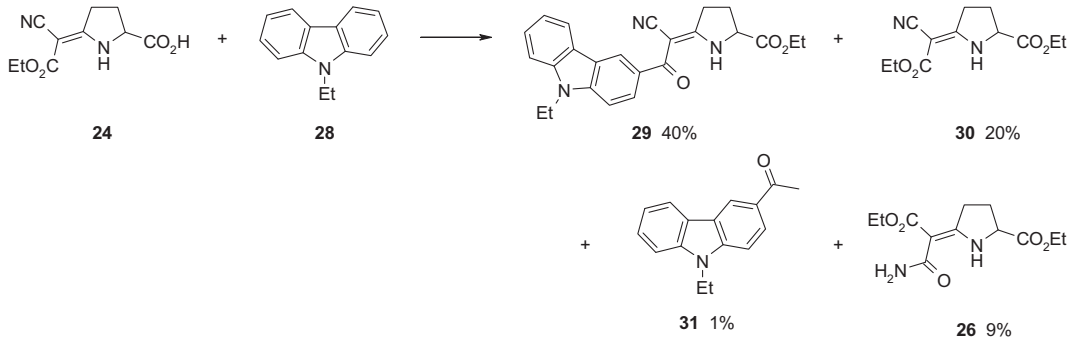
Scheme 3. Reagents and conditions: (i) 1,2,3-trimethoxybenzene (**15**) 1 equiv, Eaton's reagent 4 equiv, 60 °C, 7 h.



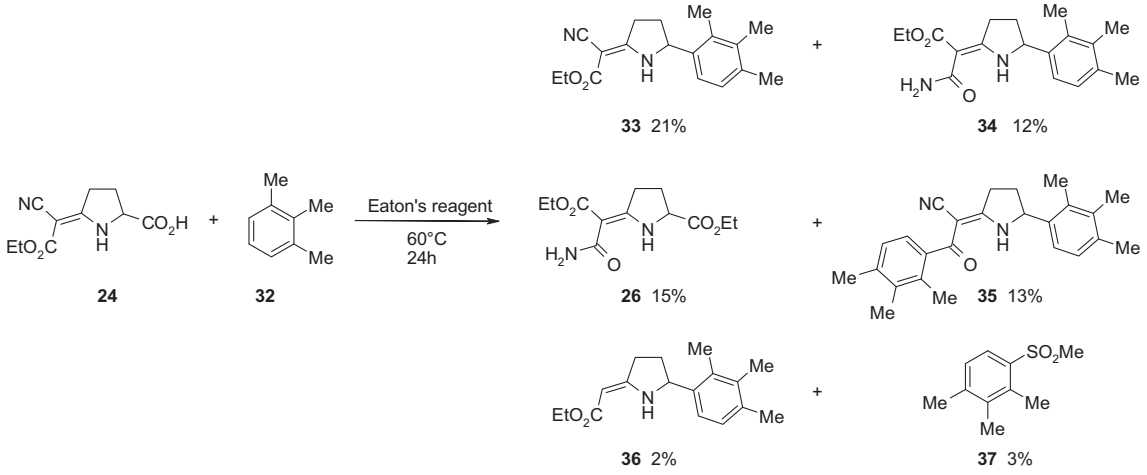
Scheme 4. Reagents and conditions: (i) 1,2,3-trimethoxybenzene (**15**) 1.15 equiv, Eaton's reagent 4 equiv, 60 °C, 24 h.



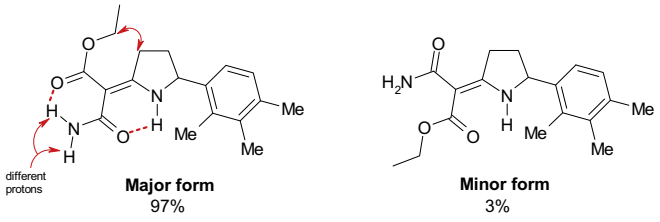
Scheme 5. Reagents and conditions: (i) NaOH, rt, 1 h; (ii) *N*-methylbenzoxazolone (**21**) 1.15 equiv, Eaton's reagent 4 equiv, 60 °C, 24 h.



Scheme 6. Reagents and conditions: (i) *N*-ethylcarbazole (**28**) 1.15 equiv, Eaton's reagent 4 equiv, 60 °C, 30 h.



Scheme 7. Reagents and conditions: (i) 1,2,3-trimethylbenzene (**32**) 1.15 equiv, Eaton's reagent 4 equiv, 60 °C, 24 h.



Scheme 8. Structure elucidation of pyrrolidine **34**.

Table 2
Chemical shift comparison of the angular hydrogen of some synthesized compounds

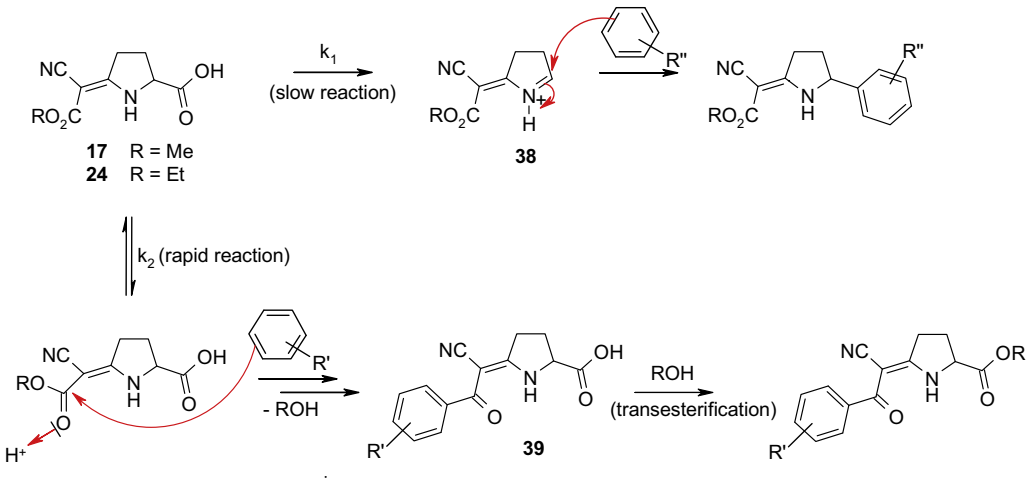
Compound	**18**	**23**	**26**	**27**	**30**	**22**	**25**	**33**	**34**	**35**	**36**
δ H (ppm)	4.67	4.58	4.47	4.60	4.54	5.06	5.07	5.29	5.22	5.42	5.12

irreversible formation of the iminium salt **38** (vinylogue of an *N*-acyliminium salt) occurs, as in case of the pyroglutamic acid. This step is followed by the condensation of the intermediate **38** with the aromatic derivative (**21** or **32**) (Scheme 9).

3. Conclusion

In this paper, we have shown that enaminoesters, vinylogues of pyroglutamic acid, are subject to decarbonylation in the same way as the parent acid, for which this condensation was optimized. However, many by-products are also formed, suggesting utilization of this reaction with compounds, more stable than the enaminoesters and enaminonitriles used in this study. The possibility of enaminoesters reacting with aromatics in bimolecular reactions to give enaminoketones also should be noted.

Compounds **5**, **12**, **18**, **22**, and **29** were selected by NCI (National Cancer Institution, USA) for screening against 60 human tumor cell lines. Molecule **18** showed very modest cell growth inhibition at a 10 μM concentration (only 34% inhibition of renal cancer line A498, 40% of HL-60 (TB) and 48% of RPMI-8226 (leukemia)), whereas all other tested compounds were inactive.



Scheme 9. Proposed mechanistic pathways for the reaction of pyroglutamic acid vinylogous with aromatic derivatives in Eaton's reagent.

4. Experimental section

4.1. General

Starting materials are commercially available. Melting points were measured on an 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 parts per million relative to TMS as internal standard. Thin layer chromatography (TLC) was realized on Macherey Nagel silica gel plates with fluorescent indicator and was visualized under a UV-lamp at 254 nm and 366 nm. Column chromatography was performed on silica gel (40–60 μm; Macherey–Nagel). IR spectra were recorded on a Varian 640–IR FT-IR Spectrometer. Elemental analysis (C, H, N, S) of new compounds was determined by 'Service de Microanalyses', Faculté de Sciences Mirande, Université de Bourgogne, Dijon, France.

4.2. General procedure 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 7–43 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 provide pure compounds.

*4.2.1. 5-(2,3,4-Trimethoxyphenyl)pyrrolidin-2-one (**7**).* The general procedure was followed using pyroglutamic acid **1** (2.00 g, 15.5 mmol), 1,2,3-trimethoxybenzene (**15**) (2.87 g, 17.0 mmol), and Eaton's reagent (0.73 g P_2O_5 in 4.91 mL CH_3SO_3H). The mixture was heated at 60 °C for 24 h. The final brown oil was purified by column chromatography on silica gel with EtOAc/*n*-heptane 5/5 to give pure pyrrolidinone **7** (53%) as an off-white solid; mp (EtOAc) 98–100 °C; R_f (EtOAc/*n*-heptane 5/5)=0.14; ^{1}H ($CDCl_3$, 200 MHz) δ (ppm) 1.90–2.06 (m, 1H, CH_2CH_2CH), 2.38–2.49 (m, 1H, CH_2CH_2CH), 2.50–2.68 (m, 2H, CH_2CH_2CH), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.99 (t, J=6.3 Hz, 1H, CH_2CH_2CH), 5.83 (s, 1H, N*H*), 6.66 (d, J=8.6 Hz, 1H, Ar*H*), 6.95 (d, J=8.6 Hz, 1H, Ar*H*). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 27.5 (CH_2), 33.0 (CH_2), 48.0 (CH), 56.6 (CH_3), 60.3 (CH_3), 60.9 (CH_3), 107.0 (CH), 115.2 (C), 119.8 (CH), 142.9 (C), 149.6 (C), 153.6 (C), 182.2 (C). IR ν cm^{-1}: 1088, 1261, 1273, 1420, 1448, 1460, 1492, 1681, 3185. Found: C, 61.75; H, 6.76; N, 5.41. Calcd for $C_{13}H_{17}O_4N$: C, 62.14; H, 6.82; N, 5.57%.

*4.2.2. 5-(2,3,4-Trimethylphenyl)pyrrolidin-2-one (**8**).* The general procedure was followed using pyroglutamic acid **1** (1.00 g, 7.75 mmol), 1,2,3-trimethylbenzene (**32**) (1.15 mL, 8.52 mmol), and Eaton's reagent (0.36 g P_2O_5 in 2.50 mL CH_3SO_3H). The mixture was heated at 60 °C for 24 h. The final solid was recrystallized from diethyl ether to give pure pyrrolidinone **8** (61%) as a white solid; mp (Et_2O) 110–111 °C; ^{1}H ($CDCl_3$, 400 MHz) δ (ppm) 1.83–1.90 (m, 1H, CH_2CH_2CH), 2.21 (s, 3H, $ArCH_3$), 2.24 (s, 3H, $ArCH_3$), 2.29 (s, 3H, $ArCH_3$), 2.32–2.46 (m, 2H, CH_2CH_2CH), 2.57–2.64 (m, 1H, CH_2CH_2CH), 5.02 (dd, J=8.0, 6.0 Hz, 1H, CH_2CH_2CH), 6.02 (s, 1H, N*H*), 7.04 (d, J=8.0 Hz, 1H, Ar*H*), 7.09 (d, J=8.0 Hz, 1H, Ar*H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.1 (CH_3), 15.8 ($2CH_3$), 20.8 (CH_2), 29.9 (CH_2), 55.0 (CH), 121.1 (CH), 127.7 (CH), 132.8 (C), 135.8 (C), 135.9 (C), 138.0 (C), 178.5 (C). IR ν cm^{-1}: 559, 796, 1025, 1126, 1247, 1275, 1511, 1574, 1683, 1731, 2941. Found: C, 76.38; H, 8.32; N, 7.27. Calcd for $C_{13}H_{17}ON$: C, 76.81; H, 8.43; N, 6.89%.

*4.2.3. 3-Methyl-6-(5-oxopyrrolidin-2-yl)-1,3-benzoxazol-2(3H)-one (**9**).* The general procedure was followed using pyroglutamic acid **1** (1.00 g, 7.75 mmol), 3-methylbenzoxazol-2-one **21** (1.27 g, 8.52 mmol), and Eaton's reagent (0.36 g P_2O_5 in 2.5 mL CH_3SO_3H). The mixture was heated at 60 °C for 24 h. The final solid was recrystallized from H_2O to give pure pyrrolidinone **9** (63%) as a white solid; mp (H_2O) 168–170 °C (lit. 166 °C);[16] R_f (dichloromethane/methanol 95/5)=0.24; ^{1}H ($CDCl_3$, 400 MHz) δ (ppm) 1.91–2.01 (m, 1H, CH_2CH_2CH), 2.38–2.55 (m, 2H, CH_2CH_2CH), 2.56–2.65 (m, 1H, CH_2CH_2CH), 3.41 (s, 3H, NCH_3), 4.78 (t, J=7.1 Hz, 1H, CH_2CH_2CH), 5.92 (s, 1H, N*H*), 6.94 (d, J=7.8 Hz, 1H, Ar*H*), 7.15 (dd, J=7.8, 1.6 Hz, 1H, Ar*H*), 7.17 (d, J=1.6 Hz, 1H, Ar*H*). Found: C, 62.34; H, 5.14; N, 12.31. Calcd for $C_{12}H_{12}O_3N_2$: C, 62.06; H, 5.21; N, 12.06%.

*4.2.4. 5-(9-Ethyl-9H-carbazol-3-yl)pyrrolidin-2-one (**10**).* The general procedure was followed using pyroglutamic acid **1** (4.00 g, 30.97 mmol), *N*-ethylcarbazole (**28**) (4.03 g, 20.65 mmol), and

Eaton's reagent (1.45 g P_2O_5 in 9.82 mL CH_3SO_3H). The mixture was heated at 60 °C for 43 h. The final brown oil was purified by column chromatography on silica gel with a gradient EtOAc/*n*-heptane from 25/75 to 100/0 and recrystallized from Et_2O to give pure pyrrolidinone **10** (52%) as a beige solid; mp (Et_2O) 126–128 °C; R_f (EtOAc)=0.22; ^{1}H ($CDCl_3$, 400 MHz) δ (ppm) 1.43 (t, *J*=7.1 Hz, 3H, CH_2CH_3), 2.05–2.15 (m, 1H, CH_2CH_2CH), 2.44–2.70 (m, 3H, CH_2CH_2CH), 4.37 (q, *J*=14.2 Hz, 2H, CH_2CH_3), 4.95 (t, *J*=7.2 Hz, 1H, CH_2CH_2CH), 5.80 (s, 1H, NH), 7.25 (td, *J*=7.1, 1.2 Hz, 1H, ArH), 7.39–7.52 (m, 4H, ArH), 8.03 (s, 1H, ArH), 8.09 (d, *J*=7.8 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8 (CH_3), 30.6 (CH_2), 32.2 (CH_2), 37.7 (CH_2), 58.6 (CH), 108.6 (CH), 108.8 (CH), 117.6 (CH), 119.1 (CH), 120.5 (CH), 122.5 (C), 123.2 (C), 123.4 (CH), 126.0 (CH), 132.8 (C), 139.7 (C), 140.4 (C), 178.2 (C). IR ν cm^{-1}: 1232, 1331, 1349, 1471, 1686, 1726, 3192. Found: C, 76.30; H, 7.39; N, 8.48. Calcd for $C_{18}H_{18}N_2O$ ½ Et_2O: C, 76.30; H, 7.39; N, 8.48%.

*4.2.5. 5-(10H-Phenothiazin-10-ylcarbonyl)pyrrolidin-2-one (**5**).* The general procedure was followed using pyroglutamic acid **1** (2.24 g, 17.34 mmol), phenothiazine **4** (3.00 g, 15.05 mmol), and Eaton's reagent (0.81 g P_2O_5 in 5.49 mL CH_3SO_3H). The mixture was heated at 60 °C for 24 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 **5** (55%) as a beige solid; mp (EtOAc/*n*-heptane) 188–190 °C; R_f (EtOAc/cyclohexane 6/4)=0.12; ^{1}H ($CDCl_3$, 400 MHz) δ (ppm) 1.76–1.90 (m, 1H, CH_2CH_2CH), 1.99–2.12 (m, 1H, CH_2CH_2CH), 2.15–2.25 (m, 1H, CH_2CH_2CH), 2.29–2.40 (m, 1H, CH_2CH_2CH), 4.77 (m, 1H, CH_2CH_2CH), 5.78 (large s, 1H, NH), 7.24–7.33 (m, 4H, ArH), 7.45–7.52 (m, 3H, ArH), 7.57 (d, *J*=8.1 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.1 (CH_2), 29.1 (CH_2), 54.3 (CH), 126.5 (CH), 127.2 (2CH), 127.3 (CH), 127.6 (CH), 127.7 (CH), 128.1 (CH), 128.5 (CH), 137.5 (2C), 138.0 (2C), 171.1 (C), 177.7 (C). IR ν cm^{-1}: 1252, 1459, 1678, 3260. LC/MS (APCI$^+$) *m*/*z* 311.0 (MH$^+$). Found: C, 65.41; H, 4.31; N, 9.29. Calcd for $C_{17}H_{14}N_2O_2S$: C, 65.79; H, 4.55; N, 9.03%.

*4.2.6. 1-(10H-phenothiazin-3-yl)ethanone (**6**).* By-product from the synthesis of compound **5**; beige solid with the same physical properties as described in the lit.;[33] 3% yield; mp (EtOAc/*n*-heptane) 186–188 °C (lit. 178–179 °C,[33a] 188–189 °C,[33b] 192–193 °C[33c]); ^{1}H ($CDCl_3$, 400 MHz) δ (ppm) 3.00 (s, 3H, $COCH_3$), 6.06 (s, 1H, NH), 6.55 (dd, *J*=7.8, 1.2 Hz, 1H, ArH), 6.58 (d, *J*=8.2 Hz, 1H, ArH), 6.88 (td, *J*=7.4, 1.2 Hz, 1H, ArH), 6.95 (dd, *J*=7.8, 1.6 Hz, 1H, ArH), 7.02 (td, *J*=7.4, 1.6 Hz, 1H, ArH), 7.47 (d, *J*=2.0 Hz, 1H, ArH), 7.51 (dd, *J*=8.2, 2.0 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 44.8 (CH_3), 113.9 (CH), 114.9 (CH), 117.2 (C), 119.8 (C), 124.0 (CH), 126.0 (CH), 126.9 (CH), 127.3 (CH), 127.9 (CH), 133.9 (C), 139.4 (C), 146.2 (C), 189.0 (C). LC/MS (APCI$^+$) *m*/*z* 242.0 (MH$^+$).

*4.2.7. 5-(10-Ethyl-10H-phenothiazin-3-yl)pyrrolidin-2-one (**12**).* The general procedure was followed using pyroglutamic acid **1** (2.00 g, 15.49 mmol), *N*-ethylphenothiazine (3.20 g, 14.08 mmol), and Eaton's reagent (0.73 g P_2O_5 in 4.91 mL CH_3SO_3H). The mixture was heated at 60 °C for 24 h. The final brown oil was purified by column chromatography on silica gel with a gradient EtOAc/*n*-heptane from 35/65 to 100/0 to give pure pyrrolidinone **12** (60%) as a white solid; mp (EtOAc/*n*-heptane) 195–198 °C; R_f (EtOAc/cyclohexane)=0.26; ^{1}H ($CDCl_3$, 400 MHz) δ (ppm) 1.41 (t, *J*=7.0 Hz, 3H, CH_2CH_3), 1.89–1.99 (m, 1H, CH_2CH_2CH), 2.35–2.57 (m, 3H, CH_2CH_2CH), 3.92 (q, *J*=7.0 Hz, 2H, CH_2CH_3), 4.64 (m, 1H, CH_2CH_2CH), 5.62 (s, 1H, NH), 6.80–6.95 (m, 3H, ArH), 7.05 (d, *J*=1.6 Hz, 2H, ArH), 7.12 (dd, *J*=7.6, 1.6 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.0 (CH_3), 30.2 (CH_2), 31.4 (CH_2), 41.8 (CH_2), 57.3 (CH), 115.1 (CH), 115.2 (CH), 122.5 (CH), 123.9 (C), 124.6 (CH), 124.7 (CH), 125.3 (C), 127.4 (CH), 127.5 (CH), 136.4 (C), 144.7 (C), 144.8 (C), 178.2 (C). IR ν cm^{-1}: 1233, 1251, 1325, 1460, 1600, 1703, 3203. Found: C, 68.70; H, 6.40; N, 9.06; S, 10.68. Calcd for $C_{18}H_{18}N_2OS$ 1/5H_2O: C, 68.85; H, 5.91; N, 8.92; S, 10.21%.

*4.2.8. Methyl 5-[1-cyano-2-oxo-2-(2,3,4-trimethoxyphenyl)ethylidene]prolinate (**18**).* The general procedure was followed using carboxylic acid **17** (4.00 g, 19.03 mmol), 1,2,3-trimethoxybenzene (**15**) (3.68 g, 21.88 mmol), and Eaton's reagent (1.45 g P_2O_5 in 9.82 mL CH_3SO_3H). The mixture was heated at 60 °C for 24 h. The final brown oil was purified by column chromatography on silica gel with EtOAc/*n*-heptane 6/4 to give pure compound **18** (51%) as a white solid; mp (EtOAc/*n*-heptane) 144–145 °C; R_f (EtOAc/*n*-heptane 5/5)=0.39; ^{1}H ($CDCl_3$, 200 MHz) δ (ppm) 2.21–2.61 (m, 2H, CH_2CH_2CH), 2.94–3.26 (m, 2H, CH_2CH_2CH), 3.83 (s, 3H, OCH_3), 3.88 (s, 6H, $2OCH_3$), 3.96 (s, 3H, OCH_3), 4.67 (dd, *J*=8.5, 5.7 Hz, 1H, CH_2CH_2CH), 6.68 (d, *J*=8.5 Hz, 1H, ArH), 7.12 (d, *J*=8.5 Hz, 1H, ArH), 10.80 (large s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.6 (CH_2), 33.1 (CH_2), 53.0 (CH_3), 56.0 (CH), 61.0 (CH_3), 62.0 (CH_3), 62.8 (CH_3), 81.4 (C), 106.5 (CH), 119.8 (C), 123.3 (CH), 126.8 (C), 141.9 (C), 151.5 (C), 155.6 (C), 170.4 (C), 174.4 (C), 190.9 (C). IR ν cm^{-1}: 1208, 1438, 1536, 1590, 1745, 2208, 3266. Found: C, 59.61; H, 5.68; N, 7.69. Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77%.

*4.2.9. 2,6-Dimethoxyphenyl methanesulfonate (**19**).* By-product from the synthesis of compound **18**; white solid; 7% yield; mp (Et_2O) 99–101 °C; R_f (EtOAc/cyclohexane 6/4)=0.76; ^{1}H ($CDCl_3$, 400 MHz) δ (ppm) 3.30 (s, 3H, SO_2CH_3), 3.89 (s, 6H, $2OCH_3$), 6.62 (d, *J*=8.6 Hz, 2H, ArH), 7.17 (t, *J*=8.5 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.9 (CH_3), 56.3 ($2CH_3$), 105.1 (2CH), 127.5 (CH), 128.3 (C), 153.4 (2C). IR ν cm^{-1}: 1109, 1264, 1364, 1448, 1481, 1605. Found: C, 48.57; H, 5.85. Calcd for $C_9H_{12}O_5S$ 1/3 Et_2O: C, 48.30; H, 6.01%.

*4.2.10. 1,2,3-Trimethoxy-4-[(2,3,4-trimethoxyphenyl)sulfonyl]benzene (**20**).* By-product from the synthesis of compound **18**; white solid with the same physical properties as described in the lit.;[30] 2% yield; mp (Et_2O) 150–151 °C (lit. 152–153 °C);[30] R_f (EtOAc/cyclohexane 6/4)=0.66; ^{1}H ($CDCl_3$, 400 MHz) δ (ppm) 3.64 (s, 6H, $2OCH_3$), 3.79 (s, 6H, $2OCH_3$), 3.93 (s, 6H, $2OCH_3$), 6.80 (d, *J*=9.0 Hz, 2H, ArH), 7.89 (d, *J*=9.0 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 56.2 ($2CH_3$), 60.9 ($2CH_3$), 61.1 ($2CH_3$), 106.2 (2CH), 125.4 (2CH), 127.9 (2C), 142.4 (2C), 151.8 (2C), 158.1 (2C). IR ν cm^{-1}: 1086, 1288, 1411, 1484, 1574. LC/MS (APCI$^+$) *m*/*z* 399.1 (MH$^+$). Found: C, 54.10; H, 5.57. Calcd for $C_{18}H_{22}O_8S$: C, 54.26; H, 5.57%.

*4.2.11. Methyl (2Z)-cyano[5-(3-methyl-2-oxo-2,3-dihydro-1,3-benzoxazol-6-yl)pyrrolidin-2-ylidene]acetate (**22**).* The general procedure was followed using carboxylic acid **17** (7.00 g, 33.30 mmol), *N*-methylbenzoxazolone **21** (4.32 g, 28.96 mmol), and Eaton's reagent (2.54 g P_2O_5 in 17.19 mL CH_3SO_3H). The mixture was heated at 60 °C for 24 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 pyrrolidine **22** (38%) as a beige solid; mp (EtOAc) 172–175 °C; R_f (EtOAc/cyclohexane 6/4)=0.31; ^{1}H ($CDCl_3$, 400 MHz) δ (ppm) 1.94–2.05 (m, 1H, CH_2CH_2CH), 2.56–2.66 (m, 1H, CH_2CH_2CH), 2.97–3.08 (m, 1H, CH_2CH_2CH), 3.11–3.20 (m, 1H, CH_2CH_2CH), 3.42 (s, 3H, NCH_3), 3.78 (s, 3H, CO_2CH_3), 5.06 (t, *J*=7.5 Hz, 1H, CH_2CH_2CH), 6.95 (d, *J*=8.0 Hz, 1H, ArH), 7.08 (dd, *J*=8.0, 1.8 Hz, 1H, ArH), 7.11 (d, *J*=1.8 Hz, 1H, ArH), 9.15 (large s, 1H, NH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.3 (CH_2), 31.6 (CH_3), 33.0 (CH_2), 51.7 (CH_3), 65.0 (CH), 68.2 (C), 107.7 (CH), 108.3 (CH), 118.2 (C), 121.5 (CH), 132.0 (C), 135.1 (C), 143.1 (C), 154.6 (C), 168.2 (C), 173.3 (C). IR ν cm^{-1}: 1242, 1444, 1565, 1628, 1680, 1746, 2207, 3289, 3514, 3597. LC/MS (APCI$^+$) *m*/*z* 314.1 (MH$^+$). Found: C, 57.57; H, 5.11; N, 12.65. Calcd for $C_{16}H_{15}N_3O_4$ 1H_2O: C, 58.00; H, 5.17; N, 12.68%.

*4.2.12. Methyl 5-(1-cyano-2-methoxy-2-oxoethylidene)prolinate (**23**).* By-product from the synthesis of compound **22**; white solid

with the same physical properties as described in the lit.;[23a] 24% yield; mp (AcOEt/*n*-heptane) 105–107 °C; ^{1}H ($CDCl_3$, 200 MHz) δ (ppm) 2.20–2.41 (m, 1H, C*H*$_2$CH$_2$CH), 2.43–2.61 (m, 1H, CH$_2$C*H*$_2$CH), 2.96–3.08 (m, 2H, CH$_2$CH$_2$C*H*$_2$), 3.78 (s, 3H, CO$_2$C*H*$_3$), 3.80 (s, 3H, CO$_2$C*H*$_3$), 4.58 (dd, *J*=8.6, 5.4 Hz, 1H, CH$_2$CH$_2$C*H*), 9.16 (large s, 1H, N*H*).

*4.2.13. Ethyl 5-[2-amino-1-(ethoxycarbonyl)-2-oxoethylidene]prolinate (**26**).* By-product from the syntheses of compounds **25**, **29**, and **33**; white solid; 27%, 9%, and 15% yield, respectively, mp (EtOAc/*n*-heptane) 148–150 °C; R_f (EtOAc/cyclohexane 6/4)=0.41; ^{1}H ($CDCl_3$, 400 MHz) δ (ppm) 1.29 (t, *J*=7.0 Hz, 3H, CO$_2$CH$_2$C*H*$_3$), 1.31 (t, *J*=7.0 Hz, 3H, CO$_2$CH$_2$C*H*$_3$), 2.12–2.22 (m, 1H, C*H*$_2$CH$_2$CH), 2.29–2.39 (m, 1H, C*H*$_2$CH$_2$CH), 3.17–3.30 (m, 2H, CH$_2$C*H*$_2$CH), 4.20 (q, *J*=7.0 Hz, 2H, CO$_2$C*H*$_2$CH$_3$), 4.22 (q, *J*=7.0 Hz, 2H, CO$_2$C*H*$_2$CH$_3$), 4.47 (dd, *J*=9.1, 5.3 Hz, 1H, CH$_2$CH$_2$C*H*), 5.17 (large s, 1H, N*H*), 8.76 (large s, 1H, N*H*), 11.68 (large s, 1H, N*H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (CH_3), 14.5 (CH_3), 25.6 (CH_2), 35.2 (CH_2), 59.8 (CH_2), 61.1 (CH), 61.8 (CH_2), 87.8 (C), 169.0 (C), 171.2 (C), 172.3 (C), 174.3 (C). IR ν cm^{-1}: 1211, 1455, 1473, 1532, 1591, 1630, 1650, 1733, 3158, 3351. Found: C, 53.18; H, 6.61; N, 9.95. Calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.71; N, 10.36%.

*4.2.14. Ethyl 5-[1-cyano-2-(9-ethyl-9H-carbazol-3-yl)-2-oxoethylidene]prolinate (**29**).* The general procedure was followed using carboxylic acid **24** (2.00 g, 8.92 mmol), *N*-ethylcarbazole (**28**) (1.16 g, 5.94 mmol), and Eaton's reagent (0.73 g P_2O_5 in 4.91 mL CH_3SO_3H). The mixture was heated at 60 °C for 30 h. The final brown oil was purified by column chromatography on silica gel with a gradient EtOAc/*n*-heptane from 40/60 to 100/0 to give pure compound **29** (40%) as a beige solid; R_f (EtOAc/cyclohexane 6/4)= 0.64; ^{1}H ($CDCl_3$, 400 MHz) δ (ppm) 1.34 (t, *J*=7.1 Hz, 3H, CO$_2$CH$_2$C*H*$_3$), 1.46 (t, *J*=7.0 Hz, 3H, CO$_2$CH$_2$C*H*$_3$), 2.30–2.39 (m, 1H, C*H*$_2$CH$_2$CH), 2.47–2.58 (m, 1H, C*H*$_2$CH$_2$CH), 3.09–3.28 (m, 2H, CH$_2$C*H*$_2$CH), 4.29 (q, *J*=7.0 Hz, 2H, CO$_2$C*H*$_2$CH$_3$), 4.40 (q, *J*=7.1 Hz, 2H, CO$_2$C*H*$_2$CH$_3$), 4.69 (dd, *J*=8.6, 5.5 Hz, 1H, CH$_2$CH$_2$C*H*), 7.27–7.31 (m, 1H, Ar*H*), 7.41–7.45 (m, 2H, Ar*H*), 7.50 (td, *J*=7.8, 1.2 Hz, 1H, ArH), 8.13 (dd, *J*=8.6, 1.9 Hz, 1H, Ar*H*), 8.16 (d, *J*=7.8 Hz, 1H, Ar*H*), 8.74 (d, *J*=1.6 Hz, 1H, Ar*H*), 11.10 (large s, 1H, N*H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8 (CH_3), 14.2 (CH_3), 24.7 (CH_2), 33.4 (CH_2), 37.8 (CH_2), 62.3 (CH_2), 63.0 (CH), 78.7 (C), 107.7 (CH), 108.8 (CH), 119.7 (CH), 120.9 (CH), 121.0 (C), 121.5 (CH), 122.6 (C), 123.3 (C), 126.2 (CH), 126.2 (C), 129.4 (C), 140.6 (C), 142.0 (C), 170.1 (C), 175.4 (C), 190.7 (C). LC/MS (APCI$^+$) *m*/*z* 402.1 (MH$^+$). Found: C, 71.46; H, 5.51; N, 10.13. Calcd for $C_{24}H_{23}N_3O_3$: C, 71.80; H, 5.77; N, 10.47%.

*4.2.15. Ethyl 5-(1-cyano-2-ethoxy-2-oxoethylidene)prolinate (**30**).* By-product from the synthesis of compound **29**; white solid; 20% yield; mp (EtOAc/*n*-heptane) 88–90 °C; R_f (EtOAc/cyclohexane 6/4)=0.63; ^{1}H ($CDCl_3$, 400 MHz) δ (ppm) 1.31 (t, *J*=7.0 Hz, 3H, CO$_2$CH$_2$C*H*$_3$), 1.32 (t, *J*=7.0 Hz, 3H, CO$_2$CH$_2$C*H*$_3$), 2.21–2.31 (m, 1H, C*H*$_2$CH$_2$CH), 2.41–2.51 (m, 1H, C*H*$_2$CH$_2$CH), 2.92–3.10 (m, 2H, CH$_2$C*H*$_2$CH), 4.23 (q, *J*=7.0 Hz, 2H, CO$_2$C*H*$_2$CH$_3$), 4.25 (q, *J*=7.0 Hz, 2H, CO$_2$C*H*$_2$CH$_3$), 4.54 (ddd, *J*=8.8, 5.5, 0.9 Hz, 1H, CH$_2$CH$_2$C*H*), 9.17 (large s, 1H, N*H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1 (CH_3), 14.4 (CH_3), 25.3 (CH_2), 32.4 (CH_2), 60.6 (CH), 62.1 (CH_2), 62.2 (CH_2), 69.3 (C), 118.1 (C), 167.5 (C), 170.2 (C), 173.3 (C). IR ν cm^{-1}: 1239, 1264, 1447, 1586, 1729, 2207, 3326. Found: C, 57.31; H, 6.33; N, 11.57. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10%.

*4.2.16. 1-(9-Ethyl-9H-carbazol-3-yl)ethanone (**31**).* By-product from the synthesis of compound **29**; yellow solid with the same physical properties as described in the lit.;[34] 1% yield; mp (EtOAc/*n*-heptane) 110–113 °C (lit. 109–111 °C,[34a] 116–118 °C,[34b] 115 °C,[34c] 114–116 °C,[34d] 113–115 °C[34e]); ^{1}H ($CDCl_3$, 400 MHz) δ (ppm) 1.47 (t, *J*=7.4 Hz, 3H, CH$_2$C*H*$_3$), 2.73 (s, 3H, COC*H*$_3$), 4.41 (q, *J*=7.4 Hz, 2H, C*H*$_2$CH$_3$), 7.27–7.57 (m, 4H, Ar*H*), 8.10–8.15 (m, 2H, Ar*H*), 8.76 (d, *J*=1.8 Hz, 1H, Ar*H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8 (CH_3), 26.7 (CH_3), 37.9 (CH_2), 108.0 (CH), 109.0 (CH), 120.0 (CH), 120.7 (CH), 122.0 (CH), 122.7 (C), 123.3 (C), 126.5 (2CH), 128.8 (C), 140.7 (C), 142.7 (C), 197.7 (C). IR ν cm^{-1}: 1241, 1327, 1346, 1435, 1464, 1588, 1620, 1659. LC/MS (APCI$^+$) *m*/*z* 238.2 (MH$^+$). Found: C, 80.64; H, 6.69; N, 5.96. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90%.

*4.2.17. Ethyl (2Z)-cyano[5-(2,3,4-trimethylphenyl)pyrrolidin-2-ylidene]acetate (**33**).* The general procedure was followed using carboxylic acid **24** (1.50 g, 6.69 mmol), 1,2,3-trimethylbenzene (**32**) (0.78 mL, 5.82 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 24 h. The final beige oil was purified by column chromatography on silica gel with EtOAc/*n*-heptane 5/5 to give pure compound **33** (21%) as a white solid; R_f (EtOAc/cyclohexane 6/4)=0.55; ^{1}H ($CDCl_3$, 400 MHz) δ (ppm) 1.32 (t, *J*=7.2 Hz, 3H, CO$_2$CH$_2$C*H*$_3$), 1.80–1.89 (m, 1H, C*H*$_2$CH$_2$CH), 2.16 (s, 3H, ArC*H*$_3$), 2.22 (s, 3H, ArC*H*$_3$), 2.27 (s, 3H, ArC*H*$_3$), 2.40–2.50 (m, 1H, C*H*$_2$CH$_2$CH), 3.13–3.22 (m, 1H, CH$_2$C*H*$_2$CH), 3.37–3.47 (m, 1H, CH$_2$C*H*$_2$CH), 4.21 (qd, *J*=7.1, 1.2 Hz, 2H, CO$_2$C*H*$_2$CH$_3$), 5.29 (dd, *J*=7.2, 5.3 Hz, 1H, CH$_2$CH$_2$C*H*), 6.96 (d, *J*=8.0 Hz, 1H, Ar*H*), 7.00 (d, *J*=8.0 Hz, 1H, Ar*H*), 11.60 (large s, 1H, N*H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.6 (CH_3), 15.3 (CH_3), 15.7 (CH_3), 20.6 (CH_3), 29.6 (CH_2), 34.2 (CH_2), 56.9 (C), 59.6 (CH_2), 118.4 (C), 121.5 (C), 123.2 (C), 127.7 (C), 132.8 (CH), 135.8 (CH), 135.9 (C), 137.0 (C), 162.5 (C), 182.2 (C). LC/MS (APCI$^+$) *m*/*z* 299.1 (MH$^+$). Found: C, 72.82; H, 7.69; N, 9.70. Calcd for $C_{18}H_{22}N_2O_2$: C, 72.46; H, 7.43; N, 9.39%.

*4.2.18. Ethyl (2Z)-3-amino-3-oxo-2-[5-(2,3,4-trimethylphenyl)pyrrolidin-2-ylidene]propanoate (**34**).* By-product from the synthesis of compound **33**; white solid; 12% yield; R_f (EtOAc/cyclohexane 6/4)= 0.48; ^{1}H ($CDCl_3$, 400 MHz) δ (ppm) 1.31 (t, *J*=7.0 Hz, 3H, CO$_2$CH$_2$C*H*$_3$), 1.74–1.83 (m, 1H, C*H*$_2$CH$_2$CH), 2.21 (s, 3H, ArC*H*$_3$), 2.25 (s, 3H, ArC*H*$_3$), 2.28 (s, 3H, ArC*H*$_3$), 2.47–2.56 (m, 1H, C*H*$_2$CH$_2$CH), 3.21–3.29 (m, 2H, CH$_2$C*H*$_2$CH), 4.21 (q, *J*=14.1 Hz, 2H, CO$_2$C*H*$_2$CH$_3$), 5.16 (large s, 1H, N*H*), 5.22 (dd, *J*=8.3, 5.9 Hz, 1H, CH$_2$CH$_2$C*H*), 6.95 (d, *J*=8.3 Hz, 1H, Ar*H*), 7.00 (d, *J*=8.3 Hz, 1H, Ar*H*), 8.81 (large s, 1H, N*H*), 11.67 (large s, 1H, N*H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.5 (CH_3), 14.6 (CH_3), 15.8 (CH_3), 20.8 (CH_3), 30.3 (CH_2), 35.5 (CH_2), 59.6 (CH_2), 61.1 (CH), 121.4 (CH), 125.0 (C), 127.7 (CH), 132.8 (C), 135.8 (C), 135.9 (C), 137.4 (C), 169.4 (C), 172.7 (C), 174.6 (C). LC/MS (APCI$^+$) *m*/*z* 317.1 (MH$^+$). Found: C, 68.71; H, 7.80; N, 9.11. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 9.11%.

*4.2.19. (2Z)-3-Oxo-3-(2,3,4-trimethylphenyl)-2-[5-(2,3,4-trimethylphenyl)pyrrolidin-2-ylidene]propanenitrile (**35**).* By-product from the synthesis of compound **33**; white solid; 13% yield; ^{1}H ($CDCl_3$, 400 MHz) δ (ppm) 1.90–2.00 (m, 1H, C*H*$_2$CH$_2$CH), 2.20 (s, 3H, ArC*H*$_3$), 2.23 (s, 3H, ArC*H*$_3$), 2.28 (s, 3H, ArC*H*$_3$), 2.30 (s, 3H, ArC*H*$_3$), 2.31 (s, 6H, 2ArC*H*$_3$), 2.60–2.70 (m, 1H, C*H*$_2$CH$_2$CH), 3.03–3.20 (m, 2H, CH$_2$C*H*$_2$CH), 5.42 (t, *J*=7.0 Hz, 1H, CH$_2$CH$_2$C*H*), 6.95 (d, *J*=7.9 Hz, 1H, Ar*H*), 7.04 (d, *J*=4.7 Hz, 1H, Ar*H*), 7.06 (d, *J*=4.7 Hz, 1H, Ar*H*), 7.14 (d, *J*=7.9 Hz, 1H, Ar*H*), 10.97 (large s, 1H, N*H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 15.4 (CH_3), 15.5 (CH_3), 15.9 (CH_3), 17.0 (CH_3), 20.9 (CH_3), 21.0 (CH_3), 29.5 (CH_2), 33.4 (CH_2), 63.4 (CH), 80.7 (C), 120.2 (C), 121.3 (CH), 123.9 (CH), 127.0 (CH), 128.0 (CH), 132.9 (C), 133.0 (C), 135.6 (C), 136.0 (C), 136.2 (C), 136.6 (C), 138.1 (C), 138.2 (C), 174.6 (C), 195.5 (C). Found: C, 80.61; H, 7.58; N, 7.52. Calcd for $C_{25}H_{28}N_2O$: C, 80.43; H, 7.56; N, 7.31%.

*4.2.20. Ethyl (2Z)-[5-(2,3,4-trimethylphenyl)pyrrolidin-2-ylidene]acetate (**36**).* By-product from the synthesis of compound **33**; white solid; 21% yield; mp (EtOAc/*n*-heptane) 184–186 °C; R_f (EtOAc/cyclohexane 6/4)=0.87; ^{1}H ($CDCl_3$, 400 MHz) δ (ppm) 1.28 (t, *J*=7.1 Hz, 3H, CO$_2$CH$_2$C*H*$_3$), 1.70–1.78 (m, 1H, C*H*$_2$CH$_2$CH), 2.20 (s, 3H, ArC*H*$_3$), 2.24 (s, 3H, ArC*H*$_3$), 2.28 (s, 3H, ArC*H*$_3$), 2.39–2.49 (m, 1H,

CH_2CH_2CH), 2.58–2.73 (m, 2H, CH_2CH_2CH), 4.12 (qd, J=7.1, 1.2 Hz, 2H, $CO_2CH_2CH_3$), 4.61 (s, 1H, $CHCO_2Et$), 5.12 (dd, J=7.4, 5.3 Hz, 1H, CH_2CH_2CH), 6.99 (d, J=8.0 Hz, 1H, Ar*H*), 7.04 (d, J=8.0 Hz, 1H, Ar*H*), 8.12 (large s, 1H, N*H*). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.8 (CH_3), 15.3 (CH_3), 15.8 (CH_3), 20.8 (CH_3), 30.7 (CH_2), 31.4 (CH_2), 58.5 (CH_2), 60.3 (CH), 97.1 (C), 121.6 (CH), 127.6 (CH), 132.8 (C), 135.6 (C), 135.7 (C), 138.2 (C), 166.2 (C), 170.7 (C). IR ν cm^{-1}: 706, 778, 1054, 1150, 1229, 1261, 1308, 1477, 1604, 1650, 3343. Found: C, 74.85; H, 8.62; N, 5.39. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12%.

*4.2.21. 1,2,3-Trimethyl-4-(methylsulfonyl)benzene (**37**).* By-product from the synthesis of compound **33**; yellowish oil; 3% yield; R_f (EtOAc/*n*-heptane 5/5)=0.46; ^1H ($CDCl_3$, 400 MHz) δ (ppm) 2.21 (s, 3H, ArCH_3), 2.24 (s, 3H, ArCH_3), 2.34 (s, 3H, ArCH_3), 2.55 (s, 3H, SO_2CH_3), 7.06 (d, J=8.0 Hz, 1H, Ar*H*), 7.70 (d, J=8.0 Hz, 1H, Ar*H*). Found: C, 60.90; H, 7.31; S, 15.98. Calcd for $C_{10}H_{14}O_2S$: C, 60.57; H, 7.12; S, 16.17%.

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