Synthesis of Condensed Pyridones by Using a New Ring Switching Reaction

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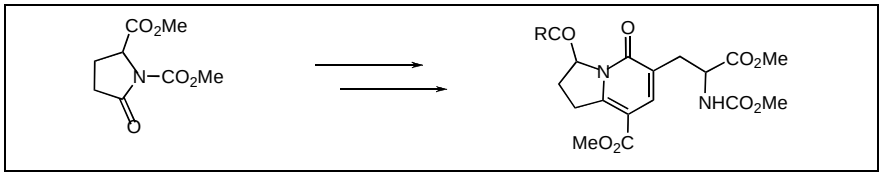

A new ring-switching reaction of enaminoesters behaving as bisnucleophiles towards other enaminoesters behaving as biselectrophiles is described. By starting from pyroglutamic derivatives, this reaction provided easy access to methyl 5-oxo-1,2,3,5-tetrahydro-3-indolizinecarboxylates substituted by an aminoester side chain in position 6.

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INTRODUCTION

The 2-pyridone unit is a key structural feature in a number of biologically active compounds [1-3]. For instance, it can be found in the toxin ricinine [4], the psychoactive huperzine A [5], or in the lead anticancer alkaloid camptothecin [6]. Other pyridones act as HIV-1 reverse transcriptase inhibitors [7], or as herbicides [8], insecticides [9], fungicides [10], antiviral [7,11], or antioxidant agents [12] (Figure 1).

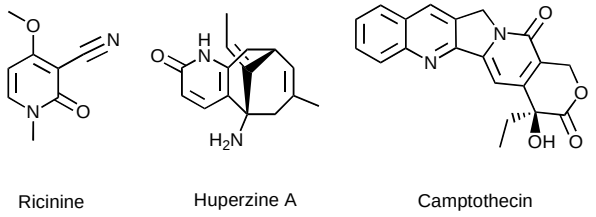
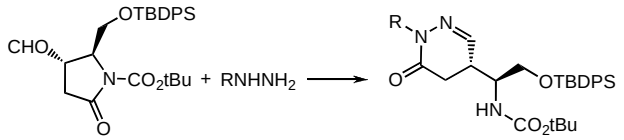


Figure 1. Structures of some active pyridones

The ring-switching reaction [13] represents a special type of ring transformation where a ring and a chain moiety in the adduct are transferred to each other giving the product [14]. Often a bisnucleophile reacts with a biselectrophile [15], and when a derivative of pyroglutamic acid is utilized, the reaction yields peptidomimetic compounds as illustrated in Scheme 1 [16].

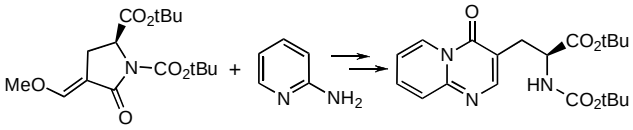
Many *N*-acyl lactams α-substituted by a carbonyl group (or the corresponding vinyl ethers or vinyl amines) have been utilized as the biselectrophile [17], often in the context of the synthesis of excitatory aminoacids. For instance, pyroglutamic derivative **3** was allowed to react with aminopyridine to give compound **4** (Scheme 2) [18].

Scheme 1. Ring-switching reaction of a bisnucleophile with a cyclic biselectrophile [16]



1 **2**

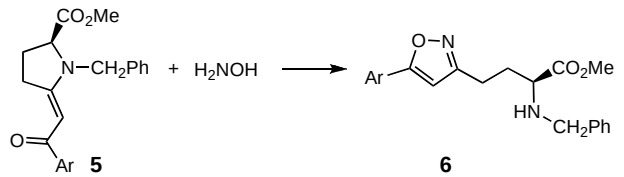
Scheme 2. Example of ring-switching reaction of a biselectrophile pyroglutamic derivative [18]



3 **4**

Enaminoesters (ketones, nitriles) derived from lactams react similarly as biselectrophiles in ring switching reactions [14,19]. In that case, the bisnucleophile generally was a hydroxylamine or hydrazine as exemplified for reaction of enaminoketone **5** [20] (Scheme 3).

Scheme 3. Example of ring-switching reaction of a biselectrophile enaminocarbonyl pyroglutamic derivative [20]



5 **6**

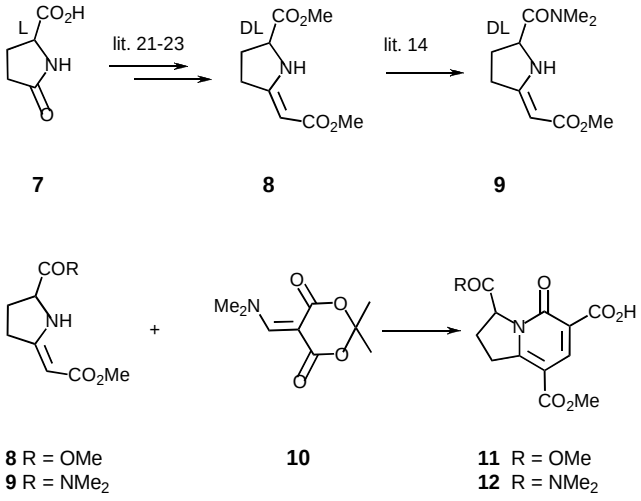
RESULTS AND DISCUSSION

To the best of our knowledge, the potential of β-enaminoesters to behave as bisnucleophiles has never been exploited in ring-switching reactions, and it appeared to us that it eventually could react with another, more electrophilic, enaminocarbonyl compound. Because we are interested in the reactivity of β-enaminoesters derived from acid **7**, we chose to work with racemic compounds **8** and **9**. The starting point of these syntheses was L-pyroglutamic acid **7**. Transformation of this lactam to enaminodiester **8** was realized in 4 steps (52% yield) as previously described [21-23], and an easy mono-amidification yielded 77% of dimethylamide **9** [24] (Scheme 4).

Then the possibility for a β-enaminoester to react as a bisnucleophile towards an α-dimethylaminomethylene carbonyl group was demonstrated by heating ester **8** and Meldrum's acid derivative **10** [25] in acetic acid for 6 h. To our delight, the new pyridone **11** was then isolated in 62% yield; in the same way amide **12** was obtained from enaminoester **9** (Scheme 4).

Scheme 4

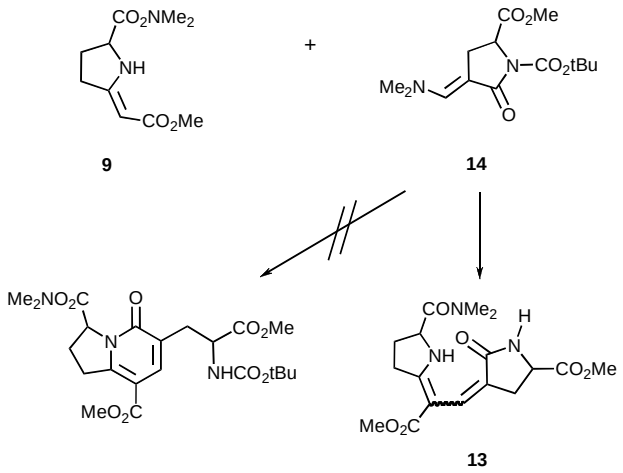
Reaction and conditions: AcOH, reflux 6 h, ~ 62%.



This concept of β-enaminoester **8**/**9** acting as bisnucleophile in ring-switching reaction was then exploited to obtain aminoindolizinones substituted by an amino chain. The first trials were rather disappointing. Indeed, only compound **13** (conformations of double bonds were not determined) was isolated in 62% yield when enaminoester **9** was allowed to react with α-dimethylaminomethylene acylcarbamate **14** [26] (Scheme 5).

Scheme 5

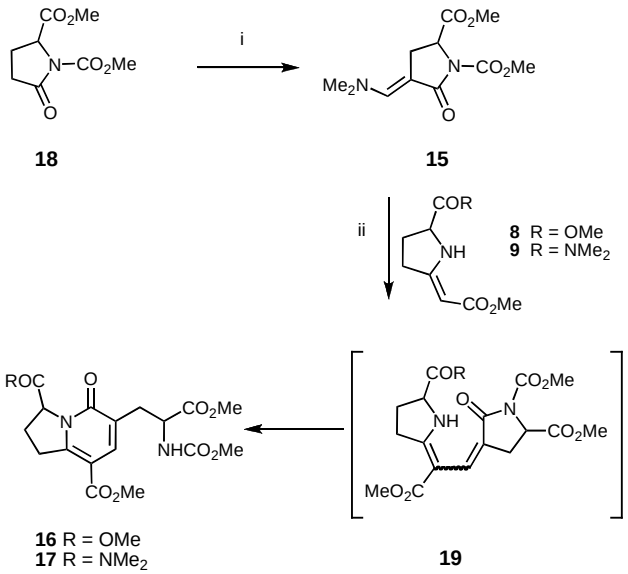
Reaction and conditions: AcOH, reflux 5 h, 62%.



However, this reaction stopped after the first nucleophilic attack of enaminoester **9** on electrophile vinyl amine **14**, and diester **13** was isolated because of the cleavage of the *tert*-butyl carbamate activating group. Thus, we repeated the reaction with the more stable methyl carbamate **15**, which was opposed to enaminoesters **8** or **9**. By refluxing the reagents in a mixture of ethanol and acetic acid, the desired pyridones **16** and **17**, substituted by a protected aminoester group were easily obtained as a mixture of diastereoisomers, in 83% and 71% respective yields. Enamine **15** was obtained from reaction of Bredereck's reagent [26] with carbamate **18** [27] in the same way as for the reported synthesis of **14** (Scheme 6) [28].

Scheme 6

Reaction and conditions: (i) $(Me_2N)_2CHO$*tert*-Bu, 90°C, 2 h, 86%; (ii) AcOH/EtOH, reflux 5 h, **16**: 83%; **17**: 71%.



CONCLUSION

We have described a new ring-switching reaction between two different β-enaminoesters. This allowed an easy synthesis of methyl 5-oxo-1,2,3,5-tetrahydro-3-indolizinecarboxylates substituted by an aminoester side chain in position 6. Because the enaminoester **8**, which is the starting point of these syntheses, can be obtained in enantiomerically pure form [29], these structures could be incorporated as building units into the design of peptidomimetic compounds.

EXPERIMENTAL

Materials. Melting points were determined using an Electrothermal apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Gemini 2000 at 200 and 50 MHz, respectively. IR spectra were obtained in ATR mode on a FTIR Bruker Tensor 27. Thin layer chromatographies were performed on precoated Kieselgel 60F_{254} plates. Microanalyses were performed by the "Service de Microanalyses" of LSEO, Université de Bourgogne, Dijon, France. Compounds **11**-**17** crystalized as solvates, and hydrogen analyses of **14** and **18** were ±0.5%. All products are obtained as mixtures of diastereoisomers.

3,8-Bis(methoxycarbonyl)-5-oxo-1,2,3,5-tetrahydroindolizine-6-carboxylic acid (11). A stirred solution of enaminoester **8** (3 g, 15 mmol) and enamine **10** (3 g, 15 mmol) in glacial acetic acid (15 mL) was refluxed for 6 h. The residue that crystallized from acetone was recrystallized from MeCN to give compounds **11**; white powder; 62% yield; TLC R_f (MeOH) = 0.32; mp 192-194°C (acetone); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.38-2.57 (m, 1H, CHCH_2CH$_2$), 2.57-2.82 (m, 1H, CHCH_2CH$_2$), 3.60 (sym m, J = 9.5 Hz, 1H, CHCH$_2$CH_2), 3.84 (s, 3H, CO_2CH_3), 3.87 (sym m, J = 9.5, 3.2 Hz, 1H, CHCH$_2$CH_2), 3.91 (s, 3H, CO_2CH_3), 5.30 (dd, J = 9.9, 3.2 Hz, 1H, C*H*N), 9.01 (s, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.7 (CH_2), 33.0 (CH_2), 52.4 (CH_3), 53.3 (CH_3), 62.4 (CH), 108.3 (C), 115.4 (C), 147.1 (CH), 162.1 (C), 162.8 (C), 163.5 (C), 163.9 (C), 169.0 (C); IR: ν cm^{-1} 3100, 1736, 1716, 1621, 1554, 1427, 1209. *Anal*. Calcd for $C_{13}H_{13}O_7N$ 1/10 MeCN: C, 52.96; H, 4.48; N, 5.15. Found: C, 52.59; H, 4.67; N, 5.26.

(Dimethylamino)carbonyl]-8-(methoxycarbonyl)-5-oxo-1,2,3,5-tetrahydro-6-indolizinecarboxylic acid (12). This compound was obtained in the same way as ester **11**, by starting from a very small amount of amide **9**. Yields, IR and elemental analyses were not recorded. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.35 (ddt, J = 12.9, 9, 2.3 Hz, 1H, CHCH_2CH$_2$), 2.47-2.71 (m, 1H, CHCH_2CH$_2$), 3.04 (s, 3H, NCH_3), 3.25 (s, 3H, NCH_3), 3.64 (sym m, J = 9.9 Hz, 1H, CHCH$_2$CH_2), 3.84 (s, 3H, CO_2CH_3), 3.87 (sym m, J = 9.9, 2.4 Hz, 1H, CHCH$_2$CH_2), 3.90 (s, 3H, CO_2CH_3), 5.63 (dd, J = 9.6, 2.0 Hz, 1H, C*H*N), 9.03 (s, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.6 (CH_2), 33.4 (CH_2), 36.1 (CH_3), 37.1 (CH_3), 52.3 (CH_3), 60.6 (CH), 108.2 (C), 115.1 (C), 147.0 (CH), 162.8 (C), 163.7 (C), 164.3 (C), 167.6 (2 C).

Methyl 4-(2-{5-[(dimethylamino)carbonyl]pyrrolidin-2-ylidene}-3-methoxy-3-oxopropylidene)-5-oxopyrrolidine-2-carboxylate (13). A stirred solution of enaminoester **9** (1 g, 4.7 mmol) and enamine **14** (1.4 g, 4.7 mmol) in glacial acetic acid (10 mL) was refluxed for 5 h. The residue obtained upon evaporation crystallized from methanol to give amide **13**; white powder; 62% yield; TLC R_f (EtOAc/MeOH 90/10) = 0.18; mp 141-143°C (acetone); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.01-2.20 (m, 1H, CHCH_2CH$_2$), 2.26-2.49 (m, 1H, CHCH_2CH$_2$), [2.73-2.84 (m, 1H), 2.84-2.90 (m, 1H), 2.90-3.03 (m, 1H), 3.03-3.21 (m, 1H), CH=CCH_2 and CHCH$_2$CH_2], 2.99 (s, 3H, NCH_3), 3.09 (s, 3H, NCH_3), 3.75 (s, 3H, CO_2CH_3), 3.76 and 3.77 (2s, 3H, CO_2CH_3), 4.22 (dd, J = 9.3, 4.1 Hz, 1H, NC*H*CO_2CH_3), 4.74 (ddd, J = 8.1, 5.5, 1.3 Hz, 1H, NC*H*$CON(CH_3)_2$), 6.20 (s, 1H, NH), 6.80-7.05 (m, 1H, C*H*=C), 6.27 (bs, deuterium oxide exchangeable, 1H, N*H*CHCO_2Me), 9.02 (td, J = 2.4, 0.9 Hz, 1 H, N*H*CHCONMe$_2$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.0 (CH_2), 31.1 (CH_2), 31.4 (CH_2), 36.0 (CH_3), 36.6 (CH_3), 50.5 (CH), 52.4 (CH_3), 52.7 (CH_3), 59.5 (CH), 89.6 (C), 121.5 (C), 128.2 (CH), 168.3 (C), 168.4 (C), 170.4 (C), 172.6 (C), 172.7 (C); IR: ν cm^{-1} 3200, 1739, 1690, 1653, 1570, 1533, 1434, 1204. *Anal*. Calcd for $C_{17}H_{23}O_6N_3$ 1/5 H_2O: C, 55.34; H, 6.39; N, 11.39. Found: C, 55.15; H, 5.92; N, 11.01.

Dimethyl 4-[(dimethylamino)methylene]-5-oxo-1,2-pyrrolidinedicarboxylate (15). A stirred mixture of carbamate **18** (5 g, 24.8 mmol) and Bredereck's reagent (6.5 g, 37.3 mmol) was heated at 90°C for 2 h. The residue obtained upon evaporation crystallized from ethyl acetate to give lactam 15; slightly orange powder; 86% yield; TLC R_f (EtOAc) = 0.15; mp 110-112°C (EtOAc); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.94 (ddd, J = 14.7, 3.6, 1.4 Hz, 1H, CH_2CH), 3.04 (s, 6H, N(CH_3)$_2$), 3.29 (ddd, J = 14.7, 10.1, 1.4 Hz, 1H, CH_2CH), 3.76 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.62 (dd, J = 10.7, 3.6 Hz, 1H, C*H*CH$_2$), 7.15 (t, J = 1.5 Hz, 1H, C*H*N$(CH_3)_2$. *Anal*. Calcd for $C_{11}H_{16}O_2N_5$, 5/8 H_2O: C, 49.39; H, 6.50; N, 10.47. Found: C, 49.01; H, 6.06; N, 10.44.

Dimethyl 6-(2-methoxycarbonylamino-3-methoxy-3-oxopropyl)-5-oxo-1,2,3,5-tetrahydroindolizine-3,8-dicarboxylate (16). A stirred solution of enaminoester **8** (2 g, 10 mmol) and enamine **15** (2.6 g, 10 mmol) in glacial acetic acid (10 mL) and ethanol (10 mL) was refluxed for 5 h. The residue obtained upon evaporation was purified by chromatography on SiO_2 (EtOAc) to give triester **16**; white powder; 83% yield; TLC R_f (EtOAc/ MeOH 90/10) = 0.67; mp 117-119°C (CH_3OH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.13-2.35 (m, 1H, CH$_2$CH_2CH), 2.37-2.50 (m, 1H, CH$_2$CH_2CH), 2.57 (ddd, J = 17.4, 2.9, 2.1 Hz, 1H, CHCH_2Ar), 2.94 (dd, J = 12.5, 4.1 Hz, 1H, CH_2CH$_2$CH), 2.94 (dd, J = 7.0, 4.9 Hz, 1H, CH_2CH$_2$CH), 3.10 (ddd, J = 17.4, 10.4, 2.7 Hz, 1H, CHCH_2Ar), 3.76 (s, 6H, 2 CO_2CH_3), 3.79 (s, 3H, CO_2CH_3), 3.89 (s, 3H, CO_2CH_3), 4.53 (ddd, J = 8.8, 5.4, 0.8 Hz, 1H, NC*H*), 4.67 (dd, J = 10.4, 2.7 Hz, 1H, NC*H*), 7.18 (dd, J = 2.7, 2.0 Hz, 1H, C*H*=C), 9.3 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.6 (CH_2), 28.9 (CH_2), 31.1 (CH_2), 50.8 (CH), 52.5 (CH_3), 52.6 (CH_3), 53.6 CH_3), 55.7 and 56.0 (CH_3), 61.0 and 61.3 (CH), 90.6 (C), 119.8 (CH), 132.3 and 132.6 (C), 152.9 (C), 167.7 (C), 168.2 (C), 169.6 (C), 171.5 (C), 171.8 (C); IR: ν cm^{-1} 3331, 1739, 1725, 1647, 1565, 1438, 1195. *Anal*. Calcd for $C_{18}H_{22}O_9N_2$, 1/2 H_2O: C, 51.55; H, 5.53; N, 6.68. Found: C, 51.71; H, 5.38; N, 6.80.

Methyl 3-{3-[(dimethylamino)carbonyl]-8-methyl-5-oxo-1,2,3,5-tetrahydroindolizin-6-yl}-2-methylpropanoate (17). A stirred solution of enaminoester **9** (3 g, 14 mmol) and enamine **15** (3.6 g, 14 mmol) in glacial acetic acid (10 mL) and ethanol (10 mL) was refluxed for 5 h. The residue obtained upon evaporation was purified by chromatography on SiO_2 (EtOAc) to give compounds **17**; slightly yellow oil; 71% yield; TLC R_f (EtOAc/MeOH 90/10) = 0.30; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.02-2.23 (m, 1H, CH$_2$CH_2CH), 2.23-2.50 (m, 1H, CH$_2$CH_2CH), 2.58 (dm, J = 17.4 Hz, 1H, CHCH_2Ar), 2.80-3.25 (m, 3H,

NHCHCH_2, CH_2CH_2CH), 2.99 (s, 3H, NCH_3), 3.08 (s, 3H, NCH_3), 3.74 (s, 3H, CO_2CH_3), 3.75 and 3.77 (2s, 3H, CO_2CH_3), 3.88 (s, 3H, CO_2CH_3), 4.65 and 4.67 (2dd, J = 10.6, 3.1 Hz, 1H, NC*H*), 4.77 and 4.79 (2dd, J = 8.7, 4.9 Hz, 1H, NC*H*), 7.20 and 7.22 (2d, J = 2.5 Hz, 1H, C*H*=C), 9.3 (d, J = 6.9 Hz, 1H, N+); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.8 (CH_2), 28.9 (CH_2), 31.4 (CH_2), 35.7 and 35.9 (CH_3), 36.4 and 36.6 (CH_3), 50.6 (CH), 52.5 (CH_3), 53.6 (CH_3), 55.7 and 55.9 (CH_3), 59.6 and 59.9 (CH), 90.1 and 90.2 (C), 118.5 and 118.9 (CH), 132.9 and 133.1 (C), 152.7 (C), 167.9 (C), 168.0 (C), 170.1 (C), 171.6 (C), 171.9 (C); IR: ν cm^{-1} 3326, 1742, 1718, 1655, 1565, 1439, 1202. *Anal*. Calcd for $C_{19}H_{25}O_8N_3$, 3/4 H_2O: C, 52.23; H, 6.11; N, 9.62. Found: C, 52.12; H, 5.79; N, 9.87.

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