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A rapid and efficient synthesis of a new pyrrolobenzodiazocines via an intramolecular Friedel–Crafts reaction

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ABSTRACT

New pyrrolobenzodiazocines **3** have been prepared by an intramolecular Friedel–Crafts process from pyrrolobenzoacrylamides **2**. The cyclisation process involving a 1,4-intramolecular addition of a pyrrole onto acrylamide led to the formation of an eight-membered ring.

The synthesis of new heterocyclic systems with biological activity is a major challenge for chemists.[1] A great number of medium-sized heterocyclic compounds such as 1,4-benzodiazepines are biologically important as these products are active on the CNS.[2]

Eight-membered heterocyclic compounds are also of importance as for example, amino heterocyclic eight-membered ring natural products, such as buflavine exhibit adrenolytic and anti-serotonin activities.[3,4] If seven-membered rings can be synthesised easily, eight-membered heterocycles are more difficult to construct as high energy activation is needed to close the ring due to torsional strains, transannular interactions and also to Pfizer strains.[5] However, pyrrolobenzodiazocines can be formed by the construction of the eight-membered ring. Up-to-date only six pyrrolobenzodiazocines were described and can be classified in three classes: pyrrolo[1,2-*e*][1,5] benzodiazocines[6] which were synthesised by lactamisation, pyrrolo-[2,1-*c*][1,4]-benzodiazocines[7] which were obtained by a Dieckman reaction and pyrrolo[1,2-*b*][2,5] benzodiazocines which were formed by using either a Ugi MCR reaction,[8] a lactamisation,[9] a Mannich reaction[10] or a reductive amination[11] (Scheme 1).

Here, we would like to report an efficient and rapid access to pyrrolo[1,2-*f*][1,6]-benzodiazocines **3** from the amino phenylpyrrole **1**[12] via acrylamides intermediates **2** taking advantage of the nucleophilicity of the pyrrole group to form one of the C–C bond of the eight-membered ring of the pyrrolobenzodiazocines.

Thus, after condensation of **1a** with acryloyl chloride (Et_3N, CH_2Cl_2, 0 °C), **2a** was obtained in good yield (87%). The cyclisation step of **2a** to **3a** was then examined and the screening of different Lewis acids was achieved in order to obtain the best yield in **3a**. The best Lewis acid revealed to be $AlCl_3$.[13] When **2a** was treated with $AlCl_3$ (2 equiv) in CH_2Cl_2 ($c = 0.005$ M),[14] at rt for 1 h, **3a**[15] was isolated in 67% yield (Table 1, entry 1). The reaction is general and the results are reported in Table 1. Compounds **3b–e**[15] were, respectively, obtained in good yields from **1b–e** (Table 1, entries 2–5). We have to point that for compound **3f**[16] (59%), the reaction has been performed in acetonitrile for 16 h at rt (Table 1, entry 6). An X-ray diffraction analysis of **3a**[17] showed that the eight-membered ring system has a boat conformation (Figs. 1 and 2).

It is worth noting that for compound **3f**, two isomers were observed by ^1H NMR and ^{13}C NMR spectra in a ratio 6:1, due to an atropoisomeric effect.[18]

The cyclisation of compounds **2** is probably due to the activation of the carbonyl group of the acrylamide by $AlCl_3$ producing intermediate **A**. Then, an intramolecular 1,4-addition of the pyrrole group onto the activated Michael intermediate takes place to pro-

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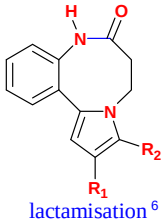
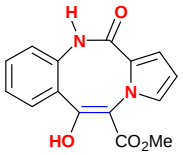


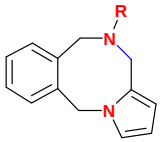
lactamisation [6]

Pyrrolo[1,2-*e*][1,*5*]benzodiazocine

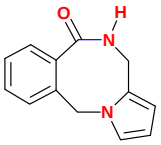


Dieckman reaction[7]

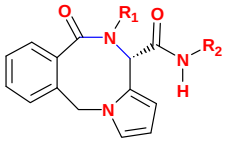
Pyrrolo[2,1-*c*][1,4]benzodiazocine



Mannich and amination reductrice[10, 11]



lactamisation[9]

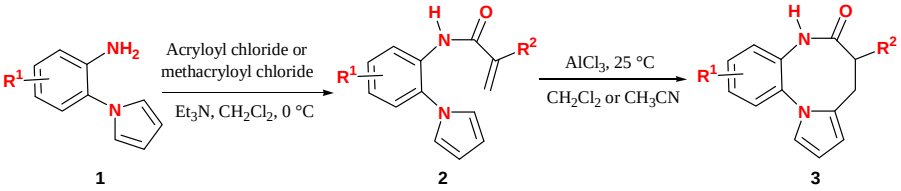


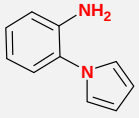
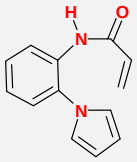
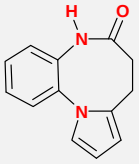
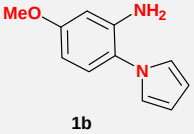
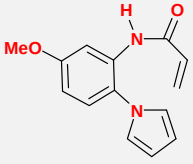
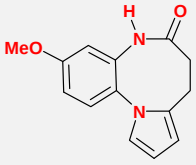
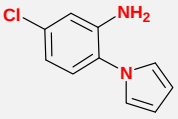
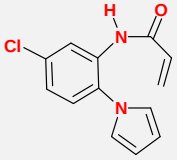
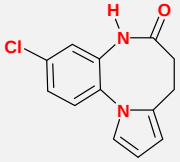
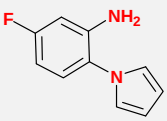
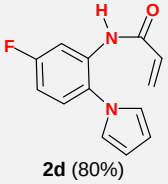
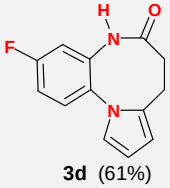
Ugi MCR reaction[8]

Pyrrolo[1,2-*b*][2,5]benzodiazocine

Scheme 1. Different classes of pyrrolobenzodiazocines.

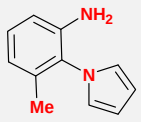
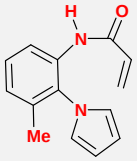
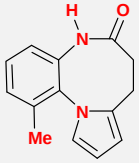
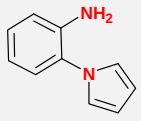
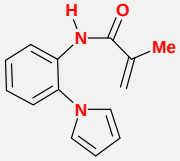
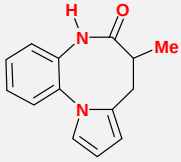
Table 1
Synthesis of different pyrrolo[1,2-*f*][1,6]-benzodiazocines



Entry	Aminopyrrole **1**	Acrylamide **2** (yield)	Pyrrolobenzodiazocine **3** (yield)
1	 **1a**	 **2a** (87%)	 **3a** (67%)
2	 **1b**	 **2b** (91%)	 **3b** (64%)
3	 **1c**	 **2c** (85%)	 **3c** (72%)
4	 **1d**	 **2d** (80%)	 **3d** (61%)

(*continued on next page*)

Table 1 (*continued*)

Entry	Aminopyrrole **1**	Acrylamide **2** (yield)	Pyrrolobenzodiazocine **3** (yield)
5	 **1e**	 **2e** (82%)	 **3e** (75%)
6	 **1a**	 **2f** (88%)	 **3f** (67%)

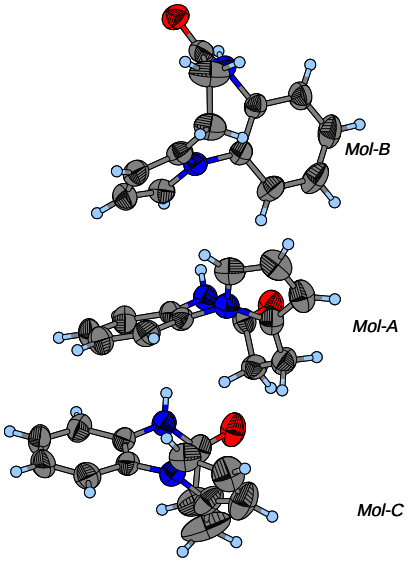


Figure 1. ORTEP representation of three molecules constitutive of the asymmetric unit of 3,4-dihydro-pyrrolo[1,2-*f*][1,6]-benzodiazocin-2-one (**3a**).

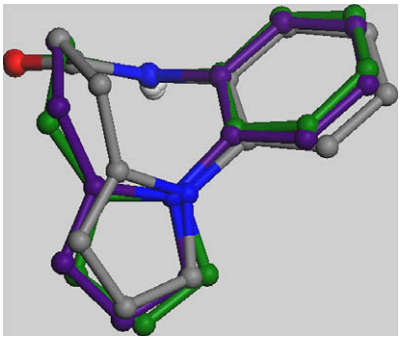
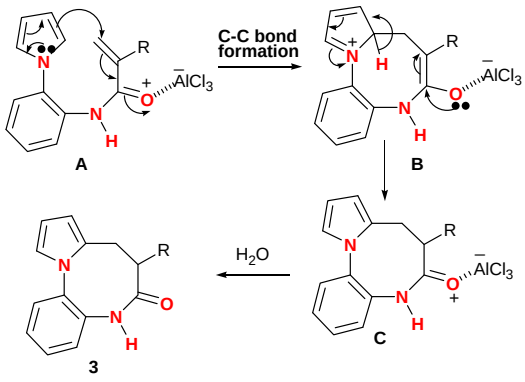


Figure 2. Superimposition of the three molecules of the Asymmetric Unit of **3a**. The molecules labelled 'A' (green) and 'C' (violet) are quite the same whereas the molecule labelled 'B' (grey) exhibits a significant difference on the eight-ring arrangement.

duce **B** which, after an 1,3-prototropy, leads to **C** and after hydrolysis, **3** can be isolated.



In order to prove that intermediate **C** is formed in the reaction media, a ^{1}H NMR[19] study was achieved on **2e**. When **2e** was treated with $AlCl_3$ in CD_2Cl_2, after 5 min, it was observed by ^{1}H NMR that **2e** disappeared and that a stable intermediate was formed. This intermediate corresponds to **C** as the treatment of **3e** with $AlCl_3$ led to the same intermediate.

In summary, we have described that pyrrolobenzodiazocines can be obtained in good yields from pyrroloacrylamides when treated with $AlCl_3$, involving an intramolecular Friedel–Crafts cyclisation. Further investigations of this efficient intramolecular cyclisation are in progress in our laboratory and the results will be reported in due course.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.145.

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11. De Martino, G.; Massa, S.; Scalzo, M.; Giuliano, R.; Artico, M. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2504.
12. Compounds **1b–d** were prepared in two steps from commercially available 4-methoxy or 4-chloro or 4-fluoro 2-nitrophenylaniline by thermal condensation with 2,5-dimethoxytetrahydrofurane in glacial acetic acid to give 1-(4-methoxy or 4-chloro or 4-fluoro 2-nitrophenyl)-1*H*-pyrrole, which was then reduced with ethanolic hydrazine hydrate in the presence of Raney nickel. Amine **1e** was prepared by reduction of 1-(6-methyl 2-nitrophenyl)-1*H*-pyrrole in an ethanolic aqueous ammonium chloride solution in the presence of zinc. Amine **1a** is commercially available from Aldrich.
13. Bouzbouz, S. Unpublished results.
14. *General procedure*: a flame-dried round-bottomed flask was charged with acrylamide **2** (1 equiv) in solvent ($c = 5 \times 10^{-3}$ M). $AlCl_3$ (2 equiv) was subsequently added as a solid, producing a yellow solution which was stirred at 25 °C. After disappearance of starting material (TLC), the solution was hydrolysed by H_2O, extracted (CH_2Cl_2) and concentrated in vacuo. The residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc).
15. Spectral data for 3,4-dihydro-pyrrolo[1,2-*f*][1,6]-benzodiazocin-2-one **(3a)**. Yellow crystal mp = 140–143 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.75 (s, 1H, NH), 7.45 (m, 3H), 7.26 (s, 1H), 6.55 (br s, 1H), 6.17 (br s, 1H), 6.07 (br s, 1H), 3.18 (dt_{app}, J = 15.2 and 9.6 Hz, 1H), 2.85–2.78 (m, 1H), 2.70–2.60 (m, 1H), 2.42 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 175.0 (s), 138.9 (s), 134,2 (s), 131.6 (s), 128.8 (d), 128.6 (d), 127.9 (d), 127.5 (d), 123.4 (d), 109.3 (d), 109.0 (d), 31.5 (t), 22.6 (t). IR (neat) ν (cm^{-1}): 3190 (NH), 1697 (CO). MS *m/z*: 212 (100), 195 (3), 183 (38), 169 (89), 156 (21), 143 (3), 129 (4), 115 (5), 91 (7), 77 (6), 65 (6).
Spectral data for 9-methoxy-3,4-dihydro-pyrrolo[1,2-*f*][1,6]-benzodiazocin-2-one **(3b)**. White solid mp = 215–218 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.99 (s, 1H, NH), 7.35 (d, J = 8.6 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 6.77 (br s, 1H), 6.51 (br s, 1H), 6.14 (br s, 1H), 6.03 (br s, 1H), 3.84 (s, 3H), 3.17 (dt_{app}, J = 15.2 and 9.6 Hz, 1H), 2.85–2.61 (m, 1H), 2.70–2.60 (m, 1H), 2.41 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 175.2 (s), 159.6 (s), 135.1 (s), 131.7 (s), 131.6 (s), 128.5 (d), 123.5 (d), 113.9 (d), 112.3 (d), 108.9 (d), 108.6 (d), 55.8 (q), 31.6 (t), 22.5 (t). IR (neat) ν (cm^{-1}): 3174 (NH), 1661 (CO). HRMS calcd: 242.1055 [(EI+), M = $C_{14}H_{14}N_2O_2$], Found: 242.1054Spectral data for 9-chloro-3,4-dihydro-pyrrolo[1,2-*f*][1,6]-benzodiazocin-2-one (**3c**). Yellow solid mp = 189–194 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.57 (br s, 1H, NH), 7.25 (br s, 2H), 7.14 (br s, 1H), 6.40 (br s, 1H), 6.06 (br s, 1H), 5.94 (br s, 1H), 3.15 (dt_{app}, J = 15.2 and 9.6 Hz, 1H), 2.70 (dd_{app}, J = 15.2 and 9.0 Hz, 1H), 2.51 (dt_{app}, J = 12.0 and 9.4 Hz, 1H), 2.31 (m, 1H), ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 175.4 (s), 137.3 (s), 135.3 (s), 134.0 (s), 131.6 (s), 128.7 (d), 128.4 (d), 127.4 (d), 123.4 (d), 109.5 (d), 109.3 (d), 31.6 (t), 22.4 (t). IR (neat) ν (cm^{-1}): 3174 (NH), 1666 (CO). HRMS calcd: 246.0560 [(EI+), M = $C_{13}H_{11}N_2OCl$], Found: 246.0567.
Spectral data for 9-fluoro-3,4-dihydro-pyrrolo[1,2-*f*][1,6]-benzodiazocin-2-one (**3d**). Yellow solide mp = 161–165 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.75 (s, 1H, NH), 7.41 (dd, J = 8.8 and 5.6 Hz, 1H), 7.10 (td, J = 8.2 and 2.8 Hz, 1H), 6.97 (dd, J = 8.7 and 2.8 Hz, 1H), 6.51 (br s, 1H), 6.15 (t, J = 3.0 Hz, 1H), 6.04 (br s, 1H), 3.16 (dt_{app}, J = 15.4 and 9.6 Hz, 1H), 2.81 (dd_{app}, J = 15.1 and 9.6 Hz, 1H), 2.62 (dt_{app}, J = 13.2 and 9.4 Hz, 1H), 2.45 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 175.5 (s), 163.4 and 160.0 two peaks (s, C–F), 135.8 and 135.7 two peaks (s, C_{aro}), 134.9 and 134.8 two peaks (s, C_{aro}), 131.6 (s), 129.0 and 128.9 two peaks (d, C_{aro}), 123.5 (d), 115.3 and 115.0 two peaks (d, C_{aro}), 114.5 and 114.2 two peaks (d, C_{aro}), 109.2 (d), 109.0 (d), 31.6 (t), 22.3 (t). IR (neat) ν (cm^{-1}): 3185 (NH), 1683 (CO).
16. Spectral data for 3-methyl-3,4-dihydro-pyrrolo[1,2-*f*][1,6]-benzodiazocin-2-one **(3f)**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.43 (br s, 0.15H, NH), 8.35 (br s, 0.85H, NH), 7.45–7.12 (m, 4H), 6.67 (br s, 0.15H), 6.44 (br s, 0.85H), 6.15 (t, J = 3.02 Hz, 0.15H), 6.08 (t, J = 3.02 Hz, 0.85H), 6.03 (br s, 0.15H), 5.94 (br s, 0.85H), 2.95–2.65 (m, 3H), 1.12 (d, J = 5.8 Hz, 0.45H), 1.05 (d, J = 5.8 Hz, 2.55H). ^{13}C NMR major diastereoisomer ($CDCl_3$, 75 MHz) δ: 178.1 (s), 139.2 (s), 133.7 (s), 131.4 (s), 128.6 (d), 128.3 (d), 127.4 (d), 127.3 (d), 123.7 (d), 109.5 (d), 108.7 (d), 33.4 (d), 32.9 (t), 17.1 (q). IR (neat) ν (cm^{-1}): 3188 (NH), 1697 (CO). MS *m/z*: 226 (78), 211 (4) 197 (11), 183 (21), 169 (100), 156 (11), 143 (2), 129 (3), 115 (4), 91 (5), 77 (7), 65 (6).
17. Crystallographic data for **3a** reported in this manuscript have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 728234 Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).
18. The interconversion of atropoisomers was characterised by a ^{1}HNMR study of compound **3f** in DMSO-d_6 at seven different temperatures from 293 to 352 K. These spectra show the broadening of the signals with increasing temperature, there is also the reduction in the intensity of signals from the minor atropoisomer their dispartion up to 352 K.
19. The spectra of compounds **2e** and **3e** and the spectra of the reaction followed by NMR are in the Supplementary data.