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CHEMISTRY OF NITROENAMINES. SYNTHESIS OF PYRROLIZINE DERIVATIVES

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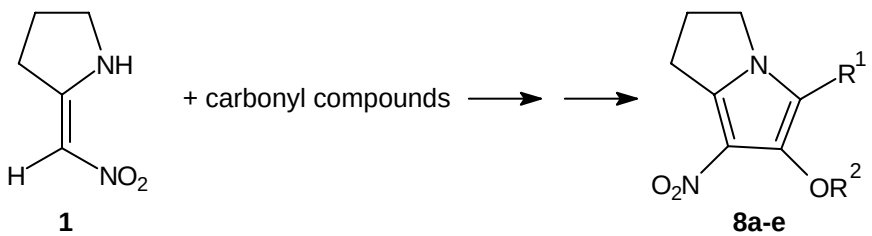
Abstract – 2-Nitromethylene-pyrrolidine (**1**) readily reacts with di- and tricarbonyl compounds resulting in addition products (**4a-d**), which could be cyclized to substituted dihydro-1H-pyrrolizines easily (**8a-e**).

INTRODUCTION

The preparation and utilization of enaminonitriles in the synthetic organic chemistry is well documented. These highly reactive compounds including a unique push-pull bonding structure were successfully used in synthesis of substituted pyridines, indolizidines and quinolizidines, and other *N*-heterocycles closely related to some types of natural products.[1] Preparation of pyrroles[2] and indeno[1,2-*b*]pyrroles[3] from enaminonitriles has also been reported.

It can be assumed that the replacement of the nitrile group of enaminonitriles with an other strongly electron withdrawing group such as $-NO_2$ will also provide compounds of high reactivity. Although several nitroenamines have been known for a long time, apart from a few reactions,[4] they have not been used in organic synthesis. These arguments prompted us to investigate the properties and preparative usefulness of nitroenamines. In this paper, we describe the reactions of 2-nitromethylene-pyrrolidine (**1**) with various carbonyl compounds, resulting in condensed pyrrole derivatives[5] (Scheme 1).



1 **8a-e**

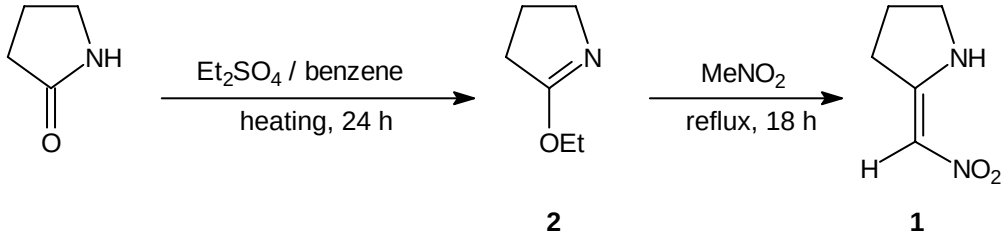
Scheme 1. Formation of substituted pyrrolizines.

Some of these products are closely related to synthetic pyrrolizines showing anti-inflammatory ananalgesic[6] or anti-leukemic[7] effect. Additionally, their functional groups offer the possibility to applythem in further transformations.

RESULTS AND DISCUSSION

Reactions of 2-nitromethylene-pyrrolidine with di- and tricarbonyl compounds

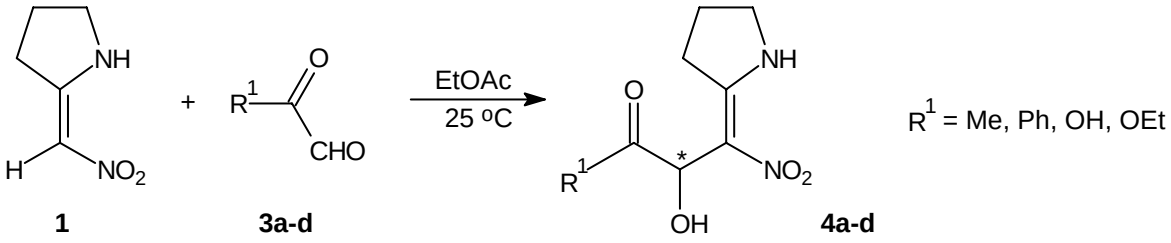
The 2-nitromethylene-pyrrolidine (**1**) was prepared in two steps. Heating 2-pyrrolidone with diethyl sulphate in benzene led to the imino ether **2**, which was then refluxed in nitromethane to afford nitroenamine **1** (Scheme 2).[8]



Scheme 2. Synthesis of 2-nitromethylene-pyrrolidine **1**.

Compound **1** may exist in two different geometric isomers. The large NMR shift of the NH proton (9.8 ppm) is due to a strong hydrogen-bonding with the NO_2 group and, consequently, it proves the presence of the energetically more favorable Z isomer. Literature[4] data clearly indicate that the highest electron density can be assigned to the C-NO_2 carbon atom, showing greater nucleophilic power than the ring nitrogen atom.

The nitroenamine **1** reacts with α-ketoaldehydes **3a,b** at room temperature in ethyl acetate solution without any catalyst furnishing crystalline adducts **4a,b** in excellent yields (Scheme 3, Table 1). The use of glyoxylic acid (**3c**) or ethyl glyoxylate (**3d**) afforded the products **4c,d** in similar nucleophilic additions.

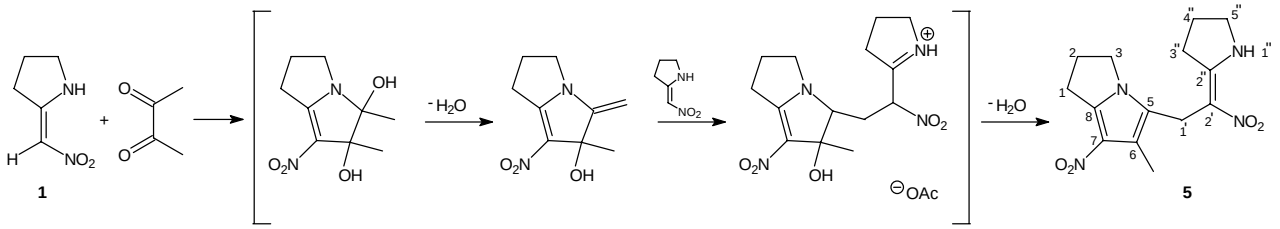


Scheme 3. The reaction of 2-nitromethylene-pyrrolidine **1** with α-carbonyl-compounds **3a-d**.

Table 1. (Reactions run at room temperature)

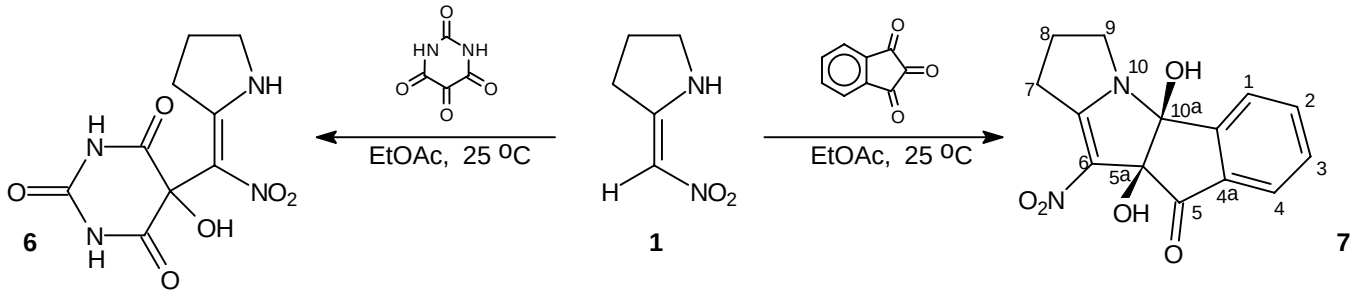
	R^1	Yield (%)	mp (^oC)	Time
4a	-Me	88	125-127	12 h
4b	-Ph	92	165-166 (MeCN)	2 h
4c	-OH	92	124-126 (MeOH)	10 min
4d	-OEt	90	110-112 (EtOAc)	10 min
6	-	86	> 230	2 h
7	-	63	162-165	2 h

In contrast to **3a-d**, the α,β-diketone such as 2,3-butanedione showed low reactivity to 2-nitromethylene-pyrrolidine (**1**), and no reaction took place at room temperature. However, heating the reactants in acetic acid, the dimeric product **5** was isolated in moderate yield. The possible reaction mechanism is depicted in Scheme 4, but the supposed intermediates could not be isolated or detected.



Scheme 4. The possible mechanism of the reaction with 2,3-butanedione.

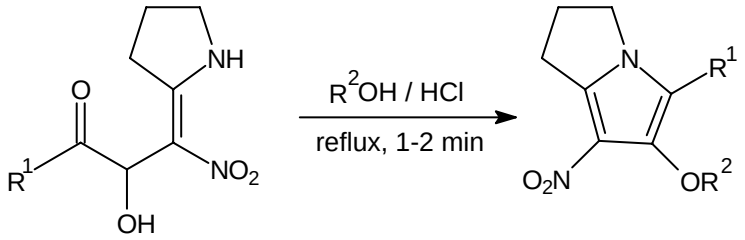
In the similar manner to that of ketoaldehyde, alloxan reacted with **1** to produce **6**. On the other hand, **1** and ninhydrin directly gave the cyclized product **7** in a double nucleophilic addition (Scheme 5). Noteworthy, that the reaction took place regio- and diastereoselectively[3] in high yield. The *cis* configuration of the hydroxy groups was confirmed by NMR (both –OH groups in H-bond), because the *trans* configuration at the 5a and 10a positions is not possible in this ring system.



Scheme 5. Reaction of **1** with alloxan and ninhydrin.

Cyclizations

When **4a,b** were heated in various alcohols in the presence of hydrochloric acid, a rapid (1-2 minutes) cyclization took place producing substituted pyrrolizines **8a-e** (Scheme 6, Table 2). Depending on the alcohol used as solvent, the corresponding alkoxy derivatives were obtained.



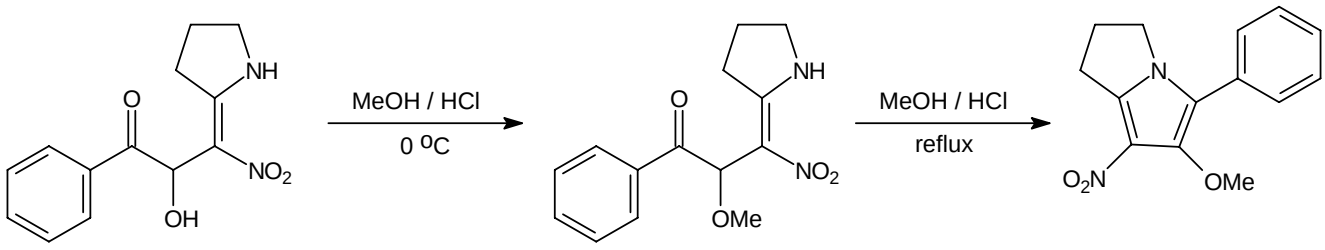
4a,b **8a-e**

Scheme 6. The cyclization of **4a,b**.

Table 2. Isolated yields and melting points of the substituted pyrrolizines.

	R^1	R^2	Yield (%)	mp (^{o}C)
8a	-Me	-Me	33	118-120
8b	-Me	-Et	31	100-102
8c	-Ph	-Me	87	131-132
8d	-Ph	-Et	75	104-105
8e	-Ph	-*i*Pr	80	140-143

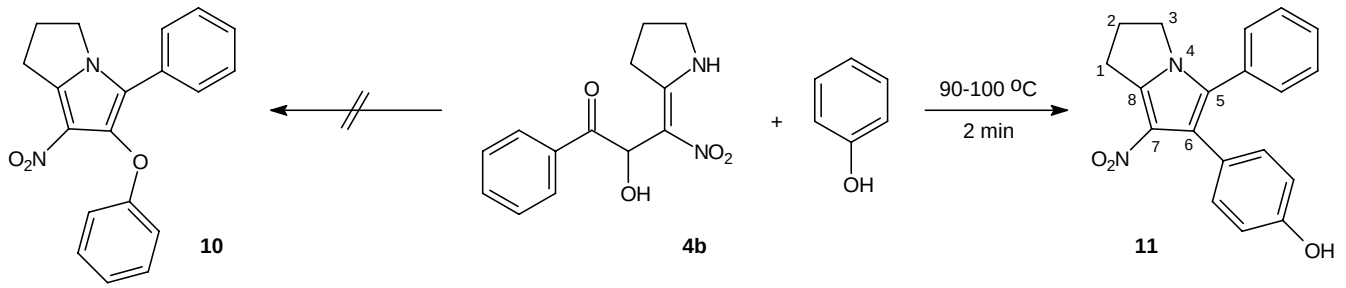
When **4b** was stirred in MeOH/HCl at 0 ^{o}C, the intermediate *O*-methyl-compound **9** was isolated (Scheme 7). Upon refluxing **9** in MeOH/HCl, the expected ring-closure rapidly took place resulting in **8c**. Compounds **4c,d** did not undergo intramolecular acylations even under different conditions.



4b **9** **8c**

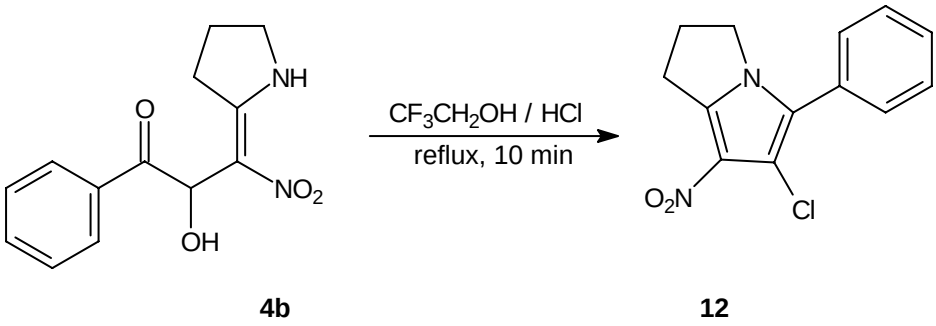
Scheme 7. Formation and cyclization of the intermediate **9**.

Interestingly, the heating **4b** in molten phenol in the presence of hydrochloric acid gave the 4-hydroxyphenyl derivative **11** resulting from a nucleophilic substitution, instead of the phenoxy-derivative **10** (Scheme 8).



Scheme 8. Reaction in molten phenol.

When the cyclization was carried out in a trifluoroethanol/HCl solution, the chloro derivative **12** was obtained (Scheme 9).



Scheme 9. The formation of the chloro-substituted pyrrolizine **15**.

CONCLUSION

A new and straightforward method was developed for synthesis of pyrrolizine derivatives. It was demonstrated that 2-nitromethylene-pyrrolidine (**1**) was a suitable starting material for construction of these condensed N-heterocycles. The reactions proceeded under mild conditions, without any special catalyst. This synthetic strategy is under further investigation for wider application.

EXPERIMENTAL

General remarks: All melting point were measured with a Büchi SMP-20 melting point apparatus and are uncorrected. NMR spectra were recorded with a Brucker Avance 400 DRX spectrometer (^{1}H: 400 MHz; ^{13}C: 100 MHz). The HPLC-MS analyses were performed with a PE, API 2000 apparatus. IR spectra were recorded with a Perkin-Elmer series 1600 FT/IR spectrometer. Column chromatography was conducted with Merck Kieselgel 60 (0,063-0,100 mm). Solvents were dried and freshly distilled according to the common practice.

General procedure for the synthesis of the compounds 4a-d, 6, 7: 2-Nitromethylene-pyrrolidine **1** (1.28 g, 10 mmol) and the α-carbonyl-compound (**3a-d**) (1.1 equiv) was stirred in EtOAc (35 mL) at ambient temperature. The reaction times are shown in Table 1. The crystalline substance formed was filtered out and recrystallized from an appropriate solvent (see Table 1) if necessary. In the case of **4b** higher temperature (50-60 ^{o}C) reduces the reaction time to 30 min.

3-Hydroxy-4-nitro-4-pyrrolidin-2'-ylidenebutan-2-one (4a): Yield: 88 %. mp 125-127 ^{o}C (decomp.). ^{1}H NMR (400 MHz, DMSO-*d6*, 25 ^{o}C): d = 2.01 (m, 2 H, H-4'), 2.09 (s, 3 H, H-1), 2.87 (m, 1 H, H-3'a), 3.02 (m, 1 H, H-3'b), 3.68 (t, 2 H, J = 7.8 Hz, H-5'), 4.69 (d, 1 H, J = 5.6 Hz, H-3), 5.28 (d, 1 H, J = 5.6 Hz, –OH), 10.14 (s, 1 H, N^{1}H) ppm. ^{13}C NMR (100 MHz, DMSO-*d6*, 25 ^{o}C): d = 20.73 (C-4'), 25.89 (C-1), 33.06 (C-3'), 49.84 (C-5'), 74.61 (C-3), 117.95 (C-4), 164.81 (C-2'), 202.5 (C-2) ppm. Anal. Calcd for $C_8H_{12}N_2O_4 \cdot H_2O$ (200.19 + 18.02): C 44.03, H 6.47, N 12.84. Found: C 44.16, H 6.86, N 12.79. EI-MS: m/z = 201.2 $[M+H]^+$.

2-Hydroxy-3-nitro-1-phenyl-3-pyrrolidin-2'-ylidenepropan-1-one (4b): Yield: 92 %. mp 165-166 ^{o}C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6, 25 ^{o}C): d = 2.07 (m, 2 H, H-4'), 2.89 (m, 1 H, H-3'a), 3.27 (m, 1 H, H-3'b), 3.67 (m, 2 H, J = 7.8 Hz, H-5'), 5.32 (d, 1 H, J = 5.2 Hz, –OH), 5.72 (d, 1 H, J = 5.2 Hz, H-2), 7.44 (t, 2 H, J = 7.6 Hz, H-Ph), 7.56 (t, 1 H, J = 7.6 Hz, H-Ph), 7.77 (d, 2 H, J = 7.2 Hz, H-Ph) 10.16 (s, 1 H, N^{1}H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25 ^{o}C): d = 20.84 (C-4'), 33.04 (C-3'), 49.77 (C-5'), 72.2 (C-2), 118.4 (C-3), 127.58 (C-Ph), 128.48 (C-Ph), 132.69 (C-Ph), 135.83 (C-Ph), 164.99 (C-2'), 197.98 (C-1) ppm. Anal. Calcd for $C_{13}H_{14}N_2O_4$ (262.26): C 59.54, H 5.38, N 10.68. Found: C 59.59, H 5.39, N 10.64. EI-MS: m/z = 263.3 $[M+H]^+$.

2-Hydroxy-3-nitro-3-pyrrolidin-2'-ylidenepropanoic acid (4c): Yield: 92 %. mp 122-124 ^{o}C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6, 25 ^{o}C): d = 2.02 (m, 2 H, H-4'), 2.86 (m, 1H, H-3'a), 2.96 (m, 1 H, H-3'b), 3.66 (t, 2 H, J = 7.2 Hz, H-5'), 4.87 (s, 1 H, H-2), 10.07 (s, 1 H, N^{1}H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25 ^{o}C): d = 21.11 (C-4'), 33.08 (C-3'), 49.88 (C-5'), 68.28 (C-2), 118.16 (C-3), 164.27 (C-2'), 173.40 (C-1) ppm. Anal. Calcd for $C_7H_{10}N_2O_5$ (202.16): C 41.59, H 4.99, N 13.86. Found: C 41.91, H 5.08, N 13.51. EI-MS: m/z = 203.2 $[M+H]^+$.

Ethyl (2-Hydroxy-3-nitro-3-pyrrolidin-2'-ylidene)propionate (4d): Yield: 90 %. mp 110-112 ^{o}C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6, 25 ^{o}C): d = 1. 12 (t, 3 H, J = 7.2 Hz, –CH_2–CH_3), 2.00 (m, 2 H, H-4'), 2.82 (q, 1 H, J = 7.7 Hz, H-3'a), 2.98 (q, 1 H, J = 7.7 Hz, H-3'b), 3.66 (t, 2 H, J = 7.0 Hz, H-5'), 4.06 (q, 2 H, J = 7.2 Hz, –CH_2–CH_3), 4.93 (s, 1 H, H-2), 5.32 (s, 1 H, –OH), 10.06 (s, 1 H, H- N^{1}H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25 ^{o}C): d = 14.44 (–CH_2–CH_3), 20.96 (C-4'), 32.44 (C-3'), 49.80 (C-5'), 60.68 (–CH_2–CH_3) 68.34 (C-2), 117.98 (C-3), 164.22 (C-2'), 171.80 (C-1) ppm. Anal. Calcd for

$C_9H_{14}N_2O_5$ (230.22): C 46.95, H 6.13, N 12.17. Found: C 46.77, H 6.39, N 11.90. EI-MS: m/z = 231.3 $[M+H]^+$.

6-Methyl-7-nitro-5-(2-nitro-2-pyrrolidin-2-ylidenyl-ethyl)-2,3-dihydro-1*H*-pyrrolizine (5): 2-Nitro-methylenepyrrolidine **1** (384 mg, 3 mmol) and 2,3-butanedione (1,1 equiv) was stirred in AcOH (10 mL) at ambient temperature for 2 h. The mixture was poured into diisopropyl ether (70 mL) and stirred at 0 °C for 1 hour. The yellowish-brown precipitate was filtered out and recrystallized from EtOH. Yield: 35 %. mp 180-183 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): d = 1.99 (m, 2 H, H-4˝), 1.99 (s, 3 H, –CH_3), 2.42 (m, 2 H, H-2), 2.89 (t, 2 H, J = 7.4 Hz, H-3˝), 3.07 (t, 2 H, J = 7.4 Hz, H-1), 3.63 (t, 2 H, J = 7.0 Hz, H-5˝), 3.83 (s, 2 H, H-1'), 3.93 (t, 2 H, J = 7.8 Hz, H-3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C): d = 9.84 (–CH_3), 21.32 (C-4˝), 25.24 (C-2), 25.45 (C-1'), 27.37 (C-1), 31.33 (C-3″), 46.13 (C-3), 48.21 (C-5″), 114.86 (C-5), 114.86 (C-2'), 123.18 (C-6), 127.34 (C-7), 140.31 (C-8), 164.07 (C-2″) ppm. Anal. Calcd for $C_{14}H_{18}N_4O_4$ (306.32): C 54.89, H 5.92, N 18.29. Found: C 54.84, H 6.12, N 18.21. EI-MS: m/z = 307.4 $[M+H]^+$

3-Hydroxy-3-[(pyrrolidin-2'-ylidene)nitromethyl]-2,4,6-trioxohexahydropyrimidine (6): Yield: 86 %. mp > 230 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): d = 2.00 (m, 2 H, H-4'), 3.19 (m, 2 H, H-3'), 3.65 (t, 2 H, J = 6.8 Hz, H-5'), 7.67 (s, 1 H, –OH), 10.75 (s, 1 H, N^{1}H), 11.34 (s, 2 H, H-NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C): d = 20.68 (C-4'), 32.74 (C-3'), 48.45 (C-5'), 74.04 (C-3), 68.34 (C-2), 116.20 (C–NO_2), 150.13 (C-6), 166.19 (C-2'), 169.83 (C=O) ppm. Anal. Calcd for $C_9H_{10}N_4O_6 \cdot H_2O$ (270.20 + 18.02): C 37.51, H 4.20, N 19.44. Found: C 37.85, H 4.57, N 19.14. EI-MS: m/z = 271.3 $[M+H]^+$

5a,10a-Dihydroxy-5-oxo-5a,8,9,10a-tetrahydro-indeno[2,1-*b*]pyrrolizine (7): Yield: 63%. mp 162-165 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6, 25 °C): d = 2.3 (m, 2 H, H-8), 2.90 (m, 1 H, H-7a), 3.15 (m, 1 H, H-7b), 3.69 (m, 1 H, H-9a), 3.81 (m, 1 H, H-9b), 6.51 (s, 1 H, 10a-OH), 7.44 (s, 1 H, 5a-OH), 7.62 (m, 1 H, H-4), 7.65-7.85 (m, 3 H, H-[1-3]) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25 °C): d = 23.93 (C-8), 28.97 (C-7), 44.00 (C-9), 86.84 (C-5a), 92.70 (C-10a), 114.99 (C-6), 124.02, 125.57, 136.49 (C-[1-3]), 131.25 (C-4), 135.03 (C-10b), 146.27 (C-4a), 167.44 (C-6a), 196.00 (C-5) ppm. Anal. calcd for $C_{14}H_{12}N_2O_5$ (288.26): C 58.33, H 4.20, N 9.72. Found: C 58,52 H 4.41, N 9.54. EI-MS: m/z = 289.3 $[M+H]^+$.

General procedure for the cyclization (8a-e): To a refluxing alcohol (MeOH, EtOH or *i*PrOH, ca. 10 mL) solution of the addition products **4a, b** (1 mmol) concentrated hydrochloric acid (400 mL) was added. After 1 min, water (20 mL) and K_2CO_3 (pH > 8-9) were added, and the reaction mixture was stirred for 30 min at ambient temperature. The crystalline substance precipitated was filtered. No further purification

was required.

6-Methoxy-5-methyl-7-nitro-2,3-dihydro-1*H*-pyrrolizine (8a): Yield: 33 %. mp 118-120 ºC. ^{1}H NMR (400 MHz, DMSO-d_6, 25 ^{o}C): d = 2.07 (s, 3 H, –CH_3), 2.38 (m, 2 H, H-2), 3.10 (t, 2 H, J = 6.7 Hz, H-1), 3.70 (s, 3 H, –O–CH_3), 3.95 (t, 2 H, J = 6.7 Hz, H-3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25 ^{o}C): d = 8.25 (–CH_3), 24.31 (C-2), 27.68 (C-1), 46.83 (C-3), 62.32 (–O–CH_3), 114.62 (C-5), 121.91 (C-7), 136.43 (C-8), 138.27 (C-6) ppm. Anal. Calcd for $C_9H_{12}N_2O_3$ (196.20): C 55.09, H 6.16, N 14.28. Found: C 55.32, H 6.42, N 14.21. EI-MS: m/z = 197.3 $[M+H]^+$.

6-Ethoxy-5-methyl-7-nitro-2,3-dihydro-1*H*-pyrrolizine (8b): Yield: 31 %. mp >265 ºC (decomp). ^{1}H NMR (400 MHz, DMSO-d_6, 25 ^{o}C): d = 1.35 (t, 3 H, J = 7.0 Hz, –CH_2–CH_3),-2.11 (s, 3 H, H-Me), 2.48 (qv, 2 H, J = 7.4 Hz, 6.8 Hz, H-2), 3.24 (t, 2 H, J = 6.8 Hz, H-1), 3.92 (t, 2 H, J = 7.4 Hz, H-3), 3.95 (q, 2 H, J = 7.0 Hz, –CH_2–CH_3) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25 ^{o}C): d = 8.20 (C-Me), 15.21 (–CH_2–CH_3), 24.35 (C-1), 27.47 (C-1), 46.48 (C-3), 70.73 (–CH_2–CH_3), 114.49 (C-5), 123.11 (C-7), 135.75 (C-8), 137.44 (C–6) ppm. Anal. Calcd for $C_{10}H_{14}N_2O_3$ (210.23): C 57.13, H 6.71, N 13.33. Found: C 57.44, H 6.34, N 13.64. EI-MS: m/z = 211.3 $[M+H]^+$.

6-Methoxy-7-nitro-5-phenyl-2,3-dihydro-1*H*-pyrrolizine (8c): Yield: 87 %. mp 131-132 ºC (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6, 25 ^{o}C): d =2.43 (m, 2 H, H-2), 3.21 (t, 2 H, J = 7.2 Hz, H-1), 3.73 (s, 3 H, –OH), 4.17 (t, 2 H, J = 7.2 Hz, H-3), 7.36 (t, 1 H, J = 7.2 Hz, H-Ph), 7.48 (t, 1 H, J = 7.2 Hz, H-Ph), 7.57 (d, 1 H, J = 7.2 Hz, H-Ph) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25 ^{o}C): d = 24.34 (C-2), 27.41 (C-1), 48.88 (C-3), 62.26 (C-CH_3), 118.63 (C-Ph), 123.10 (C-7), 127.55 (C-Ph), 127.64 (C-Ph), 128.96 (C-Ph), 129.26 (C-5), 138.94 (C-8), 159.52 (C-6) ppm. Anal. Calcd for $C_{14}H_{14}N_2O_3$ (258.27): C 65.11, H 5.46, N 10.85. Found: C 64,77, H 5.47, N 10.48. EI-MS: m/z = 259.3 $[M+H]^+$.

6-Ethoxy-7-nitro-5-phenyl-2,3-dihydro-1*H*-pyrrolizine (8d): Yield: 75 %. mp 104-105 ^{o}C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6, 25 ^{o}C): d = 1.15 (t, 3 H, J = 7.0 Hz, –CH_2–CH_3), 2.44 (m, 2 H, H-2), 3.2 (t, 2 H, J = 7.4 Hz, H-1), 3.91 (q, 2 H, J = 7.0 Hz, –CH_2–CH_3), 4.16 (t, 2 H, J = 7.0 Hz, H-3), 7.34 (t, 1 H, J = 7.0 Hz, H-Ph), 7.46 (t, 1 H, J = 7.8 Hz, H-Ph), 7.57 (d, 1 H, J = 7.2 Hz, H-Ph) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25 ^{o}C): d = 15.48 (–CH_2–CH_3), 24.51 (C-2), 27.60 (C-1), 49.05 (C-3), 70.70 (–CH_2–CH_3), 119.18 (C-5), 122.79 (C-7), 127.70 (C-Ph), 127.70 (C-Ph), 129.04 (C-Ph), 129.65 (C-Ph), 137.89 (C-6), 139.04 (C-8) ppm. Anal. Calcd for $C_{15}H_{16}N_2O_3$ (272.30): C 66.16, H 5.92, N 10.29. Found: C 66,28, H 6.03, N 10.48. EI-MS: m/z = 273.4 $[M+H]^+$.

6-Isopropoxy-7-nitro-5-phenyl-2,3-dihydro-1*H*-pyrrolizine (8e): Yield: 80 %. mp 140-143 ^{o}C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6, 25 ^{o}C): d = 1.12 (d, 6 H, J = 6,0 Hz, H-Me), 2.52 (m, 2 H,

H-2), 3.33 (t, 2 H, J = 7.6 Hz, H-1), 4.14 (t, 2 H, J = 7.2 Hz, H-3), 4.22 (m, 1 H, –CH(CH_3)$_2$), 7.30 (t, 1 H, J = 7.2 Hz, H-Ph), 7.42 (t, 1 H, J = 7.2 Hz, H-Ph), 7.52 (d, 1 H, J = 7.2 Hz, H-Ph) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25 ^{o}C): d = 21.94 (–CH(CH_3)$_2$), 24.47 (C-1), 24.56 (C-2), 48.61 (C-3), 77.79 (–CH(CH_3)$_2$), 120.20 (C-5), 126,15 (C-7), 127.13 (C-Ph), 127.71 (C-Ph), 128.41 (C-Ph), 135.05 (C-Ph), 138.14 (C-8), 156 (pred.) (C-5) ppm. Anal. Calcd for $C_{16}H_{18}N_2O_3$ (286.33): C 67.12, H 6.34, N 9.78. Found: C 67.28, H 6.48, N 9.54. EI-MS: m/z = 287.4 $[M+H]^+$.

2-Methoxy-3-nitro-1-phenyl-3-pyrrolidin-2-ylidenepropan-1-one (9): 2-Hydroxy-1-phenyl-3-nitro-3-pyrrolidin-2'-ylidenepropan-1-one (**4b)** (786 mg, 3 mmol) and concentrated hydrochloric acid (50 mL) was stirred in MeOH (60 mL) at 0 ^{o}C for 1 h. The solvent was removed under reduced pressure. The residue was purified with chromatography (EtOAc/hexane, 4:1), afforded **9**. Yield: 27 %. ^{1}H NMR (400 MHz, DMSO-d_6, 25 ^{o}C): d = 2.06 (m, 2 H, H-4'), 2.05 (dt, 1 H, J = 7.5 Hz, 16 Hz, H-3'a), 3.03 (dt, 1 H, J = 7.5 Hz, 16 Hz, H-3'b), 3.45 (s, 3 H, –CH_3), 3.57 (t, 1 H, J = 7.4 Hz, H-5'a), 3.69 (t, 1 H, J = 7.4 Hz, H-5'b), 6.43 (s, 1 H, H-2), 7.35 (td, 1 H, J = 7.2 Hz, 1.5 Hz, H-Ph), 7.49 (td, 1 H, J = 1.5 Hz, 7.1 Hz, H-Ph) 7.92 (dd, 1 H, J = 1.5 Hz, 7.1 Hz, H-Ph) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25 ^{o}C): d = 21.46 (C-4'), 31.33 (C-3'), 48.21 (C-5'), 57.05 (–CH_3), 79.82 (C-2), 115.59 (C-3), 127.89 (C-Ph), 128.64 (C-Ph), 133.45 (C-Ph), 166.06 (C-2'), 195.36 (C-1) ppm. Anal. Calcd for $C_{14}H_{18}N_2O_4$ (278.30): C 60.42, H 6.52, N 10.07. Found: C 60,54, H 6.72, N 10.22. EI-MS: m/z = 279.4 $[M+H]^+$.

6-(4-Hydroxyphenyl)-7-nitro-5-phenyl-2,3-dihydro-1*H*-pyrrolizine (11): The mixture of 2-hydroxy-1-phenyl-3-nitro-3-pyrrolidin-2'-ylidene-propan-1-one (**4b**) (262 mg, 1 mmol), concentrated hydrochloric acid (250 mL) and phenol (2 mL) was heated at 90-100 ^{o}C for 2 min, diluted with NaOH solution (10 mass%, 30 mL) and extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were dried with Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The residue was triturated in diisopropyl ether, affording **11** as yellow crystals. Yield: 41 %. mp. 170-173 ^{o}C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6, 25 ^{o}C): d = 2.49 (m, 2 H, H-2), 3.25 (t, 2 H, J = 7.2 Hz, H-1) 4.08 (t, 2 H, J = 6.9 Hz, H-3), 6.95 (d, 4 H, J = 8.3 Hz, H-6Ph), 7.20 (d, 2 H, J = 7.6 Hz, H-5Ph), 7.26 (t, 3 H, J = 7.4 Hz, H-5Ph), 9.36 (s, 1 H, –OH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25 ^{o}C): d = 25.65 (C-2), 27.30 (C-1), 48.00 (C-3), 115.02 (C-6Ph), 120.79 (C-6Ph), 123.62 (C-6), 126.79 (C-5), 127.51 (C-7), 127.86 (C-5Ph), 128.68 (C-5Ph), 129.49 (C-5Ph), 130.73 (C-5Ph), 132.08 (C-6Ph), 142.11 (C-8), 156.64 (C-6Ph) ppm. Anal. Calcd for $C_{19}H_{16}N_2O_3$ (320.34): C 71.24, H 5.03, N 8.74. Found: C 71.52, H 5.18, N 8.64. EI-MS: m/z = 321.4 $[M+H]^+$.

6-Chloro-7-nitro-5-phenyl-2,3-dihydro-1*H*-pyrrolizine (12): The mixture of 2-hydroxy-1-phenyl-3-nitro-3-pyrrolidin-2'-ylidenepropan-1-one (**4b**) (786 mg, 3 mmol) and concentrated hydrochloric acid (0.5 mL) was stirred in refluxing trifluoroethanol (10 mL). After 10 min the solution was cooled to rt. The

solid precipitate was recrystallized from trifluoroethanol (8 mL). Yield: 88 %. mp 155-156 ^{o}C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6, 25 ^{o}C): d = 2.47 (m, 2 H, H-2), 3.24 (t, 2 H, J = 7.5 Hz, H-1), 4.12 (t, 2 H, J = 7.2 Hz, H-3), 7.5 (m, 2 H, H-Ph), 7.55 (m, 3 H, H-Ph) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 25 ^{o}C): d = 25.07 (C-2), 27.75 (C-1), 48.97 (C-3), 104.74 (C-6), 125.96 (C-7), 126.23 (C-5), 129.00 (C-Ph), 129.10 (C-Ph), 129.12 (C-Ph), 129.15 (C-Ph), 141.89 (C-8) ppm. Anal. Calcd for $C_{13}H_{11}ClN_2O_2$ (262.69): C 59.44, H 4.22, Cl 13.50, N 10.66. Found: C 59.52, H 4.38, Cl 13.8, N 10.78. EI-MS: m/z = 263.8 $[M+H]^+$.

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