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Novel synthesis of 2-aminopentanedinitriles from 2-(bromomethyl)aziridines and their transformation into 2-imino-5-methoxypyrrolidines and 5-methoxypyrrolidin-2-ones

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Dedicated to Professor C. Szantay on the occasion of his 80th birthday

Abstract—1-Arylmethyl-2-(bromomethyl)aziridines were transformed into 2-[*N*-(arylmethyl)amino]pentanedinitriles upon treatment with an excess of potassium cyanide in DMSO through an unprecedented and peculiar reaction mechanism, involving base-induced ring opening of intermediate 2-(cyanomethyl)aziridines into allylamines, followed by migration of the double bond out of the conjugation towards aldimines via enamine intermediates. The resulting aminopentanedinitriles served as substrates for the synthesis of novel 2-imino-5-methoxypyrrolidines upon treatment with sodium methoxide in methanol, which were either acetylated at the free imino group to afford the more stable *N*-acetylimino derivatives or hydrolyzed towards the corresponding synthetically relevant 5-methoxypyrrolidin-2-ones.
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1. Introduction

Glutamic acid is a major excitatory neurotransmitter in the central nervous system (CNS) of vertebrates and responsible for a large spectrum of physiological functions.[1] Consequently, the design of new ligands for the glutamic acid receptors is of high current interest in the CNS drug discovery process, and many synthetic efforts have been devoted to this matter.[2]

In recent years, the synthesis of amino nitriles has gained more and more interest due to the availability of new and improved (bio)chemical methodologies for their conversion into the corresponding amino acid derivatives.[3,4] In the present report, a novel and straightforward approach towards 2-aminopentanedinitriles[5] from 2-(bromomethyl)aziridines is disclosed through an unusual reaction mechanism. The former amino nitriles can be considered as precursors of the corresponding glutamic acid derivatives, hence the interest in their preparation.

Besides their biological relevance, glutamic acid derivatives are versatile synthons in azaheterocyclic chemistry, mainly used as precursors for the synthesis of the corresponding pyrroglutamic acid analogues.[6] Whereas plentiful reports are available for the synthesis of γ-lactams from glutamic acid derivatives, their cyclisation towards 2-iminopyrrolidines has never been described before, and will be discussed here. The presence of a free imino group in the latter 2-iminopyrrolidines enables the incorporation of this new azaheterocyclic moiety into larger systems with potential biological applications.

2. Results and discussion

The synthesis of 1-arylmethyl-2-(cyanomethyl)aziridines **2** has been reported previously by treatment of 1-arylmethyl-2-(bromomethyl)aziridines **1**[7] with 1 equiv of potassium cyanide in DMSO and heating at 60–70 °C for 3 h (Scheme 1).[8] In some cases, however, prolonged reaction times (up to 6 h) and higher temperatures (up to 100 °C) were required in order to drive the reaction to completion. Therefore, the premised syntheses were performed using an excess of potassium cyanide at elevated temperatures to achieve a faster and better conversion of 2-(bromomethyl)aziridines **1** into the corresponding 2-(cyanomethyl)aziridines **2**. Surprisingly, treatment of 1-arylmethyl-2-(bromomethyl)aziridines **1** with 3 equiv of KCN in DMSO and heating at 80–100 °C for 2–5 h afforded in all cases a totally different type of reaction products, in which the aziridine moiety was no longer

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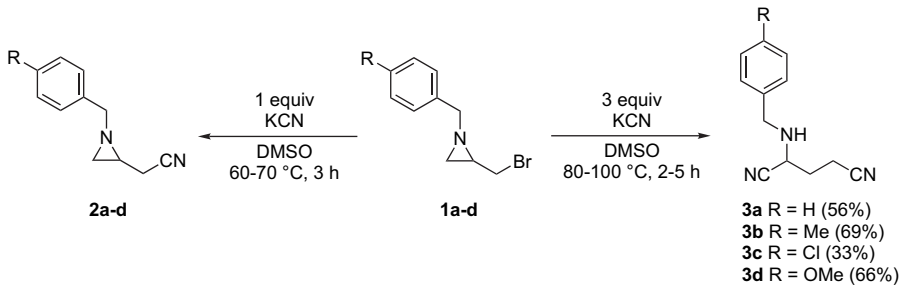
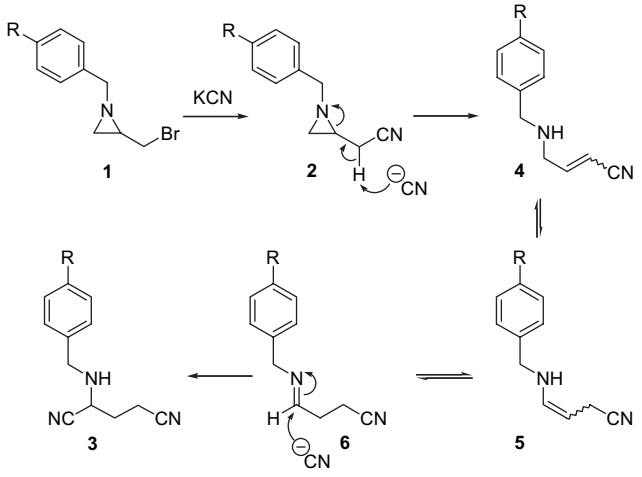


Scheme 1.

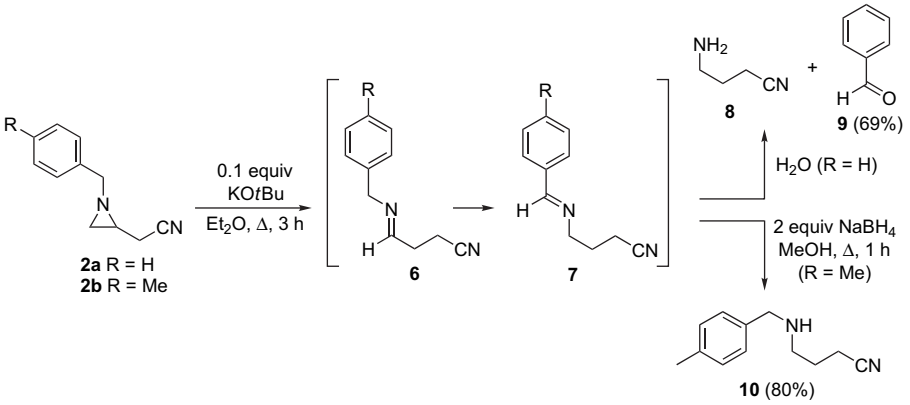
present (Scheme 1). Purification by means of column chromatography and detailed spectroscopic analysis revealed the unexpected molecular structure of 2-[*N*-(arylmethyl)-amino]pentanedinitriles **3**. Very few reports on similar compounds are available in the literature.[5,9] The latter amino nitriles **3** can be considered as precursors of the corresponding 2-aminopentane-1,5-dicarboxylic acids, which are derivatives of the naturally occurring neurotransmitter glutamic acid and of interest as potential drugs for the treatment of neurodegenerative diseases. Moreover, α-amino nitriles are of synthetic use as building blocks for a variety of transformations.[3b]



Scheme 2.

Since no similar transformations have been described in the literature, a profound study of the underlying reaction mechanism urged itself. The most plausible explanation involves substitution of the bromo atom in aziridines **1** by cyanide towards the corresponding 2-(cyanomethyl)aziridines **2**, followed by α-deprotonation with respect to the cyano group by the excess of cyanide and ring opening towards allylic amines **4** (Scheme 2). Isomerization of the double bond in amines **4** and tautomerization of the resulting enamines **5** afford the corresponding imines **6**, which are susceptible for nucleophilic addition of cyanide across the imino bond resulting in 2-aminopentanedinitriles **3** as the final reaction products (Scheme 2). The migration of the double bond in γ-amino-α,β-unsaturated nitriles **4** out of conjugation with the nitrile group towards γ-amino-β,γ-unsaturated nitriles **5** is remarkable and new, although a few literature precedents are available describing analogous observations, e.g., the isomerisation of γ-amino-α,β-unsaturated phosphine oxides to γ-amino-β,γ-unsaturated phosphine oxides,[10] of γ-azido-α,β-unsaturated esters to γ-azido-β,γ-unsaturated esters[11] and of γ-amino-α,β-unsaturated esters and ketones to γ-amino-β,γ-unsaturated esters and ketones.[12]

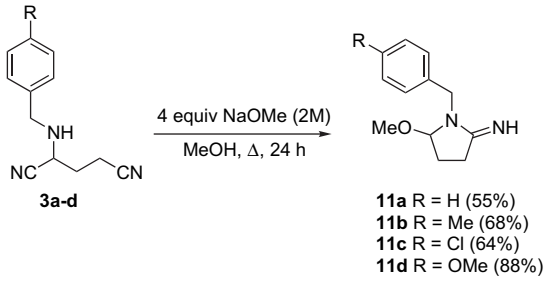
A few experiments were conducted to validate the proposed reaction mechanism. Upon treatment of 2-(cyanomethyl)-aziridines **2** with a catalytic amount of potassium *tert*-butoxide in refluxing Et_2O and subsequent hydrolysis, benzaldehyde **9** was isolated and identified (Scheme 3). Amine **8**, however, could not be retrieved and was probably lost during work up. Alternatively, reduction of the intermediate imine **7** with sodium borohydride (instead of hydrolysis) afforded the corresponding amine **10**, which was



Scheme 3.

isolated and characterized (Scheme 3). It is clear that, in the absence of a suitable nucleophile such as cyanide, imines **6** (formed through α-deprotonation by KO*t*Bu, subsequent ring opening, isomerization and tautomerization) undergo further isomerization towards the more stable conjugated imines **7**, which can then either be hydrolyzed or reduced. The above described observations support the suggested mechanism for the formation of 2-aminopentanedinitriles **3** from 2-(bromomethyl)aziridines **1** as depicted in Scheme 2.

In order to evaluate the synthetic potential of 2-aminopentanedinitriles **3**, attempts were made to induce a functional group transformation of the cyano group(s) into an imidate by reaction with methoxide. Upon treatment of pentanedinitriles **3** with 4 equiv of 2 M sodium methoxide in methanol and reflux for 24 h, the starting material was completely consumed and transformed into a single reaction product. However, detailed spectroscopic analysis showed that no imidate moiety was present, but instead 2-imino-5-methoxypyrrolidines **11** were formed (Scheme 4). These compounds comprise an unexplored and promising class of heterocycles with potential applications in medicinal chemistry.[13]



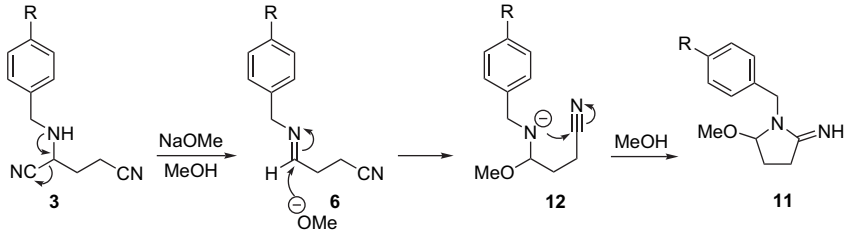
Scheme 4.

The formation of 2-iminopyrrolidines **11** can be explained considering the base mediated expulsion of cyanide from pentanedinitriles **3** towards imines **6**, followed by nucleophilic addition of methoxide across the imino bond of imines **6** and subsequent intramolecular attack of the amide anion **12** onto the ω-cyano group, affording 2-imino-5-methoxypyrrolidines **11** as the reaction products (Scheme 5).

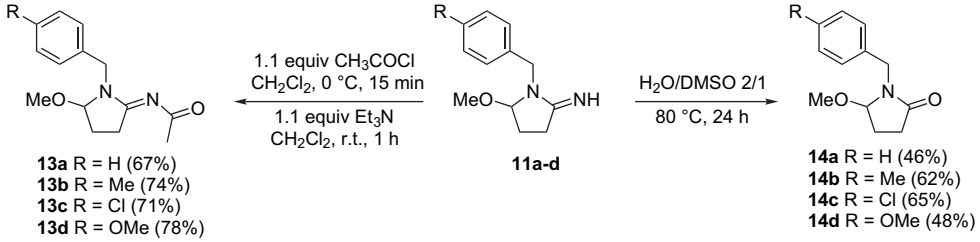
The presence of a free imino group in pyrrolidines **11** enables the incorporation of this azaheterocyclic moiety into larger systems. On the other hand, the free C=NH hampered the purification by means of column chromatography, resulting in complex mixtures. In order to circumvent this problem, and as a proof for its presence, the imino group was acetylated by means of 1.1 equiv of acetyl chloride in dichloromethane in the presence of Et_3N, affording stable 2-(acetylimino)pyrrolidines **13** in good yields after 1 h at room temperature, which were purified by column chromatography in order to obtain analytically pure samples (Scheme 6).

Due to the general interest in γ-lactams as biologically relevant targets and suitable substrates for further elaboration, 2-iminopyrrolidines **11** were converted into the corresponding 5-methoxy-γ-lactams **14** upon stirring in a H_2O/DMSO (2:1) mixture for 24 h at 80 °C (Scheme 6). 5-Alkoxypyrrolidin-2-ones[14] are of importance in organic chemistry as precursors for synthetically useful cyclic *N*-acyliminium intermediates upon treatment with a suitable Lewis acid.[15]

In conclusion, 1-arylmethyl-2-(bromomethyl)aziridines have been transformed very efficiently into 2-[*N*-(arylmethyl)amino]pentanedinitriles via an unprecedented reaction mechanism upon treatment with an excess of potassium cyanide in DMSO. Proof of principle for this unusual mechanism has been provided. The thus obtained 2-aminopentanedinitriles can be considered as precursors of the corresponding glutamic acid derivatives and were used as substrates for the smooth and straightforward synthesis of novel 2-imino-5-methoxypyrrolidines upon treatment with sodium methoxide in methanol. The latter 2-iminopyrrolidines were either acetylated at the free imino group to afford the more stable *N*-acetylimino derivatives or hydrolyzed towards the corresponding synthetically relevant



Scheme 5.



Scheme 6.

5-methoxypyrrolidin-2-ones. In this way, both biologically and synthetically interesting new azaheterocyclic compounds have been prepared.

3. Experimental part

3.1. General

^{1}H NMR spectra were recorded at 270 MHz (JEOL JNM-EX 270) or at 300 MHz (JEOL ECLIPSE+) with $CDCl_3$ as solvent and tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded at 68 MHz (JEOL JNM-EX 270) or at 75 MHz (JEOL ECLIPSE+) with $CDCl_3$ as solvent. Mass spectra were obtained with a mass spectrometer VARIAN MAT 112, 70 eV using a GC–MS coupling (RSL 200, 20 m glass capillary column, i.d. 0.53 mm, He carrier gas) or AGILENT 1100, 70 eV. IR spectra were measured with a Spectrum One FTIR spectrophotometer. Dichloromethane was distilled over calcium hydride, while diethyl ether was dried over sodium benzophenone ketyl. Other solvents were used as received from the supplier.

3.1.1. Synthesis of 2-[*N*-(arylmethyl)amino]pentanedinitriles 3. To a stirred solution of 1-arylbenzyl-2-(bromomethyl)aziridine **1**[7] in DMSO was added crushed potassium cyanide (3 equiv), and the resulting solution was stirred for 2–5 h at 80–100 °C. The reaction mixture was poured into water and extracted three times with diethyl ether. The combined organic extracts were washed two times with water and brine. Drying ($MgSO_4$), filtration of the drying agent and removal of the solvent in vacuo afforded 2-[*N*-(arylmethyl)amino]pentanedinitrile **3**, which was purified by means of column chromatography (hexane/EtOAc).

3.1.1.1. 2-(Benzylamino)pentanedinitrile 3a. Yield 56%. Yellow oil. R_f=0.33 (hexane/EtOAc 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.60 (1H, s(broad), NH); 2.02–2.22 (2H, m, CHCH_2); 2.51–2.69 (2H, m, CH_2CN); 3.63 (1H, d×d, J=8.8, 6.1 Hz, CHCN); 3.85 and 4.07 (2H, 2×d, J=12.8 Hz, N(HCH)Ar); 7.30–7.36 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz): δ 13.96 (*C*H_2CN); 29.22 (NCH*C*H_2); 47.94 (CHN); 51.47 (NCH_2Ar); 118.08 and 118.79 (CH_2*C*N and CH*C*N); 127.92 (HC_{para}); 128.37 and 129.76 (2×$HC_{ortho}HC_{meta}$); 137.60 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν_{NH}=3318, ν_{CN}=2249. MS (70 eV): *m*/*z* (%): 200 (M^++1, 100). Anal. Calcd for $C_{12}H_{13}N_3$: C 72.33, H 6.58, N 21.09. Found: C 72.48, H 6.79, N 20.92.

3.1.1.2. 2-[(4-Methylbenzyl)amino]pentanedinitrile 3b. Yield 69%. Yellow oil. R_f=0.30 (hexane/EtOAc 4:1). ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.01–2.20 (2H, m, CHCH_2); 2.34 (3H, s, CH_3); 2.50–2.64 (2H, m, CH_2CN); 3.60 (1H, d×d, J=8.9, 6.3 Hz, CHCN); 3.79 and 4.01 (2H, 2×d, J=12.7 Hz, N(HCH)Ar); 7.14–7.17 and 7.21–7.25 (4H, 2×m, CH_{arom}). ^{13}C NMR (68 MHz): δ 13.84 (*C*H_2CN); 21.08 (CH_3); 28.99 (NCH*C*H_2); 47.87 (CHN); 51.01 (NCH_2Ar); 118.38 and 118.92 (CH_2*C*N and CH*C*N); 128.26 and 129.32 (2×$HC_{ortho}HC_{meta}$); 134.75 (*C*CH_3); 137.41 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν_{NH}=3344, 3312, ν_{CN}=2248. MS (70 eV): *m*/*z* (%): 213 (M^+, 27); 186 (71); 120 (46); 106 (43); 105 (100); 104 (25); 103 (26); 91 (23); 84 (30); 79 (24); 77 (35); 49 (29). Anal. Calcd for $C_{13}H_{15}N_3$: C 73.21, H 7.09, N 19.70. Found: C 73.39, H 7.24, N 19.57.

3.1.1.3. 2-[(4-Chlorobenzyl)amino]pentanedinitrile 3c. Yield 33%. Yellow oil. R_f=0.38 (hexane/EtOAc 4:1). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.67 (1H, s(broad), NH); 2.06–2.18 (2H, m, CHCH_2); 2.52–2.63 (2H, m, CH_2CN); 3.61 (1H, d×d, J=8.9, 6.2 Hz, CHCN); 3.81 and 4.04 (2H, 2×d, J=13.0 Hz, N(HCH)Ar); 7.27–7.35 (4H, m, CH_{arom}). ^{13}C NMR (68 MHz): δ 13.96 (*C*H_2CN); 29.13 (NCH*C*H_2); 47.98 (CHN); 50.73 (NCH_2Ar); 118.08 and 118.63 (CH_2*C*N and CH*C*N); 128.88 and 129.67 (2×$HC_{ortho}HC_{meta}$); 133.62 (CCl); 136.13 ($C_{arom,quat}$). IR (NaCl, cm^{-1}): ν_{NH}=3320, ν_{CN}=2249. MS (70 eV): *m*/*z* (%): no M^+; 207/9 (M^+−CN, 12); 125/7 (100); 89 (15); 86 (33); 84 (67). Anal. Calcd for $C_{12}H_{12}ClN_3$: C 61.67, H 5.18, N 17.98. Found: C 61.93, H 5.34, N 18.14.

3.1.1.4. 2-[(4-Methoxybenzyl)amino]pentanedinitrile 3d. Yield 66%. Yellow oil. R_f=0.35 (hexane/EtOAc 3:2). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.61 (1H, s(broad), NH); 2.01–2.18 (2H, m, CHCH_2); 2.50–2.60 (2H, m, CH_2CN); 3.60 (1H, d×d, J=8.9, 5.9 Hz, CHCN); 3.78 (3H, s, CH_3O-C_{arom}); 3.77 and 3.99 (2H, 2×d, J=12.7 Hz, N(HCH)Ar); 6.85–6.90 and 7.23–7.30 (4H, 2×m, CH_{arom}). ^{13}C NMR (68 MHz): δ 13.00 (*C*H_2CN); 28.88 (NCH*C*H_2); 47.80 (CHN); 50.66 (NCH_2Ar); 55.26 (*C*H_3OC_{arom}); 114.00 (2×$OMeHC_{ortho}$); 118.52 and 119.01 (CH_2*C*N and CH*C*N); 129.58 (2×$OMeHC_{meta}$); 129.94 (NCH_2*C*$_{arom,quat}$); 159.06 ($OC_{arom,quat}$). IR (NaCl, cm^{-1}): ν_{NH}=3318, ν_{CN}=2249. MS (70 eV): *m*/*z* (%): no M^+; 228 (M^+−H, 2); 138 (100); 137 (69); 121 (49); 109 (77); 107 (32); 94 (28); 86 (26); 84 (43); 77 (44). Anal. Calcd for $C_{13}H_{15}N_3O$: C 68.10, H 6.59, N 18.33. Found: C 68.29, H 6.80, N 18.18.

3.1.2. Synthesis of 1-(arylmethyl)-2-imino-5-methoxypyrrolidines 11. To a stirred solution of 2-[*N*-(arylmethyl)-amino]pentanedinitrile **3** in methanol was added sodium methoxide in methanol (2 M, 4 equiv), and the resulting solution was heated under reflux for 24 h. The reaction mixture was poured into water and extracted three times with diethyl ether. Drying ($MgSO_4$), filtration of the drying agent and removal of the solvent in vacuo afforded 1-(arylmethyl)-2-imino-5-methoxypyrrolidine **11** in acceptable purity (>85% based on NMR). 2-Iminopyrrolidines **11** are unstable upon purification (SiO_2) and were used as such in the next step.

3.1.2.1. 2-Imino-1-benzyl-5-methoxypyrrolidine 11a. Yield 55%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.89–2.09 (2H, m, CH_2CH); 2.48 (1H, d×d×d, J=16.4, 9.2, 3.1 Hz, (*H*CH)C═NH); 2.73 (1H, d×d×d, J=16.4, 9.4, 9.4 Hz, (HC*H*)C═NH); 3.19 (3H, s, OCH_3); 4.17 and 4.89 (2H, 2×d, J=15.3 Hz, (HCH)N); 4.72 (1H, d×d, J=5.6, 1.5 Hz, CH); 7.25–7.36 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 25.34 (*C*H_2CHO); 30.10 (*C*H_2C═NH); 45.02 (CH_2N); 53.16 (OCH_3); 91.85 (CHO); 127.33, 128.06 and 128.63 (HC_{arom}); 137.36 ($C_{arom,quat}$); 168.60 (C═NH). IR (NaCl, cm^{-1}): ν_{NH}=3339, $\nu_{C=NH}$=1638. MS (70 eV): *m*/*z* (%): 205 (M^++1, 100).

3.1.2.2. 2-Imino-1-(4-methylbenzyl)-5-methoxypyrrolidine 11b. Yield 68%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.87–2.06 (2H, m, CH_2CH); 2.33 (1H, s,

CH_3C_{arom}); 2.47 (1H, d×d×d, J_{gem}=16.3, 9.1, 3.2 Hz, (*H*CH)C=NH); 2.72 (1H, d×d×d, *J*=16.4, 9.4, 9.4 Hz, (HC*H*)C=NH); 3.19 (3H, s, OCH_3); 4.11 and 4.84 (2H, 2×d, *J*=15.1 Hz, (HCH)N); 4.70 (1H, d×d, *J*=5.5, 1.4 Hz, CHO); 7.06–7.23 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): *δ* 21.20 (*C*H_3C); 25.32 (*C*H_2CH); 30.15 (*C*H_2C=NH); 44.74 (CH_2N); 53.13 (OCH_3); 91.77 (CHO); 128.12 and 129.30 (CH_{arom}); 134.22 (CH_3*C*); 136.96 ($NCH_2C_{arom,quat}$); 168.54 (C=NH). IR (NaCl, cm^{-1}): ν_{NH}=3310, $\nu_{C=NH}$=1636. MS (70 eV): *m*/*z* (%): 219 (M^++1, 100).

3.1.2.3. 2-Imino-1-(4-chlorobenzyl)-5-methoxypyrrolidine 11c. Yield 64%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 1.89–2.09 (2H, m, C*H*$_2$CH); 2.46 (1H, d×d×d, *J*=16.4, 9.2, 3.2 Hz, (*H*CH)C=NH); 2.71 (1H, d×d×d, *J*=16.4, 9.3, 9.3 Hz, (HC*H*)C=NH); 3.19 (3H, s, OCH_3); 4.17 and 4.82 (2H, 2×d, *J*=15.3 Hz, (HCH)N); 4.70 (1H, d×d, *J*=5.5, 1.7 Hz, CHO); 7.22–7.32 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz): *δ* 25.22 (*C*H_2CH); 29.94 (*C*H_2C=NH); 44.40 (CH_2N); 53.04 (OCH_3); 91.81 (CHO); 128.63–129.38 (HC_{arom}); 132.94 (CCl); 135.96 ($NCH_2C_{arom,quat}$); 168.48 (C=NH). IR (NaCl, cm^{-1}): ν_{NH}=3312, $\nu_{C=NH}$=1638. MS (70 eV): *m*/*z* (%): 239/41 (M^++1, 100).

3.1.2.4. 2-Imino-1-(4-methoxybenzyl)-5-methoxypyrrolidine 11d. Yield 88%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 1.88–2.06 (2H, m, C*H*$_2$CH); 2.41–2.52 (1H, m, (*H*CH)C=NH); 2.64–2.74 (1H, m, (HC*H*)C=NH); 3.19 (3H, s, CHOC*H*$_3$); 3.79 (3H, s, CH_3OC_{arom}); 4.09 and 4.82 (2H, 2×d, *J*=15.0 Hz, (HCH)N); 4.69 (1H, d×d, *J*=5.5, 1.7 Hz, CHO); 6.83–6.88 and 7.20–7.27 (4H, 2×m, CH_{arom}). ^{13}C NMR (75 MHz): *δ* 25.16 (*C*H_2CH); 30.11 (*C*H_2C=NH); 44.34 (CH_2N); 52.95 (CHO*C*H_3); 55.24 (*C*H_3OC_{arom}); 91.58 (CHO); 113.88 (2×MeOH*C*$_{ortho}$); 129.38 (2×MeOH*C*$_{meta}$); 134.86 ($NCH_2C_{arom,quat}$); 158.80 ($OC_{arom,quat}$); 168.44 (C=NH). IR (NaCl, cm^{-1}): ν_{NH}=3315, $\nu_{C=NH}$=1638. MS (70 eV): *m*/*z* (%): 235 (M^++1, 100).

3.1.3. Synthesis of 2-acetylimino-1-(arylmethyl)-5-methoxypyrrolidines 13. To an ice-cooled solution of acetyl chloride (1.1 equiv) in dichloromethane was added 1-(arylmethyl)-2-imino-5-methoxypyrrolidine **11**, and the resulting solution was stirred for 15 min at 0 °C. Subsequently, triethylamine was added (1.1 equiv) and the mixture was stirred for 1 h at room temperature. The reaction mixture was poured into water and extracted three times with dichloromethane. Drying ($MgSO_4$), filtration of the drying agent and removal of the solvent in vacuo afforded 2-acetylimino-1-(arylmethyl)-5-methoxypyrrolidine **13**, which was purified by means of column chromatography (hexane/EtOAc 1:1).

3.1.3.1. 2-Acetylimino-5-methoxy-1-benzylpyrrolidine 13a. Yield 67%. Yellow oil. R_f=0.27 (hexane/EtOAc 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 1.95–2.05 (2H, m, C*H*$_2$CH); 2.20 (3H, s, CH_3C=O); 2.99–3.05 (2H, m, CH_2C=N); 3.19 (3H, s, CHOC*H*$_3$); 4.14–5.16 (2H, 2×d, *J*=14.6 Hz, (HCH)N); 4.77 (1H, d×d, *J*=5.2, 2.8 Hz, CH); 7.28–7.34 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz): *δ* 25.02 (*C*H_2CH); 27.91 (CH_3C=O); 28.58 (*C*H_2C=N); 45.39 (CH_2N); 53.10 (CHO*C*H_3); 90.20 (CHO); 127.64 ($HC_{arom,para}$); 128.50–128.62 (2×$HC_{ortho}HC_{meta}$); 136.13 ($C_{arom,quat}$); 169.12 (C=N); 184.96 (C=O). Anal. Calcd for $C_{14}H_{18}N_2O_2$: C 68.27, H 7.37, N 11.37. Found: C 68.48, H 7.50, N 11.52.

3.1.3.2. 2-Acetylimino-5-methoxy-1-(4-methylbenzyl)-pyrrolidine 13b. Yield 74%. Yellow oil. R_f=0.15 (hexane/EtOAc 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 1.96–2.03 (2H, m, C*H*$_2$CH); 2.19 (3H, s, CH_3C=O); 2.33 (3H, s, CH_3C); 2.98–3.04 (2H, m, CH_2C=N); 3.19 (3H, s, CHOC*H*$_3$); 4.08–5.12 (2H, 2×d, *J*=14.4 Hz, (HCH)N); 4.76 (1H, d×d, *J*=5.0, 3.0 Hz, CH); 7.03–7.23 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): *δ* 21.22 (*C*H_3C); 25.13 (*C*H_2CH); 28.03 (CH_3C=O); 28.73 (*C*H_2C=N); 45.20 (CH_2N); 53.22 (CHO*C*H_3); 90.21 (CHO); 128.63–129.39 (HC_{arom}); 133.13 (CH_3*C*); 137.44 ($NCH_2C_{arom,quat}$); 169.18 (C=N); 185.03 (C=O). IR (NaCl, cm^{-1}): $\nu_{C=O}$=1757, $\nu_{C=N}$=1655. MS (70 eV): *m*/*z* (%): 261 (M^++1, 100). Anal. Calcd for $C_{15}H_{20}N_2O_2$: C 69.20, H 7.74, N 10.76. Found: C 69.38, H 7.94, N 10.67.

3.1.3.3. 2-Acetylimino-5-methoxy-1-(4-chlorobenzyl)-pyrrolidine 13c. Yield 71%. Yellow oil. R_f=0.15 (hexane/EtOAc 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 2.00–2.06 (2H, m, C*H*$_2$CH); 2.19 (3H, s, CH_3C=O); 2.98–3.03 (2H, m, CH_2C=N); 3.19 (3H, s, CHOC*H*$_3$); 4.16 and 5.05 (2H, 2×d, *J*=14.6 Hz, (HCH)N); 4.78 (1H, d×d, *J*=5.2, 3.0 Hz, CHO); 7.20–7.37 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): *δ* 25.13 (*C*H_2CH); 27.97 (CH_3C=O); 28.54 (*C*H_2=N); 45.00 (CH_2N); 53.11 (CHO*C*H_3); 90.44 (CHO); 128.86 and 129.39 (HC_{arom}); 133.64 and 134.95 (2×$C_{arom,quat}$); 168.97 (C=N); 184.72 (C=O). IR (NaCl, cm^{-1}): $\nu_{C=O}$=1756, $\nu_{C=N}$=1653. MS (70 eV): *m*/*z* (%): 281/283 (M^++1, 100). Anal. Calcd for $C_{14}H_{17}ClN_2O_2$: C 59.89, H 6.10, N 9.98. Found: C 60.07, H 6.21, N 9.81.

3.1.3.4. 2-Acetylimino-5-methoxy-1-(4-methoxybenzyl)pyrrolidine 13d. Yield 78%. Yellow oil. R_f=0.15 (hexane/EtOAc 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): *δ* 1.96–2.09 (2H, m, C*H*$_2$CH); 2.21 (3H, s, CH_3C=O); 2.99–3.05 (2H, m, CH_2C=N); 3.19 (3H, s, CHOC*H*$_3$); 3.80 (3H, s, CH_3O-C_{arom}); 4.08 and 5.09 (2H, 2×d, *J*=14.4 Hz, (HCH)N); 4.78 (1H, d×d, *J*=5.2, 3.0 Hz, CHO); 6.97–6.95 and 7.15–7.27 (4H, 2×m, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): *δ* 25.02 (*C*H_2CH); 28.00 (*C*H_3C=O); 28.90 (*C*H_2C=N); 44.99 (CH_2N); 53.05 (CHO*C*H_3); 55.36 (*C*$H_3OC_{arom,quat}$); 90.17 (CHO); 114.06 (2×MeO*C*$_{ortho}$); 128.18 ($NCH_2C_{arom,quat}$); 130.08 (2×MeO*C*$_{meta}$); 159.23 ($OC_{arom,quat}$); 169.39 (C=N); 185.24 (C=O). IR (NaCl, cm^{-1}): $\nu_{C=O}$=1740, $\nu_{C=N}$=1691. MS (70 eV): *m*/*z* (%): 277 (M^++1, 100). Anal. Calcd for $C_{15}H_{20}N_2O_3$: C 65.20, H 7.30, N 10.14. Found: C 65.34, H 7.52, N 10.00.

3.1.4. Synthesis of 1-(arylmethyl)-5-methoxypyrrolidin-2-ones 14. A solution of 2-acetylimino-1-(arylmethyl)-5-methoxypyrrolidine **11** in a water/DMSO mixture (2:1) was heated at 80 °C for 24 h. The reaction mixture was poured into water and extracted three times with diethyl ether. The combined organic extracts were washed two times with water and brine. Drying ($MgSO_4$), filtration of the drying agent and removal of the solvent in vacuo afforded 1-(arylmethyl)-5-methoxypyrrolidin-2-one **14**, which was purified by means of column chromatography (hexane/EtOAc).

3.1.4.1. 1-Benzyl-5-methoxypyrrolidin-2-one 14a. Yield 46%. Yellow oil. R_f=0.31 (hexane/EtOAc 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.94–2.16 (2H, m, CH_2CH); 2.37 (1H, d×d×d, J_{gem}=17.3, 9.6, 3.6 Hz, (*H*CH)C=O); 2.48–2.65 (1H, m, (HC*H*)C=O); 3.21 (3H, s, OCH_3); 4.01 and 4.95 (2H, 2×d, J=14.6 Hz, (HCH)N); 4.73 (1H, d×d, J=6.2, 1.3 Hz, CHO); 7.25–7.36 (5H, m, CH_{arom}). ^{13}C NMR (75 MHz): δ 23.70 (*C*H_2CH); 29.01 (CH_2C=O); 43.77 (CH_2N); 52.90 (OCH_3); 88.97 (CHO); 127.57 ($HC_{arom,para}$); 128.40, 128.63 (2×$HC_{ortho}HC_{meta}$); 136.44 ($C_{arom,quat}$); 174.84 (C=O). IR (NaCl, cm^{-1}): $\nu_{C=O}$=1750, 1694. MS (70 eV): *m*/*z* (%): 206 (M^++1, 100). Anal. Calcd for $C_{12}H_{15}NO_2$: C 70.22, H 7.37, N 6.82. Found: C 70.40, H 7.59, N 6.71.

3.1.4.2. 1-(4-Methylbenzyl)-5-methoxypyrrolidin-2-one 14b. Yield 62%. Yellow oil. R_f=0.20 (hexane/EtOAc 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.92–2.13 (2H, m, CH_2CH); 2.33 (CH_3C); 2.38 (1H, d×d×d, J_{gem}=17.3, 9.4, 3.6 Hz, (*H*CH)C=O); 2.57 (1H, d×d×d, J_{gem}=17.3, 8.9, 8.9 Hz, (HC*H*)C=O); 3.22 (3H, s, OCH_3); 3.96 and 4.93 (2H, 2×d, J=14.6 Hz, (HCH)N); 4.72 (1H, d×d, J=6.1, 1.7 Hz, CH); 7.17–7.29 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 21.20 (*C*H_3C); 23.80 (*C*H_2CH); 29.16 (CH_2C=O); 43.58 (CH_2N); 52.97 (OCH_3); 88.98 (OCH); 128.55–129.41 (HC_{arom}); 133.48 (CH_3*C*); 137.36 ($NCH_2C_{arom,quat}$); 174.83 (C=O). IR (NaCl, cm^{-1}): $\nu_{C=O}$=1758. MS (70 eV): *m*/*z* (%): 220 (M^++1, 100). Anal. Calcd for $C_{13}H_{17}NO_2$: C 71.21, H 7.81, N 6.39. Found: C 71.36, H 8.03, N 6.27.

3.1.4.3. 1-(4-Chlorobenzyl)-5-methoxypyrrolidin-2-one 14c. Yield 65%. Yellow oil. R_f=0.38 (hexane/EtOAc 2:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.93–2.15 (2H, m, CH_2CH); 2.36 (1H, d×d×d, J=17.4, 9.6, 3.6 Hz, (*H*CH)C=O); 2.55 (1H, d×d×d, J=17.4, 8.8, 8.8 Hz, (HC*H*)C=O); 3.18 (3H, s, OCH_3); 4.00 and 4.83 (2H, 2×d, J=14.7 Hz, (HCH)N); 4.70 (1H, d×d, J=6.1, 1.7 Hz, CHO); 7.17–7.29 (4H, m, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 23.78 (*C*H_2CH); 29.03 (CH_2C=O); 43.37 (CH_2N); 52.94 (CH_3); 89.14 (CH); 128.90–129.91 (HC_{arom}); 133.56–135.15 (2×$C_{arom,quat}$); 174.95 (C=O). IR (NaCl, cm^{-1}): $\nu_{C=O}$=1694. MS (70 eV): *m*/*z* (%): 240/2 (M^++1, 100). Anal. Calcd for $C_{12}H_{14}ClNO_2$: C 60.13, H 5.89, N 5.84. Found: C 60.22, H 6.11, N 5.90.

3.1.4.4. 1-(4-Methoxybenzyl)-5-methoxypyrrolidin-2-one 14d. Yield 48%. Yellow oil. R_f=0.20 (hexane/EtOAc 7:3). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.92–2.13 (2H, m, CH_2CH); 2.36 (1H, d×d×d, J=17.3, 9.6, 3.7 Hz, (*H*CH)C=O); 2.48–2.60 (1H, m, (HC*H*)C=O); 3.21 (3H, s, $CHOCH_3$); 3.80 (3H, s, CH_3OC_{arom}); 3.95 and 4.90 (2H, 2×d, J=14.2 Hz, (HCH)N); 4.72 (1H, d×d, J=6.3, 1.7 Hz, CHO); 6.80–6.90 and 7.08–7.31 (4H, 2×m, CH_{arom}). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 23.75 (*C*H_2CH); 29.23 (CH_2C=O); 43.31 (CH_2N); 52.87 (CHO*C*H_3); 55.36 (*C*$H_3OC_{arom,quat}$); 88.92 (CHO); 114.09 (2×$MeOHC_{ortho}$); 129.93 (2×$MeOHC_{meta}$); 134.98 ($NCH_2C_{arom,quat}$); 159.15 ($CH_3OC_{arom,quat}$); 174.80 (C=O). IR (NaCl, cm^{-1}): $\nu_{C=O}$=1748, 1696. MS (70 eV): *m*/*z* (%): 236 (M^++1, 100). Anal. Calcd for $C_{13}H_{17}NO_3$: C 66.36, H 7.28, N 5.95. Found: C 66.52, H 7.39, N 6.10.

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