Synthesis of Masked Vicinal Amino Aldehydes of Pyrrolizine and Pyrrolo [1,2-*c*]thiazole Series

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Abstract: Acylation of (1,3-dihydro-1,3-dimethyl-2*H*-benzimidazol-2-ylidene)acetonitrile with mixed anhydrides of *N*-Boc proline and 4-thiazolidinecarboxylic acid was found to proceed at the exocyclic carbon atom yielding the corresponding *C*-acyl derivatives. Removal of the protecting group with equimolar amount of hydrochloric acid effected simultaneous cyclization affording 2-(3-amino-5,6,7,7a-tetrahydro-1-oxo-1*H*-pyrrolizin-2-yl)- and 2-(5-amino-7,7a-dihydro-7-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazol-6-yl)-1,3-dimethylbenzimidazolium chlorides. Reduction of the prepared salts with sodium borohydride resulted in 3-amino-2-(2,3-dihydro-1,3-dimethyl-1*H*-benzimidazol-2-yl)-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-1-one and 5-amino-6-(2,3-dihydro-1,3-dimethyl-1*H*-benzimidazol-2-yl)-1,7a-dihydro-3*H*,7*H*-pyrrolo[1,2-*c*]thiazol-7-one, respectively. These compounds were shown to be masked aldehydes. Their reactions with phenylhydrazine and hydroxylamine yielded corresponding hydrazones and oximes, whereas condensation with malononitrile furnished 2-amino-5a,6,7,8-tetrahydro-5-oxo-5*H*-pyrido[3,2-*b*]pyrrolizine-3-carbonitrile and 2-amino-5a,6-dihydro-5*H*,8*H*-thiazolo[3′,4′:1,5]pyrrolo[2,3-*b*]pyridine-3-carbonitrile.

Key words: acylations, amino aldehydes, heterocycles, nitriles, reduction

Vicinal (hetero)aromatic amino aldehydes are powerful synthons in heterocyclic chemistry.[1] However, within the pyrrole series these derivatives are poorly represented,[2] whereas for the fused pyrroles like pyrrolizine they are hitherto unknown. Among all isomeric aminopyrrolizines, the 3(5)-substituted derivatives are of especial interest because of their structural relation to jenamidines alkaloid family.[3] At the same time the 3(5)-aminopyrrolizines are the least investigated in comparison with other amines of this structural framework. Only a few syntheses have been reported,[3–5] and most of them included various intramolecular nucleophilic additions of nitrogen or carbon to the nitrile group.[3,4] Furthermore, attempts of electrophilic introduction of nitrogen functionalities into the pyrrolizine were examined,[5] but sometimes it was complicated with formation of a mixture of positional isomers.[5a]

In turn, 2(6)-formylpyrrolizines are the least studied derivatives among all the isomeric aldehydes of the pyrrolizine series. To the best of our knowledge, there are only 5 papers dealing with these compounds,[6] while more than 50 publications are devoted to other aldehydes of this structural framework. The single relatively general approach to pyrrolizine-2(6)-carboxaldehydes is the reaction of 2-acylpyrrole derivatives with acrolein[6a,b] or its equivalents.[6c] Evidently, this method is incompatible with the presence of an amino group. A few less common syntheses known[6d,e] also do not tolerate amine functionality. Hence, the 3-aminopyrrolizine-2-carboxaldehyde moiety represents a synthetic challenge we decided to meet.

N,*N*′-Dimethylbenzimidazolium moiety is an equivalent of the aldehyde functionality.[7] Its reduction to 2,3-dihydro derivative provides the masked formyl group,[7] which can be liberated by hydrolytic cleavage, if necessary.[7a] Recently we have applied such an approach to the preparation of 2-aminopyrrole-3-carboxaldehyde derivatives **1** (Figure 1) by reduction of the corresponding benzimidazolium salt precursors **2**.[8] The latter were obtained in two steps from the nitrile **3** (Scheme 1) by means of C-acylation with chloroacetyl chloride followed by amination with primary amines.[8] As a continuation of our research in this field, the utility of the compound **3** for the synthesis of vicinal amino aldehyde derivatives of fused pyrroles has been studied, and the results obtained are reported herein.

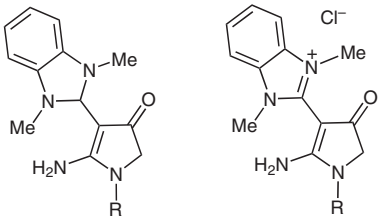

Figure 1 3-Carboxaldehyde derivatives **1** and their precursors **2** (R is alkyl or substituted phenyl)

Compound **3** reacts with certain electrophiles at the exocyclic carbon atom.[8,9] Its reaction with mixed anhydrides of Boc-protected proline (**4a**, n = 1) and pipecolic acid (**4b**, n = 2) occurs smoothly affording derivatives **5a**,**b** in 70–80% yields. The anhydrides **4a**,**b** were generated in situ from the appropriate acids and ethyl chloroformate. It

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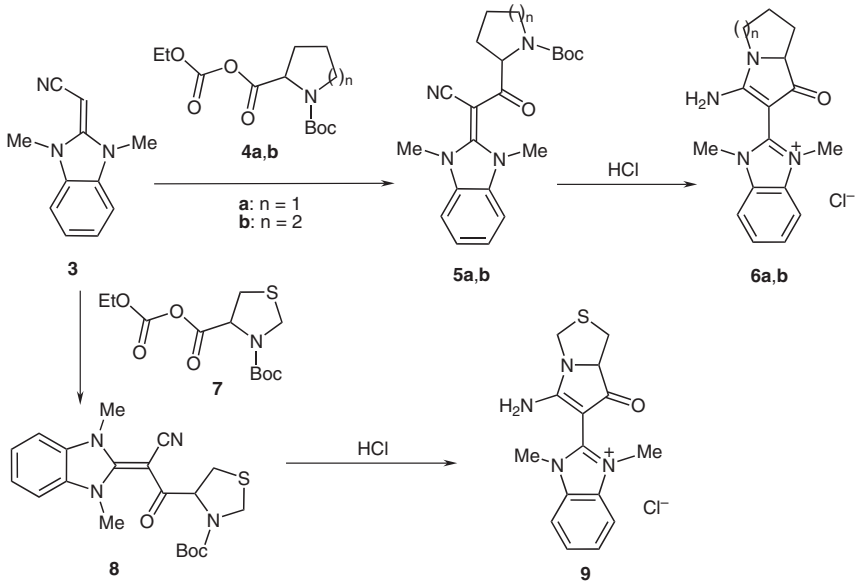

Scheme 1

is noteworthy that previously the mixed anhydrides of protected proline were used for acylation of diazomethane only.[10] Other *C*-acyl derivatives were prepared by either Claisen type condensation of proline esters[11] and imidazolides[12] or addition of organometallics to appropriate esters,[13] Weinreb amides,[14] and carboxylates.[15] Furthermore, the carbodiimide assisted acylation of certain phosphorus ylides was reported.[16] Thus, the present reaction has revealed applicability of mixed anhydrides of α-amino acids for acylation of the enamine type carbon.

Deprotection of the compounds **5a**,**b** with an equimolar amount of hydrochloric acid furnished the benzimidazolium salts **6a**,**b** in nearly quantitative yield. Obviously, derivatives **6** are formed through the hydrogen chloride assisted intramolecular addition of the liberated amine to the nitrile, which is accompanied by the transfer of charge to the benzimidazole moiety. Moreover, the sequence was successfully extended to the cysteine derived anhydride **7**, thus leading to the salt **9** via the intermediate compound **8**. The *S*,*N*-acetal fragment in the derivatives **8** and **9** survived completely the hydrolytic conditions of deprotection-cyclization step.

The structure of the compounds prepared **6** and **9** was initially deduced from their ^{1}H and ^{13}C NMR spectra and then confirmed unambiguously by X-ray crystallographic study carried out for the derivative **6a** (Figure 2).

Further, reduction of the quaternary salts **6** and **9** was examined (Scheme 2). Treatment of compounds **6a** and **9** with excess sodium borohydride in methanol resulted in the masked amino aldehyde derivatives of pyrrolizine **10** and pyrrolo[1,2-*c*]thiazole **11** in moderate yields (30–40%). It should be noted that in the case of pyrroles **2** the yield of the reduction was at least twice higher.[8] Nonetheless, at the expense of the good yields on the previous steps, the method allows preparation of the target compounds **10** and **11** in 20–25% overall yield from the starting nitrile **3**. However, in the case of indolizine derivative **6b** even traces of the appropriate products like **10** and **11** were not detected in the reaction mixture and the starting salt **6b** was completely recovered.[17] The reason for the different behavior of compound **6b** is unclear. Nevertheless, we have noted the difference in the chemical shifts of 2-C of benzimidazolium moiety in derivatives **6a**, **9** and **6b**. Thus, in the ^{13}C NMR spectra of compounds **6a** and **9** this signal was observed at 170.8 and 170.6 ppm, respectively, whereas for the derivative **6b** it appeared at 162.6 ppm. So far as the chemical shift value could be considered as indirect measure of electrophilicity of the appropriate carbon atom, these data showed lower reactivity of compound **6b** compared to **6a** and **9** thus agreeing with the experiment. Perhaps, another geometry of the molecule **6b** results in different conjugation degree between the two bicyclic parts, thus influencing the reactivity. For more detailed conclusions the quantum chemical calculations are required.

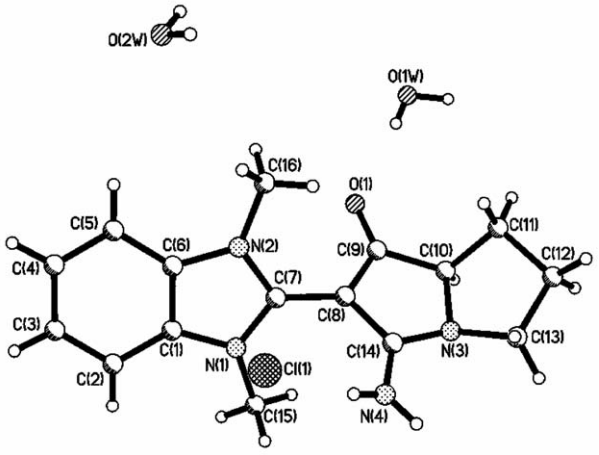

Figure 2 X-ray molecular structure of compound **6a**·2H_2O with the atom numbering used in the crystallographic analysis

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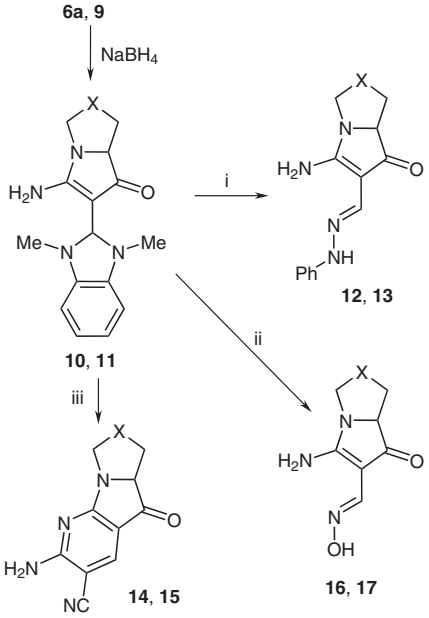

Scheme 2 X = CH_2 (**10**, **12**, **14**, **16**); S (**11**, **13**, **15**, **17**). *Reagents and conditions*: (i) $PhNHNH_2$·HCl, EtOH, reflux; (ii) NH_2OH·HCl, EtOH, reflux; (iii) cat. NH_4Cl, $CH_2(CN)_2$, EtOH, reflux.

The amino aldehyde nature of the derivatives **10** and **11** was demonstrated by several transformations. Thus, their treatment with phenylhydrazine afforded the corresponding hydrazones **12** and **13**. Similarly, the oximes **16** and **17** were obtained by reaction with hydroxylamine. Finally, the ammonium chloride catalyzed condensation with malononitrile yielded derivatives of tricyclic systems **14** and **15**. It is noteworthy that compound **15** is the representative of the novel hitherto unknown heterocyclic skeleton of thiazolo[3′,4′:1,5]pyrrolo[2,3-*b*]pyridine. At the same time the pyrido[3,2-*b*]pyrrolizine system **14** is little known. To the best of our knowledge only four derivatives of this structural framework have been reported to date.[18]

In summary, the present investigation has resulted in the preparation of the first examples of vicinal amino aldehydes of the pyrrolizine and pyrrolo[1,2-*c*]thiazole series. Moreover, during the synthesis the acylation of the enamine type carbon with mixed anhydrides of N-protected α-amino acids has been carried out for the first time, thus revealing the principal applicability of the mixed anhydrides for C-acylations. Compound **3** turned out to be suitable starting material for the synthesis of amino aldehyde derivatives of monocyclic[8] and fused pyrroles. However, some limitations of the method have been also found. At present the dependence of the reduction of the salts of type **6**,**9** on the size and nature of the fused ring remains vague. Therefore, further research in the field is in progress.

The starting nitrile **3** was prepared according to the described procedure.[9a] *N*-Boc proline, pipecolic acid, and 4-thiazolidinecarboxylic acid were obtained as reported.[19] All melting points were determined in open capillary tubes in a Thiele apparatus and are uncorrected. Elemental analyses were performed at the microanalytical department of the Institute of Organic Chemistry, NAS, Kiev, Ukraine. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity plus 400 spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) in DMSO-d_6. Chemical shifts (δ) are given in ppm downfield from internal Me_4Si. *J* values are in Hz. The purity of all compounds obtained was checked by ^{1}H NMR and LC/MS on an Agilent 1100 instrument.

Nitriles 5a,b and 8; General Procedure

Ethyl chloroformate (0.77 g, 7.1 mmol) was added dropwise to an ice-cooled and stirred solution of the appropriate *N*-Boc amino acid (7.1 mmol) and Et_3N (0.98 mL, 7.1 mmol) in anhyd dioxane (15 mL). After the addition was complete, the mixture was stirred at 10–15 °C for 1h. Then compound **3** (1.02 g, 5.5 mmol) was added in one portion and resulting mixture was slowly heated up to the boiling point and stirred at reflux for 1 h. Upon cooling the precipitated Et_3N·HCl was removed by filtration and the dioxane was evaporated to dryness in vacuo. The residue was triturated with H_2O (20 mL), filtered, and recrystallized from aq *i*-PrOH to give derivatives **5a**,**b** and **8**.

2-[Cyano(1,3-dihydro-1,3-dimethyl-2*H*-benzimidazol-2-ylidene)acetyl]-1-pyrrolidinecarboxylic Acid *t*-Butyl Ester (5a)

Yield: 1.64 g (78%); mp 128 °C (H_2O–*i*-PrOH).

^{1}H NMR: δ = 1.41 (s, 9 H, *t*-C_4H_9), 1.84–1.94 (m, 3 H, 3,3,4-H), 2.31 (m, 1 H, 4-H), 3.39–3.49 (m, 2 H, 5-CH_2), 3.74 (s, 6 H, 2 NCH_3), 4.73 (m, 1 H, 2-H), 7.40 (m, 2 H, H_{Ar}), 7.61 (m, 1 H, H_{Ar}), 7.67 (m, 1 H, H_{Ar}).

^{13}C NMR: δ = 24.0 (4-CH_2), 28.6 [C(*C*H_3)$_3$], 31.1 (3-CH_2), 33.3 (2 NCH_3), 47.2 (5-CH_2), 56.9 (*C*CN), 61.7 (2-CH), 78.7 [*C*(CH_3)$_3$], 112.1 (4,7-C_{Bim}), 121.9 (CN), 125.1 (5,6-C_{Bim}), 132.3 (3a,7a-C_{Bim}), 153.0 (2-C_{Bim}), 153.8 (COO), 189.7 (C=O).

Anal. Calcd for $C_{21}H_{26}N_4O_3$: C, 65.95; H, 6.85; N, 14.65. Found: C, 66.01; H, 6.82; N, 14.50.

2-[Cyano(1,3-dihydro-1,3-dimethyl-2*H*-benzimidazol-2-ylidene)acetyl]-1-piperidinecarboxylic Acid *t*-Butyl Ester (5b)

Yield: 1.59 g (73%); mp 119 °C (H_2O–*i*-PrOH).

^{1}H NMR: δ = 1.47 (s, 9 H, *t*-C_4H_9), 1.67–1.76 (m, 4 H, 4,5-CH_2), 1.92 (m, 1 H, 3-H), 2.33 (m, 1 H, 3-H), 3.46 (m, 1 H, 6-H), 3.79 (s, 6 H, 2 NCH_3), 3.96 (m, 1 H, 6-H), 5.23 (m, 1 H, 2-H), 7.44 (m, 4 H, H_{Ar}).

^{13}C NMR: δ = 19.9 (4-CH_2), 24.9 (5-CH_2), 28.1 (3-CH_2), 28.6 [C(*C*H_3)$_3$], 33.3 (2 N CH_3), 42.1 (6-CH_2), 43.0 (2-CH), 56.2 (*C*CN), 78.9 [*C*(CH_3)$_3$], 112.1 (4,7-C_{Bim}), 121.8 (CN), 125.2 (5,6-C_{Bim}), 132.4 (3a,7a-C_{Bim}), 153.1 (2-C_{Bim}), 155.6 (COO), 191.0 (C=O).

Anal. Calcd for $C_{22}H_{28}N_4O_3$: C, 66.65; H, 7.12; N, 14.13. Found: C, 66.60; H, 7.30; N, 14.20.

4-[Cyano(1,3-dihydro-1,3-dimethyl-2*H*-benzimidazol-2-ylidene)acetyl]-3-thiazolidinecarboxylic Acid *t*-Butyl Ester (8)

Yield: 1.87 g (85%); mp 103 °C (H_2O–*i*-PrOH).

^{1}H NMR: δ = 1.48 (s, 9 H, *t*-C_4H_9), 3.28 (dd, ^2J = 11.5 Hz, ^3J = 5.5 Hz, 1 H, 5-H), 3.57 (m, 1 H, 5-H), 3.81 (s, 6 H, 2 NCH_3), 4.61 (d, *J* = 6.5 Hz, 1 H, 2-H), 4.75 (m, 1 H, 4-H), 5.28 (d, *J* = 6.5 Hz, 1 H, 2-H), 7.45–7.48 (m, 4 H, H_{Ar}).

^{13}C NMR: δ = 28.5 [C(*C*H_3)$_3$], 33.3 (2 NCH_3), 35.3 (5-CH_2), 50.0 (4-CH), 57.2 (*C*CN), 64.3 (2-CH_2), 80.1 [*C*(CH_3)$_3$], 112.2 (4,7-C_{Bim}), 121.6 (CN), 125.3 (5,6-C_{Bim}), 132.3 (3a,7a-C_{Bim}), 152.5 (2-C_{Bim}), 153.1 (COO), 186.9 (C=O).

Anal. Calcd for $C_{20}H_{24}N_4O_3S$: C, 59.98; H, 6.04; N, 13.99; S, 8.01. Found: C, 59.92; H, 6.17; N, 13.90; S, 7.77.

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Benzimidazolium Chlorides 6a,b and 9; General Procedure
A solution of the appropriate compound **5a**,**b**, **8** (3 mmol) and concd HCl (0.33 mL) in *i*-PrOH (10 mL) was refluxed for 30–40 min. After cooling, the solid formed was filtered and washed with cold *i*-PrOH (5 mL) yielding pure derivatives **6a**,**b**, **9**. *i*-PrOH filtrate was evaporated to dryness in vacuo and the residue was crystallized from anhyd MeCN affording additional portion of compounds **6a**,**b**, **9**.

2-(3-Amino-5,6,7,7a-tetrahydro-1-oxo-1*H*-pyrrolizin-2-yl)-1,3-dimethyl-3*H*-benzimidazolium Chloride (6a)
Yield: 0.92 g (96%); mp >300 °C (*i*-PrOH).

^{1}H NMR: δ = 1.60 (m, 1 H, 6-H), 2.10–2.17 (m, 3 H, 6,7,7-H), 3.37 (m, 2 H, 5-CH_2), 3.79 (s, 3 H, NCH_3), 3.83 (s, 3 H, NCH_3), 4.11 (dd, *J* = 9.5, 6.5 Hz, 1 H, 7a-H), 7.57 (m, 2 H, H_{Ar}), 7.91 (m, 2 H, H_{Ar}), 8.41 (s, 1 H, NH_2), 8.62 (s, 1 H, NH_2).

^{13}C NMR: δ = 26.9 (6-C), 27.9 (7-C), 32.8 (NCH_3), 33.2 (NCH_3), 47.9 (5-C), 70.5 (7a-C), 79.5 (2-C), 112.8 (4-C_{Bim}), 113.1 (7-C_{Bim}), 125.9 (5-C_{Bim}), 126.0 (6-C_{Bim}), 132.3 (3a-C_{Bim}), 132.5 (7a-C_{Bim}), 147.3 (3-C), 170.8 (2-C_{Bim}), 191.3 (1-C=O).

Anal. Calcd for $C_{16}H_{19}ClN_4O$: C, 60.28; H, 6.01; N, 17.57; Cl, 11.12. Found: C, 60.09; H, 5.82; N, 17.38; Cl, 11.37.

X-ray Crystal Structure[20]
Suitable crystals of **6a** were grown from aq EtOH in the form of hydrate with two molecules of H_2O. Intensities of 28391 reflections (5137 independent, R_{int} = 0.038) were measured with 'Xcalibur-3' diffractometer operating in the ω-2Θ scan mode, $2\Theta_{max}$ = 60°, and using graphite monochromated MoKα radiation (λ = 0.71073 Å). Crystal data: $C_{16}H_{19}ClN_4O{\cdot}2H_2O$, M_r = 354.83, monoclinic, *a* = 13.820(1), *b* = 9.191(1), *c* = 13.976(1) Å, *β* = 97.43(1)°, V = 1760.4(1) Å^3, T = 293 K, space group $P2_1/n$, Z = 4, μ(MoKα) = 0.239 mm^{-1}. The structure was solved by direct method using SHELXTL program package.[21] Positions of hydrogen atoms were located from electron density difference maps and refined by riding model with $U_{iso} = nU_{eq}$ of the carrier atom (n = 1.5 for methyl groups and n = 1.2 for the rest of hydrogens). Hydrogen atoms participating in hydrogen bonds were refined isotropically. Full-matrix least-squares refinement against F^2 in anisotropic approximation for nonhydrogen atoms using 5061 reflections was converged to *R*1 = 0.038, *wR*2 = 0.105 [for 2504 reflections with F>4σ(F)], S = 0.851.

2-(3-Amino-1,5,6,7,8,8a-hexahydro-1-oxo-2-indolizin-yl)-1,3-dimethyl-3*H*-benzimidazolium Chloride (6b)
Yield: 0.99 g (99%); mp 245–246 °C (MeCN).

^{1}H NMR: δ = 1.36 (m, 2 H, 7-CH_2), 1.52 (m, 1 H, 6-H), 1.73 (m, 1 H, 6-H), 1.85 (m, 1 H, 8-H), 2.06 (m, 1 H, 8-H), 3.04 (m, 1 H, 5-H), 4.32 (m, 1 H, 5-H), 4.72 (m, 7 H, 2 NCH_3, 8a-H), 7.59 (m, 2 H, H_{Ar}), 7.91 (m, 2 H, H_{Ar}), 8.19 (s, 2 H, NH_2).

^{13}C NMR: δ = 22.8 (7-C), 25.9 (8-C), 28.9 (6-C), 33.0 (2 NCH_3), 41.9 (5-C), 64.2 (8a-C), 76.9 (2-C), 113.0 (4-C_{Bim}), 113.1 (7-C_{Bim}), 125.9 (5-C_{Bim}), 126.0 (6-C_{Bim}), 132.4 (3a-C_{Bim}), 132.5 (7a-C_{Bim}), 147.6 (3-C), 162.6 (2-C_{Bim}), 189.9 (1-C=O).

Anal. Calcd for $C_{17}H_{21}ClN_4O$: C, 61.35; H, 6.36; N, 16.83; Cl, 10.65. Found: C, 61.45; H, 6.22; N, 16.93; Cl, 10.53.

2-(5-Amino-7,7a-dihydro-7-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazol-6-yl)-1,3-dimethyl-3*H*-benzimidazolium Chloride (9)
Yield: 0.96 g (95%); mp 302 °C (*i*-PrOH).

^{1}H NMR: δ = 3.10 (dd, ^2J = 11.5 Hz, ^3J = 6.0 Hz, 1 H, 1-H), 3.30 (dd, ^2J = 11.5, ^3J = 9.0 Hz, 1 H, 1-H), 3.82 (s, 6 H, 2 NCH_3), 4.32 (d, *J* = 10.5 Hz, 1 H, 3-H), 4.38 (dd, ^3J = 6.0 Hz, ^3J = 9.0 Hz, 1 H, 7a-H), 5.04 (d, *J* = 10.5 Hz, 1 H, 3-H), 7.59–7.62 (m, 2 H, H_{Ar}), 7.92–7.94 (m, 2 H, H_{Ar}), 8.74 (s, 1 H, NH_2), 9.13 (s, 1 H, NH_2).

^{13}C NMR: δ = 31.4 (1-C), 32.8 (NCH_3), 33.1 (NCH_3), 50.7 (3-C), 71.0 (7a-C), 80.0 (6-C), 113.1 (4-C_{Bim}), 113.3 (7-C_{Bim}), 126.2 (5-C_{Bim}), 126.3 (6-C_{Bim}), 132.3 (3a-C_{Bim}), 132.5 (7a-C_{Bim}), 146.5 (5-C), 170.6 (2-C_{Bim}), 189.5 (7-C=O).

Anal. Calcd for $C_{15}H_{17}ClN_4OS$: C, 53.49; H, 5.09; N, 16.63; Cl, 10.52; S, 9.52. Found: C, 53.68; H, 4.87; N, 16.70; Cl, 10.54; S, 9.31.

Pyrrolizine 10 and Pyrrolo[1,2-*c*]thiazole 11; General Procedure
$NaBH_4$ (0.45 g, 14 mmol) was added in portions to a stirred and ice-cooled solution of the salts **6a** or **9** (3.5 mmol) in MeOH (15 mL). After the addition was complete, the stirring was continued for 1 h and then the mixture was left overnight. The precipitate formed was filtered, washed with H_2O (10 mL) and recrystallized from *i*-PrOH to give derivatives **10**, **11**.

3-Amino-2-(2,3-dihydro-1,3-dimethyl-1*H*-benzimidazol-2-yl)-5,6,7,7a-tetrahydro-1*H*-pyrrolizin-1-one (10)
Yield: 0.32 g (32%); mp 185 °C (*i*-PrOH).

^{1}H NMR: δ = 1.38 (m, 1 H, 6-H), 1.96 (m, 3 H, 6,7,7-H), 2.45 (s, 3 H, NCH_3), 2.48 (s, 3 H, NCH_3), 3.16 (m, 2 H, 5-CH_2), 3.70 (m, 1 H, 7a-H), 4.58 (s, 1 H, 2-CH_{Bim}), 6.41 (m, 2 H, H_{Ar}), 6.58 (m, 2 H, H_{Ar}), 7.59 (br s, 2 H, NH_2).

^{13}C NMR: δ = 27.3 (6-C), 27.4 (7-C), 33.6 (NCH_3), 33.7 (NCH_3), 47.8 (5-C), 69.2 (7a-C), 84.7 (2-C_{Bim}), 88.3 (2-C), 106.8 (4-C_{Bim}), 107.2 (7-C_{Bim}), 119.3 (5-C_{Bim}), 119.6 (6-C_{Bim}), 143.0 (3a-C_{Bim}), 143.3 (7a-C_{Bim}), 174.5 (3-C), 195.2 (1-C=O).

Anal. Calcd for $C_{16}H_{20}N_4O$: C, 67.58; H, 7.09; N, 19.70. Found: C, 67.81; H, 7.10; N, 19.70.

5-Amino-6-(2,3-dihydro-1,3-dimethyl-1*H*-benzimidazol-2-yl)-1,7a-dihydro-3*H*,7*H*-pyrrolo[1,2-*c*]thiazol-7-one (11)
Yield: 0.43 g (41%); mp 172–173 °C (*i*-PrOH).

^{1}H NMR: δ = 2.44 (s, 3 H, NCH_3), 2.47 (s, 3 H, NCH_3), 2.94 (dd, ^2J = 11.5 Hz, ^3J = 3.5 Hz, 1 H, 1-H), 3.17 (dd, ^2J = 11.5 Hz, ^3J = 9.5 Hz, 1 H, 1-H), 3.95 (dd, ^3J = 3.5, 9.5 Hz, 1 H, 7a-H), 4.10 (d, *J* = 11.0 Hz, 1 H, 3-H), 4.57 (s, 1 H, 2-CH_{Bim}), 4.77 (d, *J* = 11.0 Hz, 1 H, 3-H), 6.43 (m, 2 H, H_{Ar}), 6.59 (m, 2 H, H_{Ar}), 6.74 (br s, 1 H, NH_2), 7.94 (br s, 1 H, NH_2).

^{13}C NMR: δ = 32.2 (1-C), 33.5 (NCH_3), 33.8 (NCH_3), 51.7 (3-C), 69.7 (7a-C), 84.4 (2-C_{Bim}), 90.5 (6-C), 107.0 (4-C_{Bim}), 107.2 (7-C_{Bim}), 119.4 (5-C_{Bim}), 119.6 (6-C_{Bim}), 142.9 (3a-C_{Bim}), 143.3 (7a-C_{Bim}), 173.6 (5-C), 193.5 (7-C=O).

Anal. Calcd for $C_{15}H_{18}N_4OS$: C, 59.58; H, 6.00; N, 18.53; S, 10.60. Found: C, 59.60; H, 5.84; N, 18.33; S, 10.46.

Phenylhydrazones 12, 13 and Oximes 16, 17; General Procedure
A solution of compound **10**, **11** (2 mmol) and phenylhydrazine hydrochloride (0.37 g, 2.6 mmol) or hydroxylamine hydrochloride (0.18 g, 2.6 mmol) in EtOH (5 mL) was refluxed for 0.5 h. Upon cooling, the solid precipitated was filtered, washed with H_2O (5 mL) and recrystallized from the appropriate solvent yielding derivatives **12**, **13** or **16**, **17**.

3-Amino-5,6,7,7a-tetrahydro-1-oxo-1*H*-pyrrolizine-2-carboxaldehyde Phenylhydrazone (12)
Yield: 0.34 g (66%); mp 229–230 °C (*i*-PrOH).

^{1}H NMR: δ = 1.35 (m, 1 H, 6-H), 1.98 (m, 3 H, 6,7,7-H), 3.21 (m, 1 H, 5-H), 3.26 (m, 1 H, 5-H), 3.74 (m, 1 H, 7a-H), 6.61 (t, *J* = 7.0 Hz, 1 H, 4-H_{Ph}), 6.81 (d, *J* = 7.0 Hz, 2 H, 2,6-H_{Ph}), 7.13 (t, *J* = 7.0 Hz, 2 H, 3,5-H_{Ph}), 7.58 (s, 1 H, NH_2), 7.67 (s, 1 H, N=CH), 8.22 (s, 1 H, NH_2), 9.46 (s, 1 H, NH).

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^{13}C NMR: δ = 26.9 (6-C), 27.7 (7-C), 47.7 (5-C), 69.5 (7a-C), 93.1 (2-C), 111.7 (2,6-C_{Ph}), 117.7 (4-C_{Ph}), 129.5 (3,5-C_{Ph}), 135.1 (1-C_{Ph}), 146.6 (N=CH), 172.0 (3-C), 192.5 (1-C=O).

Anal. Calcd for $C_{14}H_{16}N_4O$: C, 65.61; H, 6.29; N, 21.86. Found: C, 65.49; H, 6.07; N, 21.80.

5-Amino-7,7a-dihydro-7-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6-carboxaldehyde Phenylhydrazone (13)
Yield: 0.37 g (67%); mp 257–258 °C (EtOH).

^{1}H NMR: δ = 2.92 (m, 1 H, 1-H), 3.18 (m, 1 H, 1-H), 4.00 (m, 1 H, 7a-H), 4.20 (d, *J* = 11.5 Hz, 1 H, 3-H), 4.81 (d, *J* = 11.5 Hz, 1 H, 3-H), 6.63 (t, *J* = 6.5 Hz, 1 H, 4-H_{Ph}), 6.85 (d, *J* = 6.5 Hz, 2 H, 2,6-H_{Ph}), 7.14 (t, *J* = 6.5 Hz, 2 H, 3,5-H_{Ph}), 7.67 (s, 1 H, N=CH), 7.79 (s, 1 H, NH_2), 8.57 (s, 1 H, NH_2), 9.61 (s, 1 H, NH).

^{13}C NMR: δ = 31.8 (1-C), 51.6 (3-C), 70.0 (7a-C), 94.4 (6-C), 111.8 (2,6-C_{Ph}), 118.0 (4-C_{Ph}), 129.5 (3,5-C_{Ph}), 133.8 (1-C_{Ph}), 146.3 (N=CH), 171.2 (5-C), 191.0 (7-C=O).

Anal. Calcd for $C_{13}H_{14}N_4OS$: C, 56.92; H, 5.14; N, 20.42; S, 11.69. Found: C, 56.74; H, 4.97; N, 20.27; S, 11.60.

3-Amino-5,6,7,7a-tetrahydro-1-oxo-1*H*-pyrrolizine-2-carboxaldehyde Oxime (16)
Yield: 0.22 g (60%); mp 220–221 °C (*i*-PrOH).

^{1}H NMR: δ = 1.33 (m, 1 H, 6-H), 1.97 (m, 3 H, 6,7,7-H), 3.16 (m, 1 H, 5-H), 3.22 (m, 1 H, 5-H), 3.73 (m, 1 H, 7a-H), 7.17 (s, 1 H, NH_2), 7.66 (s, 1 H, N=CH), 8.20 (s, 1 H, NH_2), 10.00 (s, 1 H, OH).

^{13}C NMR: δ = 26.9 (6-C), 27.8 (7-C), 47.6 (5-C), 69.7 (7a-C), 90.3 (2-C), 142.9 (N=CH), 172.2 (3-C), 192.4 (1-C=O).

Anal. Calcd for $C_8H_{11}N_3O_2$: C, 53.03; H, 6.12; N, 23.19. Found: C, 52.87; H, 6.19; N, 23.20.

5-Amino-7,7a-dihydro-7-oxo-1*H*,3*H*-pyrrolo[1,2-*c*]thiazole-6-carboxaldehyde Oxime (17)
Yield: 0.25 g (63%); mp 242–243 °C (EtOH).

^{1}H NMR: δ = 2.88 (m, 1 H, 1-H), 3.17 (m, 1 H, 1-H), 4.00 (m, 1 H, 7a-H), 4.17 (d, *J* = 10.5 Hz, 1 H, 3-H), 4.75 (d, *J* = 10.5 Hz, 1 H, 3-H), 7.43 (s, 1 H, NH_2), 7.67 (s, 1 H, N=CH), 8.56 (s, 1 H, NH_2), 10.22 (s, 1 H, OH).

^{13}C NMR: δ = 31.7 (1-C), 51.2 (3-C), 70.2 (7a-C), 91.6 (6-C), 142.1 (N=CH), 171.5 (5-C), 190.8 (7-C=O).

Anal. Calcd for $C_7H_9N_3O_2S$: C, 42.20; H, 4.55; N, 21.09; S, 16.09. Found: C, 42.16; H, 4.79; N, 21.10; S, 16.24.

Pyrido[3,2-*b*]pyrrolizine 14 and Thiazolo[3′,4′:1,5]pyrrolo[2,3-*b*]pyridine 15; General Procedure
A solution of compound **10**, **11** (2 mmol), malononitrile (0.17 g, 2.6 mmol) and NH_4Cl (0.01 g, 0.2 mmol) in EtOH (5 mL) was refluxed for 1 h. After cooling, the precipitate formed was filtered, washed with H_2O (10 mL) and recrystallized from aq DMF affording derivatives **14**,**15**.

2-Amino-5a,6,7,8-tetrahydro-5-oxo-5*H*-pyrido[3,2-*b*]pyrrolizine-3-carbonitrile (14)
Yield: 0.17 g (40%); mp 260 °C (DMF–H_2O).

^{1}H NMR: δ = 1.25 (m, 1 H, 7-H), 2.20 (m, 3 H, 7,6,6-H), 3.09 (m, 1 H, 8-H), 3.28 (m, 1 H, 8-H), 4.53 (dd, *J* = 10.0, 6.0 Hz, 1 H, 5a-H), 8.00 (s, 1 H, 4-H), 8.16 (s, 1 H, NH_2), 8.27 (s, 1 H, NH_2).

^{13}C NMR: δ = 24.1 (7-C), 27.1 (6-C), 47.2 (8-C), 74.6 (5a-C), 83.1 (3-C), 108.3 (4a-C), 117.4 (CN), 141.7 (4-C), 163.9 (2-C), 173.8 (9a-C), 193.6 (5-C=O).

Anal. Calcd for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.15. Found: C, 61.53; H, 4.73; N, 26.20.

2-Amino-5a,6-dihydro-5-oxo-5*H*,8*H*-thiazolo-[3′,4′:1,5]pyrrolo[2,3-*b*]pyridine-3-carbonitrile (15)
Yield: 0.32 g (68%); mp 207 °C (DMF–H_2O).

^{1}H NMR: δ = 2.92 (m, 1 H, 6-H), 3.28 (m, 1 H, 6-H), 4.33 (m, 2 H, 5a-H, 8-H), 4.94 (d, *J* = 9.0 Hz, 1 H, 8-H), 8.04 (s, 1 H, 4-H), 8.18 (br s, 2 H, NH_2).

^{13}C NMR: δ = 31.5 (6-C), 49.6 (8-C), 71.4 (5a-C), 85.2 (3-C), 106.5 (4a-C), 117.2 (CN), 140.6 (4-C), 164.5 (2-C), 172.5 (9a-C), 193.7 (5-C=O).

Anal. Calcd for $C_{10}H_8N_4OS$: C, 51.71; H, 3.47; N, 24.12; S, 13.80. Found: C, 51.70; H, 3.64; N, 24.19; S, 13.94.

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