The reaction of 1-ethylthio-3-iminopyrrolizines with hydroxylamine. A new synthesis of 3-aminoisoxazoles

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Dedicated to Prof. Vladimir Minkin on the occasion of his 70th birthday
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Abstract
The reaction of 1-ethylthio-3-iminopyrrolizine-2-carbonitriles with hydroxylamine leads to 1-hydroxyamino-3-iminopyrrolizine-2-carbonitriles, whereas 1-ethylthio-3-iminopyrrolizine-2-carboxamides and hydroxylamines give 3-aminoisoxazoles, as major products. The exchange of the ethylthio group for the hydroxylamine moiety is a side reaction of this approach.

Keywords: 1-Ethylthio-3-iminopyrrolizine-2-carbonitriles, 1-ethylthio-3-iminopyrrolizine-2-carboxamides, hydroxylamine, 3-aminoisoxazoles, exchange

Introduction

The pyrrolizine and indolizine alkaloids constitute a very large family of natural products having a wide range of biological activities and are isolated from a wide variety of plants, insects, animals, marine organisms and microbes. Derivatives of pyrrolizines are used for antiinflammation and analgesia, as aromatase and tumor inhibitors. In view of the intense interest in these compounds and the scarcity of natural samples, a number of new methodologies and strategies have been developed towards their synthesis. We have recently reported that 1-ethylthio-3-iminopyrrolizines, the products of intramolecular cyclization of 2-(1-ethylthio-2-cyanoethenyl)pyrroles, when treated with secondary amines in methanol, readily exchange their ethylthio group for the amine moiety, thus forming the corresponding 1-aminopyrrolizines. In the presence of water, the direction of the reaction of 1-ethylthio-3-iminopyrrolizines with secondary amines is determined by the nature of the substituents in the pyrrolizine cycle: pyrrolizine-2-carbonitriles exchange its ethylthio group for an amine residue only, whereas pyrrolizine-2-carboxamides undergo ring-opening to give the corresponding 2-(1-amino-2-
carbamoyl-2-cyanoethyl)pyrroles. With hydrazine hydrate as the amine component, both pyrrolizine-2-carbonitriles and pyrrolizine-2-carboxamides give 1-hydrazino-3-iminopyrrolizines in high yields. With the goal of further studying the reaction of 1-ethylthiopyrrolizines with amines and establishing its scope and selectivity, as well as for the synthesis of new functionalized aminopyrrolizines with nitrile and carbamide substituents available for further modifications, we have investigated the interaction of 1-ethylthio-3-iminopyrrolizines 1a,b and 1c-e with hydroxylamine.

**Results and Discussion**

As found, 1-ethylthio-3-iminopyrrolizines 1a,b upon heating (40-45°C, 30 min) in methanol with aqueous hydroxylamine readily exchanges the ethylthio group for the hydroxylamino moiety to form 1-hydroxylamino-3-iminopyrrolizines 2a,b in 35 and 41% yield, respectively (Scheme 1). The low yield can probably be explained by the formation of oligomers during the reaction.

![Scheme 1](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>R¹</th>
<th>R²</th>
<th>Yield 2a,b, %</th>
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<tr>
<td>1a-3a</td>
<td>n-Pr</td>
<td>Et</td>
<td>35</td>
</tr>
<tr>
<td>1b-3b</td>
<td>(CH₂)₄</td>
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<td>41</td>
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</table>

The reaction was found to be chemoselective: other products were not detected in the reaction mixture (the reaction was monitored by TLC). However, 1-hydroxylamino-3-iminopyrrolizines 2a,b are unstable in DMSO solutions and transform to 2-(2,2-dicyano-1-hydroxylaminoethyl)pyrroles 3a,b, the concentration of which reaches 12% after 1 h (¹H NMR). However, it was impossible to reach completion of this transformation.

Under analogous conditions, with 1-ethyl-3-iminopyrrolizin-2-carboxamides 1c-e the reaction chemoselectivity breaches and 3-aminoisoxazoles 4c-e, as major products, are formed unexpectedly because of a different stability of the compounds in methanol compared to the nitrile analogues. The exchange of the ethylthio group for hydroxylamine in 3-iminopyrrolizines...
1c-e, bearing a carbamoyl group, to form 1-hydroxylamino-3-iminopyrrolizines 5c-e is a side reaction of this approach. The ratio of products 4c-e : 5c-e is ~ 2.5 : 1. 3-Aminoisoxazoles 4c-e were isolated by column chromatography (Al₂O₃, eluent: methanol), while 1-hydroxylamino-3-iminopyrrolizines 5c-e could not be isolated and were characterized by their ¹H NMR spectra in the reaction mixtures.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R₁</th>
<th>R₂</th>
<th>Yield 4c-e, %</th>
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</thead>
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<tr>
<td>1c-5c</td>
<td>n-Pr</td>
<td>Et</td>
<td>49</td>
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<tr>
<td>1d-5d</td>
<td>n-Bu</td>
<td>n-Pr</td>
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<tr>
<td>1e-5e</td>
<td>(CH₂)₄</td>
<td></td>
<td>40</td>
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</table>

Scheme 2

The formation of 3-aminoisoxazoles is likely to be the result of the ring opening of the pyrrolizines 5c-e and formation of the pyrroles 6c-e with the syn-disposition of the nitrile function relative to the NH group of the pyrrole ring. Thus, pyrroles 6c-e add a second molecule of hydroxylamine at the nitrile group and the adducts 7c-e ring close to eliminate hydroxylamine giving the major products 3-aminoisoxazoles 4c-e (Scheme 3).

Scheme 3
Reacting the pyrrolizine 1e with hydroxylamine in n-propanol (85°C, 10 min) leads to the isolation of 3-aminoisoxazole 4e from the reaction mixture in pure form (as precipitates). 1-Hydroxylamino-3-iminopyrrolizines 2a,b are orange solids, 3-aminoisoxazoles 4c-e are cream-coloured lustrous crystals.

According to elemental analyses, 1-hydroxylamino-3-iminopyrrolizine 2b incorporates a molecule of acetone, which is also confirmed by 1H NMR.

In the 1H NMR spectra of 1-hydroxylamino-3-iminopyrrolizines 2a,b H-3 pyrrole hydrogen appears as a singlet at 6.33-6.45 ppm, the hydroxyl hydrogen signals are in the 10.88-11.00 ppm region. The NH hydrogens resonate at 7.77-7.84 ppm.

Structures of 3-aminoisoxazoles 4c-e were reliably confirmed by a series of 1H and 13C NMR experiments including homo- (NOESY, COSY) and heteronuclear (HMBC and HSQC) 2D correlations. Additionally, using the 2D HSQC technique optimized for the value of the direct 1J(H,N) coupling constant, which equals 90 Hz, 15N chemical shifts for nitrogen atoms in 3-amino groups were obtained. They are in agreement with the known values.13

The 1H NMR spectra of 3-aminoisoxazoles 4c-e show peaks of the pyrrole ring hydrogens (H-3) as a doublet as well as broadened peaks of NH hydrogens of pyrrole, amino and carbamoyl moieties. The amino group hydrogens in 3-aminoisoxazoles 4c-e resonate at 6.92-7.53 ppm.

In the 2D HMBC spectrum of 3-aminoisoxazole 4e, the hydrogens of 3-amino group, representing a narrow singlet in 1H NMR spectrum (in DMSO), show cross-peaks with the 13C signals at 162.1 ppm (isoxazole C-3) and 98.52 ppm (isoxazole C-4). The peak of H-3 in the pyrrole ring has cross-peaks with the 13C resonances of quaternary carbon atoms in the pyrrole ring and the signal at 162.95 ppm, assigned to C-5 in isoxazole.

Analysis of 2D NOESY spectra allows to determine exactly the position of CONH2 group as C-4. This group shows a NOE effect with the H-3 hydrogen and the 3-amino group.

Physical constants and spectral characteristics of all compounds synthesized are given in the Experimental section.

Analogously, one could think about a further reaction of compounds 3a,b with hydroxylamine. However, the compounds 3a,b can be transformed into 5-amino-3-(pyrrole-2-yl)isoxazole without treatment with hydroxylamine. 2-(1H-Pyrrol-2-yl)(hydroxyimino)-methyl-N'1,N'3-dihydroxypropanediimidamides are the products of hydroxylamine binding to both nitrile groups.14

In summary, the reaction of 1-ethylthio-3-iminopyrrolizine-2-carbonitrides with hydroxylamine leads to 1-hydroxylamino-3-iminopyrrolizine-2-carbonitrides, whereas 1-ethylthio-3-iminopyrrolizine-2-carboxamides and hydroxylamines give 3-aminoisoxazoles, as major products.
Experimental Section

General Procedures. Melting points are uncorrected. IR spectra (400-4000 cm⁻¹) were recorded in KBr pellets on a Bruker IFS-25 spectrometer. ¹H and ¹³C NMR spectra were recorded on a Bruker DPX 250 [250.13 (¹H) and 62.9 (¹³C) MHz, respectively] and Bruker DPX 400 [400.13 (¹H) MHz] instruments in DMSO- d₆ and referenced to internal HMDS. Structure of compounds was established by ¹H and ¹³C NMR data obtained using 2D NMR techniques. Assignment of ¹³C resonances was made by employing the 2D HSQC¹⁵ and HMBC¹⁶ heteronuclear correlation techniques.

For recording of 2D HMBC spectra, pulse sequence delays optimized for values of the direct ¹J(H,C) = 145 Hz and far ²J(H,C) = 5 Hz coupling constants were used.

Analysis of reaction mixtures and purity control of compounds obtained were performed by TLC on Silufol UV-254 plates, eluent: diethyl ether – ethanol, 10 : 1. 3-Aminoisoaxazoles were recrystallized from a 1 : 1 acetone-water mixture.

The starting 1-ethylthio-3-iminopyrrolizines were synthesized according to a procedure published in.⁹ Commercial hydroxylamine (Aldrich) was used as a 50% aqueous solution.

Reaction of 2-cyano-1-ethylthio-3-iminopyrrolizines 1a,b with hydroxylamine
A suspension of 3-iminopyrrolizine 1a, b (1 mmol) in 9 ml of methanol was heated with aqueous hydroxylamine (5 mmol) at 40-45°C for 30 min. The solvent was partially removed under vacuum, water was added, and the precipitate formed was filtered off and washed with aqueous methanol. Recrystallization from aqueous acetone gave 1-hydroxylamino-3-iminopyrrolizines 2a,b in 92 and 99% purity, respectively.

6-Ethyl-1-(hydroxyamino)-3-imino-5-propyl-3H-pyrrolizine-2-carbonitrile (2a). Yield 35%, purity 92% (NMR data), mp 223-224°C. v max(KBr) 3392, 3071, 2191, 1656, 1476 cm⁻¹; ¹H NMR (400.13 MHz): δ 11.00 (1H, br s, OH), 7.77 (2H, br s, NH), 6.45 (1H, s, H-3), 2.75 (2H, m, CH₂-1 of propyl), 2.34 (2H, q, 3 J = 7.6 Hz, CH₂ of ethyl), 1.47 (2H, m, CH₂-2 of propyl), 1.08 (3H, t, 3 J = 7.6 Hz, CH₃ of ethyl), 0.86 (3H, t, 3 J = 7.1 Hz, CH₃ of propyl). ¹³C NMR (62.5 MHz): δ 155.14 (C-3), 143.57 (C-1), 130.08 (C-5), 127.45 (C-6), 123.86 (C-7), 115.64 (CN), 112.02 (C-8), 64.79 (C-2), 24.63 (C-1 of propyl), 22.55 (C-2 of propyl), 18.40 (C-1 of ethyl), 15.01 (C-2 of ethyl), 13.02 (C-3 of propyl). Anal. Calcd. for C13H16N4O: C, 63.93; H, 6.56; N, 22.95. Found: C, 63.99; H, 6.59; N, 22.69.

1-(Hydroxyamino)-3-imino-5,6,7,8-tetrahydro-3H-pyrrolo[1,2-a]indole-2-carbonitrile (2b). Yield 41%, mp 243-244°C. v max(KBr) 3388, 3192, 2197, 1662, 1468 cm⁻¹; ¹H NMR (400.13 MHz): δ 10.97 (1H, br s, OH), 7.77 (2H, br s, NH), 6.34 (1H, s, H-3), 2.75 (2H, m, CH₂-5), 2.43 (2H, m, CH₂-8), 1.69 (4H, m, CH₂-6,7). ¹³C NMR (62.5 MHz): δ 154.73 (C-3), 143.57 (C-1), 130.08 (C-5), 127.45 (C-6), 123.86 (C-7), 115.64 (CN), 112.02 (C-8), 64.79 (C-2), 24.63 (C-1 of propyl), 22.55 (C-2 of propyl), 18.40 (C-1 of ethyl), 15.01 (C-2 of ethyl), 13.02 (C-3 of propyl). Anal. Calcd. for C13H16N4O•(CH₃)₂CO: C, 63.93; H, 6.56; N, 22.95. Found: C, 63.99; H, 6.59; N, 22.69.
Reaction of 2-carbamoyl-1-ethylthio-3-iminopyrrolizines 1c-e with hydroxylamine

A. A suspension of 3-iminopyrrolizine 1c-e (1 mmol) in 9 ml of methanol was heated with aqueous solution of hydroxylamine (5 mmol) at 40-45°C for 30 min. The solvent was then removed under vacuum, the residue was analyzed (according to 1H NMR, in all cases, the mixtures of 3-aminoisoxazoles 4c-e and 1-hydroxylamino-3-iminopyrrolizines 5c-e, ~2.5 : 1, are formed) and then recrystallized from aqueous methanol to give either pure 3-aminoisoxazole (in the case of the pyrrolizine 1d) or a mixture of isoxazoles 4c,e and 1-hydroxy-3-iminopyrrolizines 1c,e (in the case of the pyrrolizines 1c-e). After isolation of the isoxazole 4d, the mixtures obtained and the mother liquor were separated by column chromatography (Al2O3, methanol). 3-Aminoisoxazoles 4c-e were isolated, while 1-hydroxylamino-3-iminopyrrolizines were lost during the workup.

B. A suspension of 3-iminopyrrolizine 1e (1 mmol) in 9 ml of n-propanol was heated with aqueous hydroxylamine (5 mmol) at 85°C for 10 min. After cooling of the reaction mixture to room temperature and partial removal of the solvent under vacuum, crystalline solid was formed. When washed with methanol, these crystals represent pure isoxazole 4e (40%).

3-Amino-5-(4-ethyl-5-propyl-1H-pyrrol-2-yl)isoxazole-4-carboxamide (4c). Yield 49%, mp 207-208°C. v_max(KBr) 3406, 3352, 3197, 1676, 1652, 1569, 1455 cm⁻¹; 1H NMR (400 MHz): δ 11.93 (1H, br s, NH), 7.35 (2H, br s, CONH₂), 6.63 (1H, d, J = 2.3 Hz, H-3), 5.62 (2H, br s, NH₂), 2.52 (2H, m, CH₂-1 of propyl), 2.37 (2H, q, J = 7.4 Hz, CH₂ of ethyl), 1.56 (2H, m, CH₂-2 of propyl), 1.10 (3H, t, J = 7.4 Hz, CH₃ of ethyl), 0.90 (3H, t, J = 7.4 Hz, CH₃ of propyl). 13C NMR (62.5 MHz): δ 164.67 (C-5 of isoxazole), 163.09 (CONH₂), 161.93 (C-3 of isoxazole), 132.88 (C-5 of pyrrole), 123.36 (C-4 of pyrrole), 116.64 (C-2 of pyrrole), 111.57 (C-3 of pyrrole), 98.44 (C-4 of isoxazole), 27.16 (C-1 of propyl), 22.43 (C-2 of propyl), 18.30 (C-1 of ethyl), 15.60 (C-2 of ethyl), 13.69 (C-3 of propyl). 15N NMR (25.36 MHz): δ -226.96 (NH), -276 (CONH₂), -340 (NH₂). Anal. Calcd. for C₁₃H₁₈N₄O₂: C, 59.54; H, 6.87; N, 21.37. Found: C, 59.29; H, 6.87; N, 21.56.

3-Amino-5-(5-butyl-4-propyl-1H-pyrrol-2-yl)isoxazole-4-carboxamide (4d). Yield 33%, mp 213-214°C. v_max(KBr) 3464, 3375, 3184, 1635, 1615 cm⁻¹; 1H NMR (400.13 MHz): δ 11.96 (1H, br s, NH), 7.41 (2H, br s, CONH₂), 6.60 (1H, d, J = 1.8 Hz, H-3), 5.61 (2H, br s, NH₂), 2.54 (2H, m, CH₂-1 of butyl ), 2.33 (2H, m, CH₂-1 of propyl), 1.50 (4H, m, CH₂-2, of butyl and propyl), 1.31 (2H, m, CH₂-3 of butyl), 0.89 (6H, m, CH₃ of butyl and propyl). 13C NMR (62.5 MHz): δ 164.70 (CONH₂), 163.13 (C-5 of isoxazole), 161.91 (C-3 of isoxazole), 133.45 (C-5 of pyrrole), 121.47 (C-4 of pyrrole), 116.66 (C-2 of pyrrole), 112.11 (C-3 of pyrrole), 98.45 (C-4 of isoxazole), 31.28 (C-2 of butyl), 27.23 (C-1 of propyl), 24.84 (C-1 of butyl), 23.86 (C-2 of propyl), 21.82 (C-3 of butyl), 13.77 (C-3 and C-4 of butyl and propyl). 15N NMR (25.36 MHz): δ -226 (NH), -273 (CONH₂), -339 (NH₂). Anal. Calcd. for C₁₅H₂₂N₄O₂: C, 62.07; H, 7.59; N, 19.31. Found: C, 61.99; H, 7.61; N, 19.26.

3-Amino-5-(4,5,6,7-tetrahydro-1H-indol-2-yl)isoxazole-4-carboxamide (4e). by the method B. Yield 40%, mp 231-232°C. v_max(KBr) 3395, 3241, 1655, 1515, 1429 cm⁻¹; 1H NMR (400.13 MHz): δ 11.70 (1H, br s, NH), 7.35 (2H, br s, CONH₂), 6.55 (1H, s, H-3), 5.61 (2H, br s, NH₂),
2.58 (2H, m, CH₂-7), 2.45 (2H, m, CH₂-4), 1.71 (4H, m, CH₂-5,6). ¹³C NMR (62.5 MHz): δ 164.51 (CONH₂), 162.95 (C-5 of isoxazole), 162.10 (C-3 of isoxazole), 131.85 (C-5 of pyrrole), 118.17 (C-4 of pyrrole), 117.15 (C-2 of pyrrole), 110.79 (C-3 of pyrrole), 98.52 (C-4 of isoxazole), 23.20 (CH₂-7), 22.70 (CH₂-5), 22.49 (CH₂-6), 21.90 (CH₂-4). ¹⁵N NMR (62.5 MHz): δ -223 (NH), -332 (NH₂). Anal. Caled. for C₁₂H₁₄N₄O₂: C, 58.54; H, 5.69; N, 22.76. Found: C, 58.17; H, 5.82; N, 22.63.

6-Ethyl-1-(hydroxyamino)-3-imino-5-propyl-3H-pyrrolizine-2-carboxamide (5c). ¹H NMR (400.13 MHz, DMSO-d₆): δ 10.90 (1H, br s, OH), 7.84 (2H, br s, NHOH, =NH), 6.80 (2H, br s, CONH₂), 6.43 (1H, s, H-3), 2.75 (2H, m, CH₂-1 of propyl), 2.37 (2H, m, CH₂ of ethyl), 1.55 (2H, m, CH₂-2 of propyl), 1.09 (3H, m, CH₃ of ethyl), 0.86 (3H, m, CH₃ of propyl).

6-Butyl-1-(hydroxyamino)-3-imino-5-propyl-3H-pyrrolizine-2-carboxamide (5d). ¹H NMR (400.13 MHz): δ 10.90 (1H, br s, OH), 7.84 (2H, br s, NHOH, =NH), 6.80 (2H, br s, CONH₂), 6.40 (1H, s, H-3), 2.75 (2H, m, CH₂-1 of butyl), 2.30 (2H, m, CH₂-1 of propyl), 1.50 (4H, m, CH₂-2, of butyl and propyl), 1.31 (2H, m, CH₃-3 of butyl), 0.89 (6H, m, CH₃ of butyl and propyl).

1-(Hydroxyamino)-3-imino-5,6,7,8-tetrahydro-3H-pyrrolo[1,2-a]indole-2-carboxamide (5e). ¹H NMR (400.13 MHz): δ 10.88 (1H, br s, OH), 7.71 (2H, br s, NHOH, =NH), 6.77 (2H, br s, CONH₂), 6.33 (1H, s, H-3), 2.75 (2H, m, CH₂-5), 2.45 (2H, m, CH₂-8), 1.70 (4H, m, CH₂-6,7). ¹³C NMR (62.5 MHz): δ 167.28 (CONH₂), 153.59 (C-3), 145.00 (C-1), 126.03 (C-10), 124.33, 124.30 (C-11, C-12), 111.90 (C-9), 83.67 (C-2), 22.92 (CH₂-5), 22.49 (CH₂-7), 22.40 (CH₂-6), 22.14 (CH₂-8).

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References