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-hydroxylamino-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

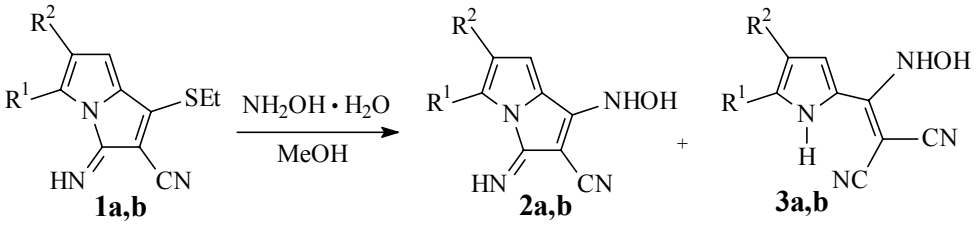
Introduction

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.[1] Derivatives of pyrrolizines are used for antiinflammation and analgesia,[2] as aromatase[3] and tumor[4] 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.[5-8] We have recently reported that 1-ethylthio-3-iminopyrrolizines, the products of intramolecular cyclization of 2-(1-ethylthio-2-cyanoethenyl)pyrroles,[9] when treated with secondary amines in methanol, readily exchange their ethylthio group for the amine moiety, thus forming the corresponding 1-aminopyrrolizines.[10] 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-cyanoethenyl)pyrroles.[11] With hydrazine hydrate as the amine component, both pyrrolizine-2-carbonitriles and pyrrolizine-2-carboxamides give 1-hydrazino-3-iminopyrrolyzines in high yields.[12] 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 functionallized 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.



Compound	R^1	R^2	Yield **2a,b**, %
1a-3a	*n*-Pr	Et	35
1b-3b	$(CH_2)_4$		41

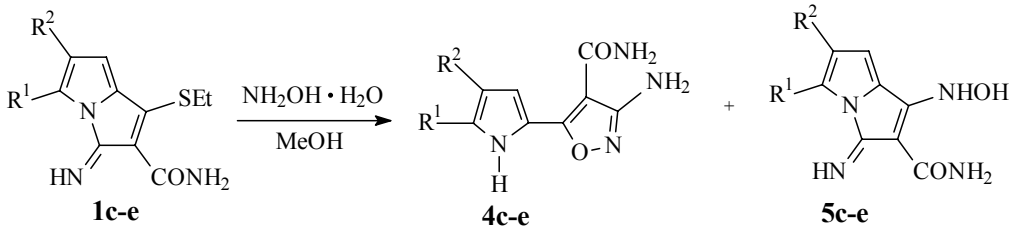
Scheme 1

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-hydroxylaminoethenyl)pyrroles **3a,b**, the concentration of which reaches 12% after 1 h (^{1}H 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 (Al_2O_3, eluent: methanol), while 1-hydroxylamino-3-iminopyrrolizines **5c-e** could not be isolated and were characterized by their ^{1}H NMR spectra in the reaction mixtures.

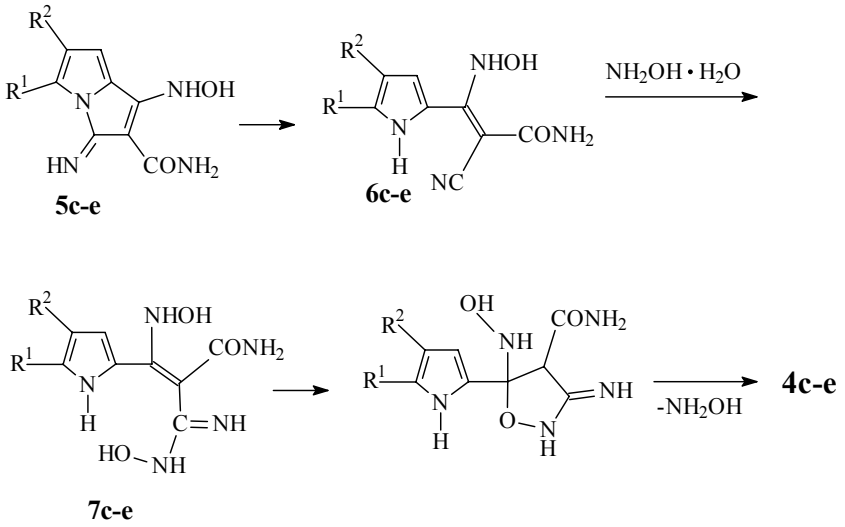


1c-e **4c-e** **5c-e**

Compound	R^1	R^2	Yield **4c-e**, %
1c-5c	*n*-Pr	Et	49
1d- 5d	*n*-Bu	*n*-Pr	33
1e-5e	$(CH_2)_4$		40

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).



5c-e **6c-e** **7c-e**

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 ^{1}H NMR.

In the ^{1}H 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 ^{1}H and ^{13}C 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 ^{1}J(H,N) coupling constant, which equals 90 Hz, ^{15}N chemical shifts for nitrogen atoms in 3-amino groups were obtained. They are in agreement with the known values.[13]

The ^{1}H 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 ^{1}H NMR spectrum (in DMSO), show cross-peaks with the ^{13}C 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 ^{13}C 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 $CONH_2$ 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-carbonitriles with hydroxylamine leads to 1-hydroxylamino-3-iminopyrrolizine-2-carbonitriles, 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 ^{13}C NMR spectra were recorded on a Bruker DPX 250 [250.13 (^1H) and 62.9 (^{13}C) MHz, respectively] and Bruker DPX 400 [400.13 (^1H) MHz] instruments in DMSO-d_6 and referenced to internal HMDS. Structure of compounds was established by ^1H and ^{13}C NMR data obtained using 2D NMR techniques. Assignment of ^{13}C resonances was made by employing the 2D HSQC[15] and HMBC[16] 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 $^nJ(H,C) = 5$ 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-Aminoisoxazoles 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-3*H*-pyrrolizine-2-carbonitrile (2a). Yield 35%, purity 92% (NMR data), mp 223-224°C. ν_{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, CH_2-1 of propyl), 2.34 (2H, q, $^3J = 7.6$ Hz, CH_2 of ethyl), 1.47 (2H, m, CH_2-2 of propyl), 1.08 (3H, t, $^3J = 7.6$ Hz, CH_3 of ethyl), 0.86 (3H, t, $^3J = 7.1$ Hz, CH_3 of propyl). ^{13}C 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 $C_{13}H_{16}N_4O$: 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-3*H*-pyrrolo[1,2-*a*]indole-2-carbonitrile (2b). Yield 41%, mp 243-244°C. ν_{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, CH_2-5), 2.43 (2H, m, CH_2-8), 1.69 (4H, m, CH_2-6,7). ^{13}C NMR (62.5 MHz): δ 154.73 (C-3), 144.10 (C-1), 126.23 (C-10), 125.19 (C-11), 123.69 (C-12), 115.89 (CN), 111.75 (C-9), 60.84 (C-2), 22.92 (CH_2-5), 22.32 (CH_2-7), 22.17 (CH_2-6), 21.88 (CH_2-8). ^{15}N NMR (25.36 MHz): δ -299 (NH). Anal. Calcd. for $C_{12}H_{12}N_4O\bullet(CH_3)_2CO$: C, 62.94; H, 6.29; N, 19.58. Found: C, 62.78; H, 6.65; N, 19.76.

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 ^{1}H 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 (Al_2O_3, 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-1*H*-pyrrol-2-yl)isoxazole-4-carboxamide (4c). Yield 49%, mp 207-208°C. ν_{max}(KBr) 3406, 3352, 3197, 1676, 1652, 1569, 1455 cm^{-1}; ^{1}H NMR (400 MHz): δ 11.93 (1H, br s, NH), 7.35 (2H, br s, $CONH_2$), 6.63 (1H, d, ^4J = 2.3 Hz, H-3), 5.62 (2H, br s , NH_2), 2.52 (2H, m, CH_2-1 of propyl), 2.37 (2H, q, ^3J = 7.4 Hz, CH_2 of ethyl), 1.56 (2H, m, CH_2-2 of propyl), 1.10 (3H, t, ^3J = 7.4 Hz, CH_3 of ethyl), 0.90 (3H, t, ^3J = 7.4 Hz, CH_3 of propyl). ^{13}C NMR (62.5 MHz): δ 164.67 (C-5 of isoxazole), 163.09 ($CONH_2$), 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). ^{15}N NMR (25.36 MHz): δ -226.96 (NH), -276 ($CONH_2$), -340 (NH_2). Anal. Calcd. for $C_{13}H_{18}N_4O_2$: 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-1*H*-pyrrol-2-yl)isoxazole-4-carboxamide (4d). Yield 33%, mp 213-214°C. ν_{max}(KBr) 3464, 3375, 3184, 1635, 1615 cm^{-1}; ^{1}H NMR (400.13 MHz): δ 11.96 (1H, br s, NH), 7.41 (2H, br s, $CONH_2$), 6.60 (1H, d, ^4J = 1.8 Hz, H-3), 5.61 (2H, br s, NH_2), 2.54 (2H, m, CH_2-1 of butyl), 2.33 (2H, m, CH_2-1 of propyl), 1.50 (4H, m, CH_2-2, of butyl and propyl), 1.31 (2H, m, CH_2-3 of butyl), 0.89 (6H, m, CH_3 of butyl and propyl). ^{13}C NMR (62.5 MHz): δ 164.70 ($CONH_2$), 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). ^{15}N NMR (25.36 MHz): δ -226 (NH), -273 ($CONH_2$), -339 (NH_2). Anal. Calcd. for $C_{15}H_{22}N_4O_2$: 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-1*H*-indol-2-yl)isoxazole-4-carboxamide (4e). by the method ***B.*** Yield 40%, mp 231-232°C. ν_{max}(KBr) 3395, 3241, 1655, 1515, 1429 cm^{-1}; ^{1}H NMR (400.13 MHz): δ 11.70 (1H, br s, NH), 7.35 (2H, br s, $CONH_2$), 6.55 (1H, s, H-3), 5.61 (2H, br s, NH_2),

2.58 (2H, m, CH_2-7), 2.45 (2H, m, CH_2-4), 1.71 (4H, m, CH_2-5,6). ^{13}C NMR (62.5 MHz): δ 164.51 ($CONH_2$), 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 (CH_2-7), 22.70 (CH_2-5), 22.49 (CH_2-6), 21.90 (CH_2-4). ^{15}N NMR (62.5 MHz): δ -223 (NH), -332 (NH_2). Anal. Calcd. for $C_{12}H_{14}N_4O_2$: 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-3*H*-pyrrolizine-2-carboxamide (5c). ^{1}H NMR (400.13 MHz, DMSO-d_6): δ 10.90 (1H, br s, OH), 7.84 (2H, br s, NHOH, =NH), 6.80 (2H, br s, $CONH_2$), 6.43 (1H, s, H-3), 2.75 (2H, m, CH_2-1 of propyl), 2.37 (2H, m, CH_2 of ethyl), 1.55 (2H, m, CH_2-2 of propyl), 1.09 (3H, m, CH_3 of ethyl), 0.86 (3H, m, CH_3 of propyl).

6-Butyl-1-(hydroxyamino)-3-imino-5-propyl-3*H*-pyrrolizine-2-carboxamide (5d). ^{1}H NMR (400.13 MHz): δ 10.90 (1H, br s, OH), 7.84 (2H, br s, NHOH, =NH), 6.80 (2H, br s, $CONH_2$), 6.40 (1H, s, H-3), 2.75 (2H, m, CH_2-1 of butyl), 2.30 (2H, m, CH_2-1 of propyl), 1.50 (4H, m, CH_2-2, of butyl and propyl), 1.31 (2H, m, CH_2-3 of butyl), 0.89 (6H, m, CH_3 of butyl and propyl).

1-(Hydroxyamino)-3-imino-5,6,7,8-tetrahydro-3*H*-pyrrolo[1,2-*a*]indole-2-carboxamide (5e). ^{1}H NMR (400.13 MHz): δ 10.88 (1H, br s, OH), 7.71 (2H, br s, NHOH, =NH), 6.77 (2H, br s, $CONH_2$), 6.33 (1H, s, H-3), 2.75 (2H, m, CH_2-5), 2.45 (2H, m, CH_2-8), 1.70 (4H, m, CH_2-6,7). ^{13}C 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 (CH_2-5), 22.49 (CH_2-7), 22.40 (CH_2-6), 22.14 (CH_2-8).

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