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Isoxazoles as Latent α-Cyanoaldehydes: Construction of the Indolo[2,3-a]quinolizine Ring System

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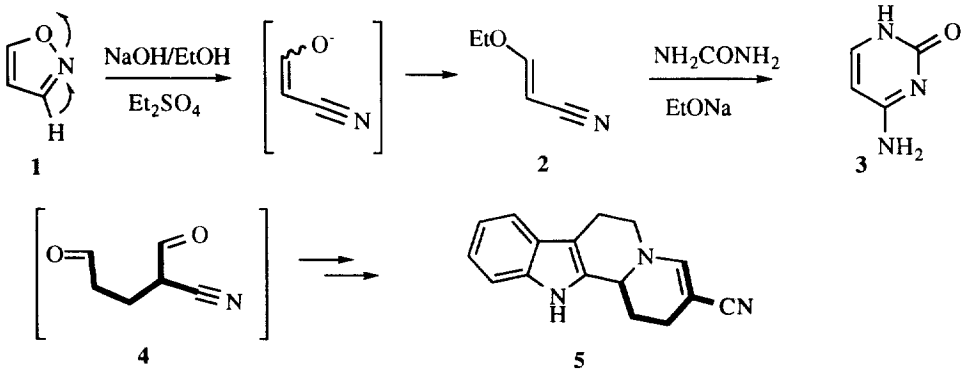
Abstract: A new access to the indolo[2,3-a]quinolizine ring system was devised using the thermal decarboxylative ring-opening of 3-carboxyl isoxazoles into α-cyano aldehydes. Thus, from acetal **8b** the indolo[2,3-a]quinolizine **5** was obtained in four steps via the β-carboline **11** which on heating gave compound **5**.

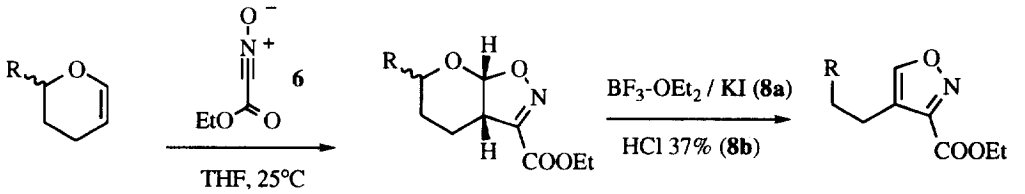
Isoxazoles have long been employed as building blocks in synthesis.[1] For example, the reductive ring opening of substituted isoxazoles provides access to highly functionalized structures such as β-hydroxy or β-amino carbonyls.[2] Another synthetically useful transformation is the base-induced opening of 3-unsubstituted isoxazoles, or the corresponding decarboxylative opening of 3-carboxyl substituted isoxazoles, to give α-cyano carbonyl compounds. These unstable intermediates have generally[1] been characterised as arylhydrazones, pyrazoles or arylidene derivatives. However, the α-cyano aldehyde arising from the reaction of isoxazole **1** with sodium hydroxide can be trapped by reaction with diethyl sulfate.[3] This method is a convenient way to prepare the otherwise difficult to obtain enol ether **2**. Amongst other applications,[4, 5] this 3 carbon synthon has been used for the preparation of cytosine **3** via a cyclocondensation with urea.[3]



Scheme 1

In the present paper we describe how isoxazole ring-opening constitutes the key step in the use of compound **9b** as an equivalent of cyanodialdehyde **4**. This is illustrated by the preparation of indolo[2,3-a]quinolizine **5**, a potentially versatile intermediate in the synthesis of Corynanthe alkaloids.

The approach adopted to prepare compounds equivalent to **4** involved the 1-3 dipolar cycloaddition[6] between the nitrile oxide **6**, generated *in situ* from chlorooximidoethylacetate,[7] and dihydropyran derivatives such as **7a-b** to give acetals **8a-b**. A simultaneous pyran cleavage and isoxazoline aromatization would lead to the target isoxazole **9a** or **9b**. In initial experiments, acetal **8a** was obtained as reported[8] in 28% yield from dihydropyran **7a**. Quite remarkably, the tetrahydropyran ring of **8a** proved resistant toward various acid hydrolysis conditions. However, small amounts of the desired aromatic alcohol **9a** were isolated upon treating this compound with *tert*-butyldimethylsilyl iodide,[9] and a non optimised 22% yield of **9a** was obtained using BF_3-OEt_2 and potassium iodide.[10] In order to have a bicyclic intermediate more susceptible to ring opening, the previously unreported diacetal **8b** was synthesized in 61% yield as a diastereoisomeric mixture of cis-fused dihydroisoxazoles from the commercially available dihydropyran **7b**. The two-fold difference of yield between the two cycloaddition reactions has been interpreted in terms of the electron withdrawing effect of the ethoxy group on the double bond[6] in **7b**. Similarly, the ethoxy moiety in compound **8b** enhanced its sensitivity toward acid hydrolysis since its reaction with concentrated hydrochloric acid at 25°C for two hours led to the crude oily aromatic aldehyde **9b**. This rate increase is probably due to the protonation of the ethoxy group of **8b**, resulting in a build-up of a positive charge on the tetrahydropyran ring oxygen thereby increasing its leaving group character in an elimination process. Since considerable material losses are encountered in the course of chromatography over silica gel, we usually used the crude aldehyde **9b** immediately after its extraction from the reaction medium.



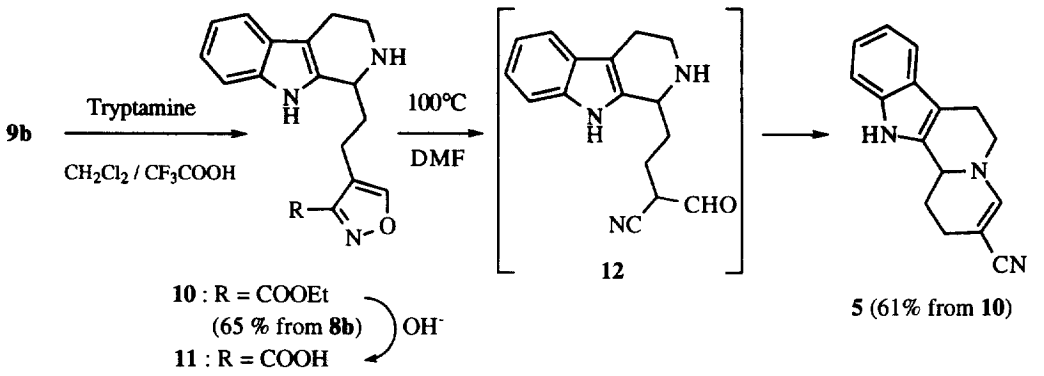
7a : R = H
7b: R = OEt

8a : R = H (28%)
8b: R = OEt (61%)

9a : R = CH_2OH
9b: R = CHO

Scheme 2

The Pictet-Spengler reaction[11] between **9b** and tryptamine in dry dichloromethane containing trifluoroacetic acid provided the β-carboline **10** (65 % yield from **8b**). Attempts to generate the cyanoaldehyde **12** directly from ester **10** were not successful. For instance heating **10** in *tert*-butanol in the presence of sodium *tert*-butoxide resulted in the formation of a mixture of unidentified compounds. Thermal decarboxylation in refluxing toluene also failed. The corresponding acid **11** was thus prepared by treatment of **10** with aqueous potassium hydroxide. This compound was fortunately much more sensitive toward decarboxylation as simple heating of its hydrochloride salt in DMF under an inert atmosphere was sufficient to effect the isoxazole ring cleavage. The intermediate α-cyano aldehyde **12** was not isolated since, as expected, it condenses spontaneously with the β-carboline nitrogen to give the indolo[2,3-a]quinolizine **5** in 61% yield from **10**.



Scheme 3

In conclusion, the use of acetal **8b** as the synthetic equivalent of the cyano dialdehyde **4** enabled us to prepare in four steps the indolo[2,3-a]quinolizine **5** from tryptamine. Many different approaches to this ring system have been reported in the literature.[12-22] In our case, the use of the decarboxylative ring-opening of isoxazole-3-carboxylic acid **11** resulted in the convergent preparation of a hexahydro indolo[2,3-a]quinolizine compound bearing a double bond at the C_1-C_2 position. In this respect, our strategy is similar to Wenkert's approach[14] consisting in the cyclization of dihydropyridine derivatives.

The use of acetal **8b** provides a convenient method to employ an α-cyanoaldehyde synthon in syntheses of biologically interesting indole derivatives.[23-27] We also believe that acetals such as **8a-b** could be useful synthetic building blocks for the synthesis of other biologically interesting heterocycles when a method to introduce a quinolizine component is required.

EXPERIMENTAL SECTION

Melting points were determined on a Reichert Thermovar apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 or 250 MHz spectrometer. Unless stated otherwise $CDCl_3$ was used as solvent. Shifts are given with respect to the TMS signal, coupling constants (*J*) are given in Hertz. Some of the signal attributions were done with the help of COSY and carbon-proton correlation techniques. Mass spectra were obtained on a MS-50 AEI (EI 70 eV) or on a MS-9 AEI (CI, isobutane) spectrometer. Elemental analyses were performed by the Service Central de Microanalyses (ICSN-CNRS, Gif-sur-Yvette, France).

6-Ethoxy-3a,5,6,7a-tetrahydro-4H-pyrano[3,2-d]isoxazole-3-carboxylic acid ethyl ester **8b** :

To a solution of 6-ethoxy-2,3-dihydropyran (28.4 ml; 0.2 mol) and dry triethylamine (2.8 ml; 0.02 mol) in dry THF (150 ml), was added dropwise over three hours a solution of chlorooximidoethylacetate[7] (3.17 g; 0.02 mol) in THF (150 ml). After stirring overnight at room temperature, the THF was evaporated and the residue dissolved in dichloromethane. The organic layer was washed with water, dried over $MgSO_4$ and evaporated to dryness. Chromatography over silica gel afforded two unseparable diastereoisomers **8b** (2.95g; 61%) as a colourless oil. An analytical sample was obtained by bulb to bulb distillation.

^1H : 6.08 (d, 1/2H, 4.48 Hz, CH-7a), 6.00 (d, 1/2H, 7.12 Hz, CH-7a), 4.91 (t, 1/2H, 5.75 Hz, CH-6), 4.85 (t, 1/2H, 5.00 Hz, CH-6), 4.37 (m, 2H, CH_2O ester), 3.93 (m, 1H, CH_2O ether), 3.58-3.40 (m, 2H, CH_2O ether and CH-3a), 2.19-1.79 (m, 4H, CH_2-5 and CH_2-4), 1.40 (m, 3H, CH_3 ester), 1.23 (m, 3H, CH_3 ether). ^{13}C: 160.2 (C=O), 154.0 and 153.4 (C-3), 103.22 and 100.5 (C-7a), 96.5 and 95.9 (C-6), 64.0 and 63.3 (CH_2 ether), 62.1 and 61.9 (CH_2 ester), 45.0 and 41.8 (C-3a), 26.75 and 25.70 (C-5), 16.4 and 16.3 (C-4), 15.1 and 14.9 (CH_3 ether), 14.0 (CH_3 ester). IR (film): 2981, 1723, 1139 cm^{-1}. m/z (IC) = 244 (MH^+). *Anal.* Calcd. for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.53; H, 7.06; N, 5.70.

4-(3-Hydroxy-propyl)-isoxazole-3-carboxylic acid ethyl ester **9a** :

Acetal[8] **8a** (0.1 g), boron trifluoride etherate (0.07 ml), and potassium iodide (0,09 g) were mixed in dry dichloromethane (20 ml; distilled over phosphorous pentoxide). The suspension was refluxed for 24 hours under an inert atmosphere. After evaporation to dryness, the residue was chromatographed on silica gel. Compound **9a** (0.023 g ; 22%) was obtained along with the starting material **8a** (0.078 g ; 77%).

^1H : 8.34 (s, 1H, H-5), 4.43 (q, 2H, 7.1 Hz, CH_2O ester), 3.66 (t, 2H, 6.1 Hz, CH_2-1), 2.79 (t, 2H, 7.6 Hz, CH_2-3), 1.85 (m, 3H, CH_2-2 and OH), 1.42 (t, 3H, 7.1 Hz, CH_3 ester). ^{13}C: 160.8 (C=O ester), 157.6 (CH-5), 153.9 (C-3), 120.7 (C-4), 61.5 and 62.2 (CH_2-1 and CH_2O ester), 32.6 (CH_2-3), 18.3 (CH_2-2), 14.2 (CH_3 ester). m/z (IE) = 199 (M^+).

4-(3-Oxo-propyl)-isoxazole-3-carboxylic acid ethyl ester **9b** :

Acetal **8b** (0.138 g) was stirred for 2 hours in 5 ml of concentrated hydrochloric acid at room temperature. The solution was then carefully neutralised with solid K_2CO_3 while cooling, and extracted with dichloromethane. Drying of the organic layer over $MgSO_4$ and evaporation to dryness yielded aldehyde **9b** (0.095 g) as an oil pure enough for the next step.

^1H : 9.80 (s, 1H, CHO), 8.37 (s, 1H, H-5), 4.47 (q, 2H, 7.1 Hz, CH_2O ester), 3.00 (t, 2H, 6.57 Hz, CH_2CHO), 2.83 (t, 2H, 6.59 Hz, CH_2), 1.43 (t, 3H, 7.08 Hz, CH_3 ester). ^{13}C: 200.5 (CHO), 160.5 (C=O ester), 158.3 (CH-5), 153.7 (C-3), 119.5 (C-4), 62.2 (CH_2O ester), 43.5 (CH_2CHO), 14.7 (CH_2), 14.2 (CH_3 ester). IR (film): 1727 cm^{-1}. m/z (IC) = 198 (MH^+).

4-[2-(2,3,4,9-Tetrahydro-1H-β-carbolin-1H-yl)-ethyl]-isoxazole-3-carboxilic acid ethyl ester **10** :

Crude aldehyde **9b** (0.2 mg), tryptamine (0.24g; 0.015 mol) and trifluoroacetic acid (0.35 ml; 0.02 mol) where dissolved in dry dichloromethane (100 ml) and stirred overnight at room temperature. The reaction medium was then neutralised with solid $NaHCO_3$. The residual salts where removed by filtration and the concentrated residue was chromatographed on silica gel to yield **10** (0.33 g; 65%). The mesylate salt of **10**, obtained by precipitation in acetone (very slow), was recrystallized from ethanol (m.p. = 249 °C) for analytical purpose.

^1H (free base) : 8.85 (s (br), 1H, NH), 8.33 (s, 1H, H-5), 7.46 (d, 1H, 7.22 Hz, H-5'), 7.33 (d, 1H, 7.94 Hz, H-8'), 7.13 (m, 2H, H-5' and H-7'), 4.43 (q, 2H, 7.08 Hz, CH_2O ester), 4.22 (m, 1H, H-1'), 3.38 (m, 1H, H-3'), 3.10 (m, 1H, H-3'), 2.78 (m, 4H, CH_2-4' and CH_2-isox), 2.14 (m, 2H, CH_2-carb), 1.41 (t, 3H, 7.16 Hz, CH_3 ester). IR (film): 3331, 2937, 1731, 1675, 1450 cm^{-1}. m/z (FAB) = 340 (MH^+). *Anal.* Calcd. for $C_{20}H_{25}N_3O_6S$ (mesylate salt) : C, 55.16; H, 5.79; N, 9.65; S, 7.36. Found: C, 55.06; H, 5.66; N, 9.48; S, 7.36.

4-[2-(2,3,4,9-Tetrahydro-1H-β-carbolin-1H-yl)-ethyl]-isoxazole-3-carboxylic acid **11** :

Ester **10** (0.1g) and potassium hydroxide (0.088g) were dissolved in a 50 % v/v water-ethanol solution (10 ml) and stirred for two hours at room temperature. The solution was acidified with hydrochloric acid and

solvents were removed in vacuo. The solid was washed with acetone and the organic solution concentrated to dryness to yield the crude gummy HCl-amino-acid salt **11** (0.11g) which was used without further treatment in the next step.

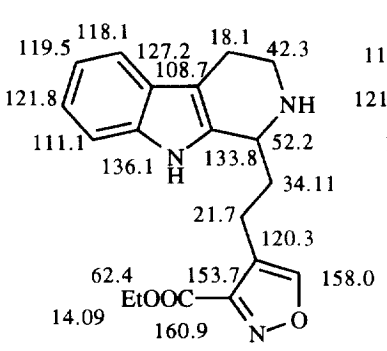
^{1}H (DMSO-d_6) 10.05 and 9.49 (2s(br), 2H, 2 NH), 9.24 (s, 1H, H-5), 7.59 (d, 1H, 7.56 Hz, H-5'), 7.48 (d, 1H, 7.88 Hz, H-8'), 7.20 (m, 2H, H-6' and H-7'), 4.81 (m, 1H, H-1'), 3.69 (m, 1H, H-3'), 3.47 (m, 1H, H-3'), 3.05 (m, 4H, CH_2-4' and CH_2-isox.), 2.35 (m, 2H, CH_2-carb.). m/z (FAB) = 311 (MH^+).

1,2,6,7,12,12b-Hexahydro-indolo[2,3-a]quinolizine-carbonitrile **5** :

A solution of 0.02 g of the crude acid was heated at 100°C in dry DMF (5 ml) under an inert atmosphere for 12 h. The solution was concentrated and the residue was quickly chromatographed over silica gel to yield 0.009g of **5** (61% from ester **10**) *Note*: we must point out that only a 10% yield of **5** is obtained if the reaction is not performed under an inert atmosphere.

^{1}H 7.82 (s(br), 1H, NH), 7.49 (d, 1H, 7.60 Hz, H-8), 7.36 (d, 1H, 7.87 Hz, H-11), 7.21 (m, 1H, H-9), 7.16 (m, 1H, H-10), 6.92 (s, 1H, H-4), 4.48 (d, 1H, 9.93 Hz, H-12b), 3.54 (m, 3H, CH_2-2 and CH-6), 2.82 (m, 1H, CH-6), 2.45 (m, 3H, CH_2-7 and CH-1), 1.89 (m, 1H, CH-1). IR (film): 3287, 2187, 1619 cm^{-1}. m/z (FAB) = 250 (MH^+).

^{13}C signals attribution for compound **10**, **11** and **5** :



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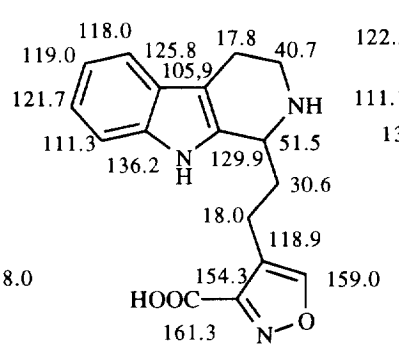
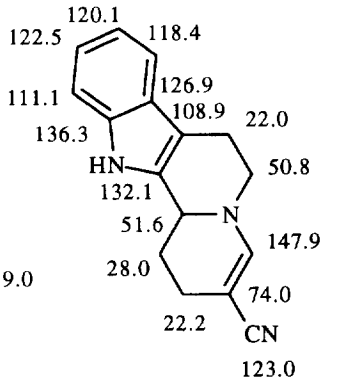


11 (HCl salt)



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