A Novel Synthesis of 4-Cyanoethylisoxazoles

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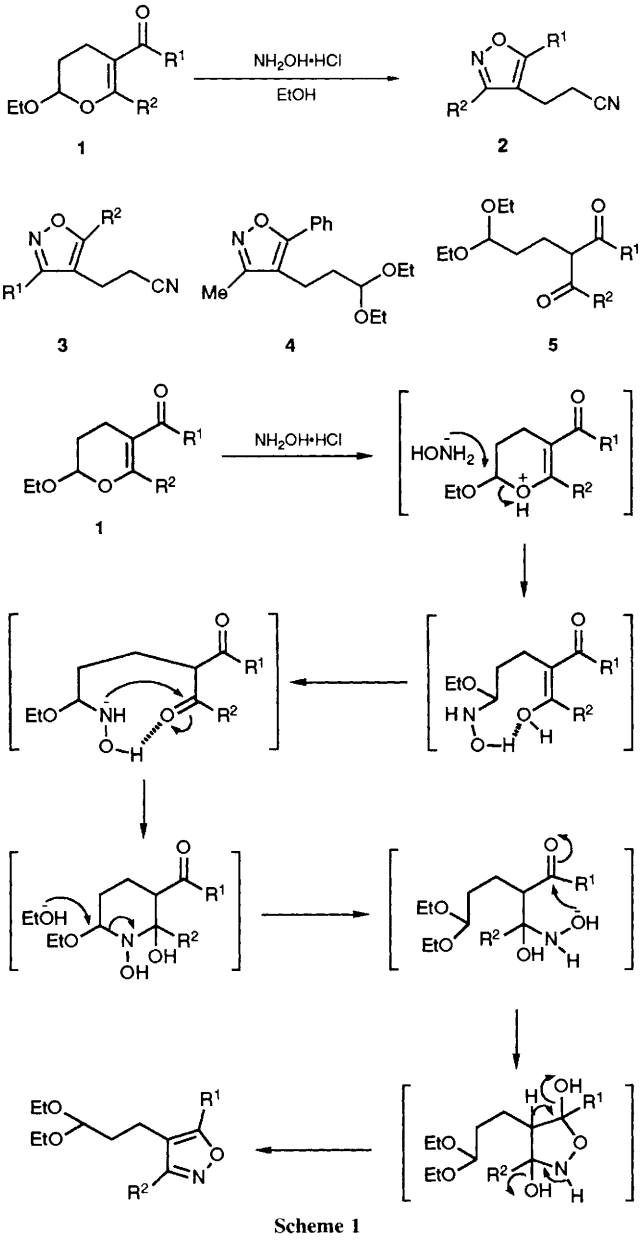
The reaction of dihydropyrans **1** with hydroxylamine hydrochloride gave 4-cyanoethylisoxazoles **2** whose substituents at the 3 and 5 positions were transformed from substituent at the 6 position and the acyl group of **1** regioselectively.

In the course of our studies of the reactivity of 2-methylene-1,3-dicarbonyl compounds we have reported its regioselective hetero Diels–Alder reaction with alkyl vinyl ethers to give dihydropyrans **1**.[1] Dihydropyran derivatives have been reported to be transformed into pyridine derivatives by treatment with ammonia[2] or hydroxylamine hydrochloride.[3] Recently, we found that both aliphatic and aromatic acetals were converted into the corresponding nitriles with hydroxylamine hydrochloride under refluxing absolute ethanol.[4] Our 2-alkoxydihydropyrans **1** have both acetal and keto groups, which are expected to react with hydroxylamine. Herein, we report a novel synthesis of 4-cyanoethylisoxazoles **2** from the reaction of 2-ethoxydihydropyrans **1** with hydroxylamine hydrochloride.



Scheme 1

Dihydropyrans **1** were refluxed with 3 equiv. of hydroxylamine hydrochloride in absolute ethanol. The IR spectra of the products† showed no absorptions due to carbonyl and oxime groups but that of nitrile groups at *ca.* 2240 cm^{-1}. In the ^1H NMR spectrum of the product from 5-benzoyl-2-ethoxy-6-methyl-3,4-dihydro-2*H*-pyran **1a** only a pair of triplets (δ 2.57 and 2.99) due to ethylene protons was observed except for phenyl (δ 7.47–7.68) and methyl (δ 2.37) groups. All products showed the characteristic ethylene signals. Taking this into consideration with the elementary analyses, the products could be trisubstituted isoxazoles **2** or **3**, having a cyanoethyl group at the 4 position. The reactions of dihydropyrans **1** with 2 equiv. of hydroxylamine hydrochloride afforded the same products **2** in almost the same yields. When **1a** was treated with equimolar amounts of hydroxylamine hydrochloride an unstable product **4** was obtained in 76% yield. The product showed no carbonyl group (IR) but an acetal proton (triplet at δ 4.47), ethoxy methylene protons (a pair of double quartets at δ 3.38–3.70), ethoxy methyl protons (triplet at δ 1.20) and ethylene protons (each multiplets at δ 1.69 and 2.70) in the ^1H NMR spectrum. Furthermore, the diethyl acetal **4** was converted into the cyanoethylisoxazole **2a** with an additional 1 equiv. of hydroxylamine hydrochloride in 88% yield. From these results we conclude that first an isoxazole ring is formed by the reaction of **1a** with 1 equiv. of hydroxylamine and the conversion of the acetal group into a nitrile group is achieved with an additional 1 equiv. of hydroxylamine. Initial forma-

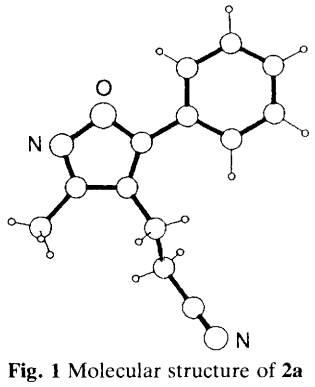


Fig. 1 Molecular structure of **2a**

Table 1 Yields of 4-cyanoethylisoxazoles **2**

Entry	R^1	R^2	Yield (%)[a]
a	Ph	Me	99
b	Ph	Et	69
c	Ph	Pr^n	81
d	Ph	Pr^i	87
e	Pr^i	Ph	83
f	Ph	CH_2CH_2Ph	95
g	Bu^t	Ph	88
h	Ph	Ph	85
i	Ph	C_6H_4-*p*-OMe	61

[a] Isolated yields.

† All new compounds described herein gave satisfactory analytical (combustion and/or high resolution MS) data.

tion of diones **5** was neglected, since isomeric dihydropyrans **1d** and **1e** gave different cyanoethylisoxazoles respectively (entries d and e). However, it is still difficult to determine which substituent occupies which position of the isoxazole ring. An X-ray structure analysis shows that the product formed from the reaction of **1a** with 2 equiv. of hydroxylamine has the structure **2a**,‡ in which the methyl group is situated at the 3 position and the phenyl group at the 5 position of the isoxazole ring. The substituent at the 6 position and alkyl or aryl groups of 5-acyl groups of dihydropyran could be transformed at the 3 and 5 positions of the isoxazole ring. In the ^{1}H NMR spectra of **2**, the signal of phenyl at the 3 position of **2e** and **2g** appeared as a broad singlet, whereas that at the 5 position (all of the remainder) appeared as a multiplet of more than 0.2 ppm. A plausible mechanism for the regioselective isoxazole ring formation is shown in Scheme 1, in which hydrogen bonding plays an important role.

The reaction provides a general preparative procedure for the isoxazole ring among the existing methods.[5]

Received, 13th July 1992; Com. 2/03716E

‡ *Crystal data* for **2a**: $C_{13}H_{12}N_2O$, M = 212.252, space group $P2_12_12_1$, a = 13.392(2), b = 10.740(1), c = 7.748(1) Å, U = 1114.3(2) Å^3. Z = 4, D_c = 1.265 g cm^{-1}, μ(Cu-Kα) = 6.665 cm^{-1}, 0° < 2θ < 120°; 978 unique reflections were measured, of which 938 with $F \neq 0$ were considered. The final R value is 0.0400 (R_W = 0.0390). Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

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