A Facile Conversion of Ethoxydihydropyrans to 4-Cyanoethylisoxazoles

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The reaction of ethoxydihydropyrans **2**, which were prepared from 2-methylene-1,3-dicarbonyl compounds **1** with ethyl vinyl ether, and hydroxylamine hydrochloride gave 4-cyanoethylisoxazoles **3** whose substituents at the 3 and 5 positions were transformed from substituent at the 2 position and the acyl group of **2** regioselectively.

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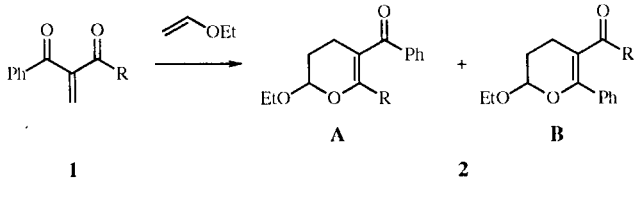
In the previous paper [1] we reported that both aliphatic and aromatic acetals were converted to the corresponding nitriles with hydroxylamine hydrochloride in the presence of acid under refluxing absolute ethanol. Especially aliphatic acetals were easily converted to the nitriles without acid. In the course of our studies of reactivity of 2-methylene-1,3-dicarbonyl compounds **1** we reported a regioselective hetero-Diels-Alder reaction [2] of **1** with alkyl vinyl ethers to give alkoxydihydropyrans **2** [3]. Dihydropyran derivatives were transformed into pyridine derivatives by treatment with ammonia [4] or hydroxylamine hydrochloride [5]. Our alkoxydihydropyrans **2** have both acetal and keto groups that are expected to react with hydroxylamine. Herein we report a novel synthesis of 4-cyanoethylisoxazoles **3** from the reaction of ethoxydihydropyrans **2** with 2 equivalents of hydroxylamine hydrochloride.

Chart 1



1 **A** **B** **2**

Dihydropyrans **2** were synthesized from the cycloaddition reaction of 2-methylene-1,3-dicarbonyl compounds **1** with ethyl vinyl ether. In the previous paper [3] we used only three 2-methylene-1,3-dicarbonyl compounds (R = Me, Ph, OEt) to prepare dihydropyrans. We examined various examples of **1**, which were obtained by the methylthiomethylation-oxidation-elimination sequence [6] of 1,3-dicarbonyl compounds [7], to prepare **2**. As shown in Table 1 regioselectivity of the cycloaddition was completely achieved in the dicarbonyl compounds **1** having smaller alkyl groups (entries a~c) and a strong electron-donating substituent (OCH_3) at the phenyl group (entry h). Increasing the balkiness of R (alkyl) led to decrease in the regioselectivities of the products. The ratio of the regioisomers were determined by the intensity of the anomeric protons in their ^1H nmr spectra. Since a pair of the regioisomers have almost equal Rf values, we could not separate each isomer completely. Fortunately, repeated column chromatography afforded pure isomers partially. Although a pair of the regioisomers were separated in the cases of **1d** and **1e**, only one isomer was isolated in the case of **1f**. The structure of each isomer was determined by the presence or absence of a benzoyl group (the phenyl proton *ortho* to the carbonyl group showed a considerably greater downfield shift than that *ortho* to the dihydropyran ring). When R was substituted phenyl groups, the products contained almost equal amounts of the two inseparable isomers except for **2i**. Only a small amount of one isomer **2Ai** was isolated by repeated column chromatography of the product of **1i**.

Dihydropyrans **2** were refluxed with 3 equivalents of hydroxylamine hydrochloride in absolute ethanol. The ir

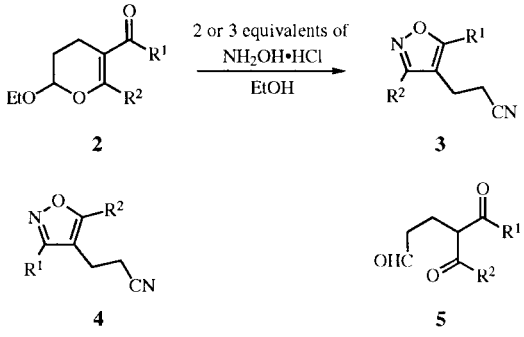
Table 1

Dihydropyrans **2**

Entry	R	Yield (%) [a]	**A**:**B** [b]
a [c]	CH_3	97	100:0
b	CH_3CH_2	79	100:0
c	$CH_3CH_2CH_2$	92	100:0
d	$(CH_3)_2CH$	86	64:36 [d]
e	$(CH_3)_3C$	83	62:38 [d]
f	$C_6H_5CH_2CH_2$	87	84:16 [e]
g [c]	C_6H_5	98	
h	4-CH_3O-C_6H_4	99	0:100
i	2-CH_3-C_6H_4	80	51:49 [f]
j	4-CH_3-C_6H_4	86	(50:50)
k	4-$(CH_3)_2CH$-C_6H_4	87	(53:47)
l	4-Br-C_6H_4	92	(50:50)

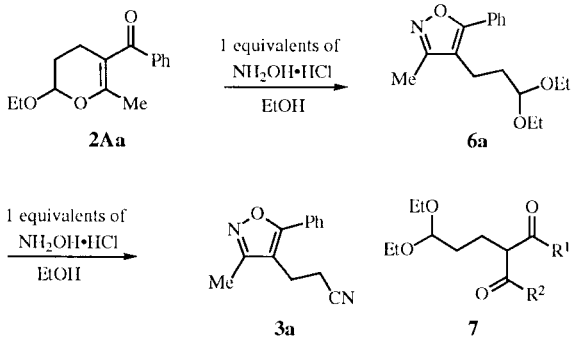
[a] Isolated yields. [b] Determined by ^1H nmr and the isomers in parentheses were not separated. [c] Reference [3]. [d] A pair of regioisomers were separated partially. [e] Only **2Af** was isolated. [f] Only a small amount of **2Ai** was isolated.

Chart 2



spectra of the products showed no absorptions due to the carbonyl and oxime groups but did show a nitrile group at *ca.* 2250 cm^{-1}. In the ^1H nmr spectrum of the product from (6-ethoxy-2-methyl-5,6-dihydro-4*H*-pyran-3-yl)phenylmethanone **2Aa** only a pair of triplets (δ 2.99 and 2.57) was observed except for the phenyl and methyl groups. All products showed the characteristic ethylene signals. Taking this into consideration with the elemental analyses, the products were shown to be trisubstituted isoxazoles **3** or **4**, having a cyanoethyl group at the 4 position. The reactions of dihydropyrans **2** with 2 equivalents of hydroxylamine hydrochloride afforded the same products **3** in almost the same yields. This suggests that hydroxylamine does not react with all three carbonyl groups in trione **5** which is regarded as an equivalent of the dihydropyran **2**.

Chart 3



When **2Aa** was treated with equimolar amounts of hydroxylamine hydrochloride an unstable product was obtained. The product **6a** 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 (multiplets at δ 1.69 and 2.70) in the ^1H nmr spectrum. Furthermore the diethyl acetal **6a** was converted to the same cyanoethylisoxazole **3a**, obtained from **2Aa** and 2 or 3 equivalents of hydroxylamine hydrochloride, with an additional 1 equivalent of hydroxylamine hydrochloride. From these results we conclude that first an isoxazole ring is formed by the reaction of **2Aa** with 1 equivalent of hydroxylamine and the conversion of the acetal group into a nitrile group is achieved with an additional 1 equivalent of hydroxylamine. Initial formation of diones **7** was also neglected, since isomeric dihydropyrans **2Ad** and **2Bd** 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 [8] shows that the product formed from the reaction of **2Aa** with 2 equivalents of hydroxylamine has structure **3a**, 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 2 position and alkyl or aryl groups of 3-acyl groups of dihydropyran could be transformed at the 3 and 5 positions of the isoxazole ring. Thus the reaction of **2Aa** with 1 equivalent of hydroxylamine gives an acetal **6a** and which afford 4-cyanoethyl-3-methyl-5-phenylisoxazole **3a** with an additional 1 equivalent of hydroxylamine. In the ^1H nmr spectrum of **3a**, the signal of the 5-phenyl group was split into two parts; downfield double doublet for two protons *ortho* to the isoxazole ring and an upfield multiplet for three remaining protons. The similar pattern in the aromatic proton field was observed in the ^1H nmr spectra of **3b-d**. The same treatment of **2Be** did not give the corresponding isoxazole derivative but an unidentified complex mixture. Furthermore the mixture of **2Ae** and **2Be** afforded **3f** only as an isoxazole isomer. When all inseparable dihydropyrans **2i-k** were treated similarly as for **2Aa**, the ratios of the starting materials were maintained the same as that of the inseparable regioisomeric isoxazle products. In Table 2 the results using pure **2** are shown.

The reaction mechanism of the regioselective isoxazole ring formation is somewhat complex. The most simple route is that of a Michael addition of the hydroxylamine to the 2 position of **2** followed by recyclization to form **3**. This is, however, unlikely because the reaction of 2-methylchromone [9], which has no acetal group, with hydroxylamine hydrochloride under the same reaction conditions as for **2** gave

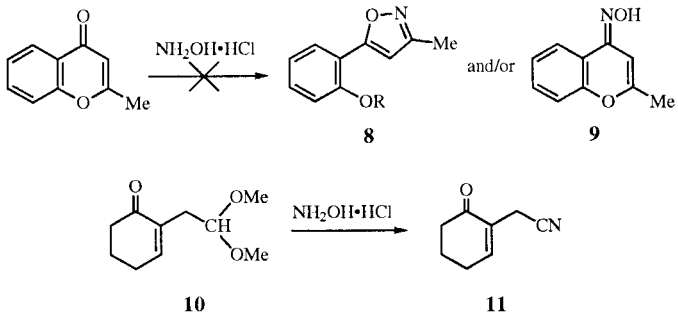
Table 2
4-Cyanoethylisoxazoles **3**

Entry	R^1	R^2	Yields (%) [a]
a	C_6H_5	CH_3	99
b	C_6H_5	CH_3CH_2	69
c	C_6H_5	$CH_3CH_2CH_2$	81
d	C_6H_5	$(CH_3)_2CH$	87
e	$(CH_3)_2CH$	C_6H_5	85
f	$(CH_3)_3C$	C_6H_5	88
g	C_6H_5	C_6H_4-CH_2CH_2	95
h	C_6H_5	C_6H_5	85
i	4-CH_3O-C_6H_4	C_6H_5	61
j	C_6H_5	2-CH_3-C_6H_4	69

[a] Isolated yield.

neither isoxazole derivative **8** nor the corresponding oxime **9**, but unreacted starting material. Furthermore the same treatment of 2-(2,2-dimethoxyethyl)cyclohex-2-en-1one **10**, which was prepared from 2-alkylcyclohex-2-en-1-one [10] *via* 2-(cyclohex-2-en-1-on-2-yl)acetaldehyde [11], gave 2-(cyclohex-2-en-1-on-2-yl)acetonitrile **11**. This suggests that the acetal group (6 position) in dihydropyrans **2** is more reactive than the carbonyl group toward hydroxylamine. We have reported a plausible mechanism for regio-selective isoxazole ring formation, in which hydrogen bonding played an important role [8]. This mechanism might also be doubtful in view of the fact that the hydrogen bonding is not so stable at such high temperature. Since the isoxazole formation reaction was not carried out at low temperature because of insolubility of hydroxylamine hydrochloride in ethanol, an attempt to capture the reaction intermediate has not been successful. Further investigations to clarify the reaction mechanism are now in progress.

Chart 4



EXPERIMENTAL

Melting points were measured on a Yanako micro melting point apparatus and are uncorrected. Extracts were dried over anhydrous magnesium sulfate. The ir spectra of solids (potassium bromide) and liquids (film) were recorded on a JASCO-IR-810 spectrophotometer. Mass spectra were observed on a JEOL JMS-DX300 instrument. The nmr spectra were obtained with JEOL JMN-EX 270 spectrometer in deuteriochloroform with tetramethylsilane as the internal reference. Column chromatography was carried out on silica gel, 100~200 mesh, Micro Bead 4B, Fuji-Davison Chemical LTD.

Dihydropyrans.

In addition to the compounds described in reference [3], the following compounds were synthesized and isolated.

(6-Ethoxy-2-ethyl-5,6-dihydro-4*H*-pyran-3-yl)phenylmethanone **2Ab**.

This compound was obtained as a viscous oil; ^{1}H nmr: δ 1.00 (3H, t, J = 7.5 Hz, CH_3), 1.28 (3H, t, J = 7.0 Hz, CH_3), 1.8-2.0 (2H, m, 5-H), 2.13 (2H, q, J = 7.5 Hz, CH_2), 2.25-2.5 (2H, m, 4H), 3.80 (2H, qABq, J = 9.5, 7.0 Hz, CH_2), 5.16 (1H, t, J = 3.1 Hz, 6-H), 7.3-7.5 (3H, m, ArH), 7.72 (2H, dd, J = 8.2, 1.2 Hz, ArH).

(6-Ethoxy-2-propyl-5,6-dihydro-4*H*-pyran-3-yl)phenylmethanone **2Ac**.

This compound was obtained as a viscous oil; ^{1}H nmr: δ 0.77 (3H, t, J = 7.5 Hz, CH_3), 1.28 (3H, t, J = 7.1 Hz, CH_3), 1.45-1.55 (2H, m, CH_2), 1.8~1.95 (2H, m, 3-H), 2.05-2.15 (2H, m, CH_2), 2.25-2.5 (2H, m, 5-H), 3.78 (2H, qABq, J = 9.5, 7.1 Hz, CH_2), 5.14 (1H, t, J = 3.1 Hz, 6-H), 7.3-7.6 (3H, m, ArH), 7.72 (2H, dd, J = 8.1, 1.5 Hz, ArH); ^{13}C nmr: δ 13.7, 15.3, 19.8, 20.8, 26.4, 34.7, 63.9, 97.3, 110.9, 128.3, 128.7, 131.9, 140.1, 159.4, 198.6.

Anal. Calcd. for $C_{17}H_{22}O$: C, 74.42; H, 8.08. Found: C, 74.35; H, 8.03.

(6-Ethoxy-2-isopropyl-5,6-dihydro-4*H*-pyran-3-yl)phenylmethanone **2Ad**.

This compound was obtained as a viscous oil; ^{1}H nmr: δ 1.01 (6H, d, J = 7.0 Hz, CH_3), 1.29 (3H, t, J = 7.0 Hz, CH_3), 1.8~2.0 (2H, m, 5-H), 2.2~2.4 (2H, m, 4-H), 2.62 (1H, heptet, CH), 3.75 (2H, qABq, J = 9.5, 7.0 Hz, CH_2), 5.16 (1H, t, J = 3.0 Hz, 6-H), 7.3-7.6 (3H, m, ArH), 7.76 (2H, br d, J = 8.0 Hz, ArH).

(6-Ethoxy-2-phenyl-5,6-dihydro-4*H*-pyran-3-yl)-2-methylpropan-1-one **2Bd**.

This compound was obtained as a viscous oil; ^{1}H nmr: δ 0.87 (3H, t, J = 6.6 Hz, CH_3), 0.97 (3H, d, J = 7.0 Hz, CH_3), 1.8-2.0 (2H, m, 5-H), 2.46 (1H, heptet, CH), 2.4-2.6 (2H, m, 4-H), 3.85 (2H, qABq, J = 9.5, 6.6 Hz, CH_2), 5.26 (1H, t, J = 2.8 Hz, 6-H), 7.3-7.6 (5H, m, ArH).

(6-Ethoxy-2-*tert*-butyl-5,6-dihydro-4*H*-pyran-3-yl)phenylmethanone **2Ae**.

This compound was obtained as a viscous oil; ^{1}H nmr: δ 1.07 (9H, s, CH_3), 1.31 (3H, t, J = 7.0 Hz, CH_3), 1.85-1.9 (2H, m, 5H), 3.4~3.6 (2H, m, 4-H), 3.87 (2H, qABq, J = 9.5, 7.0 Hz, CH_2), 5.11 (1H, t, J = 3.1 Hz, 6-H), 7.4-7.6 (3H, m, ArH), 7.97 (2H, br d, J = 7.0 Hz, ArH).

(6-Ethoxy-2-phenyl-5,6-dihydro-4*H*-pyran-3-yl)-2,2-dimethylpropan-1-one **2Be**.

This compound was obtained as a viscous oil; ^{1}H nmr: δ 0.90 (9H, s, CH_3), 1.30 (3H, t, J = 7.0 Hz, CH_3), 1.85-1.9 (2H, m, 5-H), 3.45-3.6 (2H, m, 4-H), 3.87 (2H, qABq, J = 9.5, 7.0 Hz, CH_2), 5.25 (1H, t, J = 3.0 Hz, 6-H), 7.2-7.4 (5H, m, ArH).

(6-Ethoxy-2-phenethyl-5,6-dihydro-4*H*-pyran-3-yl)phenylmethanone **2Af**.

This compound was obtained as a viscous oil; ^{1}H nmr: δ 1.26 (3H, t, J = 7.0 Hz, CH_3), 1.8-1.95 (2H, m, 5-H), 2.3-2.55 (2H, m, 4-H), 2.54 (2H, t, J = 7.5 Hz, CH_2), 2.71 (2H, t, J = 7.5 Hz, CH_2), 3.80 (2H, qABq, J = 9.5, 7.0 Hz, CH_2), 5.16 (1H, t, J = 3.1 Hz, 6-H), 7.0-7.6 (8H, m, ArH), 7.60 (2H, dd, J = 8.0, 1.2 Hz, ArH).

(6-Ethoxy-2-phenyl-5,6-dihydro-4*H*-pyran-3-yl)(4-methoxyphenyl)methanone **2Bh**.

This compound was obtained as a viscous oil; ^{1}H nmr: δ 1.36 (3H, t, J = 7.0 Hz, CH_3), 2.0-2.05 (2H, m, 5-H), 2.55-2.65 (2H, m, 4-H), 3.73 (3H, s, CH_3), 3.98 (2H, qABq, J = 9.5, 7.0 Hz, CH_2), 5.37 (1H, t, J = 3.1 Hz, 6-H), 6.63 (2H, d, J = 9.8 Hz, ArH), 7.0-7.3 (5H, m, ArH), 7.61 (2H, d, J = 9.8 Hz, ArH); ^{13}C nmr: δ 15.4, 20.4, 26.3, 55.2, 64.2, 97.8, 113.8, 127.7, 128.8, 129.0, 130.6, 131.3, 131.6, 135.7, 153.5, 162.6, 197.7.

(6-Ethoxy-2-phenyl-5,6-dihydro-4*H*-pyran-3-yl)(2-methylphenyl)methanone **2Ai**.

This compound was obtained as a viscous oil; ^{1}H nmr: δ 1.34 (3H, t, J = 7.1 Hz, CH_3), 1.9-2.2 (2H, m, 5-H), 2.34 (3H, s, CH_3), 2.6-2.9 (2H, m, 4-H), 3.91 (2H, qABq, J = 9.5, 7.0 Hz, CH_2), 5.34 (1H, t, J = 3.0 Hz, 6-H), 6.8-7.2 (8H, m, ArH), 7.44 (2H, br d, J = 8.1 Hz, ArH).

Reaction of 3,4-Dihydropyrans with Hydroxylamine Hydrochloride.

General Procedure.

A mixture of dihydropyran **2** (1 mmole) and hydroxylamine hydrochloride (139 mg, 2 mmoles) in absolute ethanol (15 ml) was refluxed for 5 hours. The solvent was evaporated *in vacuo* and water (20 ml) was added to the residue. The organic phase was separated and extracted with ether. The ether layer was washed with brine, dried and evaporated. The resulting residue was subjected to column chromatography to give the products. The same results were almost obtained by using 209 mg (3 mmoles) of hydroxylamine hydrochloride.

3-(3-Methyl-5-phenylisoxazol-4-yl)propionitrile **3a**.

This compound was obtained as colorless needles mp 99-100° (from benzene-hexane); ^{1}H nmr: δ 2.37 (3H, s, CH_3), 2.57 (2H, t, J = 7.5 Hz, CH_2), 2.99 (2H, t, J = 7.5 Hz, CH_2), 7.45-7.55 (3H, m, ArH), 7.65 (2H, dd, J = 8.1, 2.0 Hz, ArH); ^{13}C nmr: δ 10.3, 17.5, 19.3, 110.5, 118.4, 126.8, 128.9, 129.2, 130.2, 160.1, 166.0.

Anal. Calcd. for $C_{13}H_{12}ON_2$: C, 73.57; H, 5.70; N, 13.20. Found: C, 73.45; H, 5.74; N, 13.22.

3-(3-Ethyl-5-phenylisoxazol-4-yl)propionitrile **3b**.

This compound was obtained as a viscous oil; ^{1}H nmr: δ 1.39 (3H, t, J = 7.5 Hz, CH_3), 2.55 (2H, t, J = 7.5 Hz, CH_2), 2.74 (2H, q, J = 7.5 Hz, CH_2), 2.99 (2H, t, J = 7.5 Hz, CH_2), 7.4-7.5 (3H, m, ArH), 7.65 (2H, dd, J = 7.7, 1.8 Hz, ArH).

Anal. Calcd. for $C_{14}H_{14}ON_2$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.13; H, 6.35; N, 12.21.

3-(3-Propyl-5-phenylisoxazol-4-yl)propionitrile **3c**.

This compound was obtained as a viscous oil; ^{1}H nmr: δ 1.07 (3H, t, J = 7.3 Hz, CH_3), 1.7-1.9 (2H, m, CH_2), 2.54 (2H, t, J = 7.7 Hz, CH_2), 2.68 (2H, t, J = 7.7 Hz, CH_2), 2.99 (2H, t, J = 7.7 Hz, CH_2), 7.4-7.5 (3H, m, ArH), 7.65 (2H, dd, J = 8.1, 1.9 Hz, ArH); ^{13}C nmr: δ 14.0, 17.5, 19.2, 21.1, 27.1, 110.2, 118.5, 126.8, 128.8, 129.2, 130.1, 163.5, 166.0.

Anal. Calcd. for $C_{15}H_{16}ON_2$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.70; H, 6.78; N, 11.47.

3-(3-Isopropyl-5-phenylisoxazol-4-yl)propionitrile **3d**.

This compound was obtained as a viscous oil; ^{1}H nmr: δ 1.41 (6H, d, J = 7.0 Hz, CH_3), 2.54 (2H, t, J = 7.7 Hz, CH_2), 3.00 (2H, t, J = 7.7 Hz, CH_2), 3.02 (1H, m, CH), 7.2-7.5 (3H, m, ArH), 7.65 (2H, dd J = 7.5, 1.7 Hz, ArH).

Anal. Calcd. for $C_{15}H_{16}ON_2$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.91; H, 6.78; N, 11.55.

3-(5-Isopropyl-3-phenylisoxazol-4-yl)propionitrile **3e**.

This compound was obtained as a viscous oil; ^{1}H nmr: δ 1.41 (6H, d, J = 7.0 Hz, CH_3), 2.33 (2H, t, J = 7.3 Hz, CH_2), 2.88 (2H, t, J = 7.3 Hz, CH_2), 3.70 (1H, m, CH), 7.4-7.6 (5H, m, ArH).

Anal. Calcd. for $C_{15}H_{16}ON_2$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.92; H, 6.81; N, 11.29.

3-(5-*tert*-Butyl-3-phenylisoxazol-4-yl)propionitrile **3f**.

This compound was obtained as colorless needles, mp 72-73° (from benzene-hexane), ^{1}H nmr: δ 1.48 (9H, s, CH_3), 2.26 (2H, t, J = 7.7 Hz, CH_2), 3.01 (2H, t, J = 7.7 Hz, CH_2), 7.49 (5H, br s, ArH); ^{13}C nmr: δ 17.6, 19.4, 29.4, 35.1, 108.3, 118.3, 128.2, 128.8, 129.1, 129.7, 163.1, 176.1.

Anal. Calcd. for $C_{16}H_{18}ON_2$: C, 75.56; H, 7.13; N, 11.01. Found: C, 75.85; H, 7.28; N, 11.00.

3-(3-Phenethyl-5-phenylisoxazol-4-yl)propionitrile **3g**.

This compound was obtained as a viscous oil; ^{1}H nmr: δ 2.29 (2H, t, J = 7.5 Hz, CH_2), 2.78 (2H, t, J = 7.5 Hz, CH_2), 2.97 (2H, m, CH_2), 3.07 (2H, m, CH_2), 7.2-7.5 (8H, m, ArH), 7.62 (2H, dd, J = 8.0, 1.5 Hz, ArH).

Anal. Calcd. for $C_{20}H_{18}ON_2$: C, 79.44; H, 6.00; N, 9.26. Found: C, 79.13; H, 6.26; N, 8.89.

3-(3-Phenyl-5-phenylisoxazol-4-yl)propionitrile **3h**.

This compound was obtained as colorless needles, mp 95-96° (from benzene-hexane); ^{1}H nmr: δ 2.38 (2H, t, J = 7.5 Hz, CH_2), 3.14 (2H, t, J = 7.5 Hz, CH_2), 7.5-7.65 (3H, m, ArH), 7.71 (2H, dd, J = 7.5, 1.7 Hz, ArH); ^{13}C nmr: δ 17.0, 19.5, 110.1, 118.3, 127.3, 127.6, 128.2, 128.9, 129.2, 129.3, 130.0, 130.5, 163.2, 167.3.

Anal. Calcd. for $C_{18}H_{14}ON_2$: C, 78.81; H, 5.14; N, 10.21. Found: C, 79.10; H, 5.18; N, 10.00.

3-[3-(4-Methoxyphenyl)-5-phenylisoxazol-4-yl]propionitrile **3i**.

This compound was obtained as colorless needles, mp 91-92° (from benzene-hexane); ^{1}H nmr: δ 2.37 (2H, t, J = 7.5 Hz, CH_2), 3.12 (2H, t, J = 7.5 Hz, CH_2), 3.89 (3H, s, OCH_3), 7.04 (2H, d, J = 8.5 Hz, ArH), 7.5-7.7 (5H, m, ArH), 7.65 (2H, d, J = 7.5 Hz, ArH); ^{13}C nmr: δ 17.0, 19.5, 55.4, 109.0, 114.7, 118.4, 128.2, 128.8, 129.0, 129.1, 129.2, 129.5, 129.9 163.1, 167.4.

Anal. Calcd. for $C_{19}H_{16}O_2N_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.78; H, 5.49; N, 9.12.

3-[3-(2-Methylphenyl)-5-phenylisoxazol-4-yl]propionitrile **3j**.

This compound was obtained as colorless needles, mp 85-86° (from benzene-hexane); ^{1}H nmr: δ 2.26 (2H, t, J = 7.7 Hz, CH_2), 2.36 (3H, s, CH_3), 2.93 (2H, t, J = 7.7 Hz, CH_2), 7.3-7.6 (7H, m, ArH), 7.67 (2H, dd, J = 6.5, 1.5 Hz, ArH).

Anal. Calcd. for $C_{19}H_{16}ON_2$: C, 79.14; H, 5.59; N, 9.71. Found: C, 78.96; H, 5.52; N, 9.58.

Reaction of 5-Benzoyl-2-ethoxy-6-methyl-3,4-dihydro-2*H*-pyran **2** with 1 Equivalent of Hydroxylamine Hydrochloride.

A mixture of **2Aa** (246 mg, 1 mmole) and hydroxylamine hydrochloride (70 mg, 1 mmole) in absolute ethanol (8 ml) was refluxed for 5 hours. The solvent was evaporated *in vacuo* and water was added to the residue. The organic layer separated was extracted with ether. The ether layer was washed with brine, dried and evaporated. The resulting residue was subjected to column chromatography to yield an oily 4-(3,3-diethoxypropyl)-3-methyl-5-phenylisoxazole **6a** (212 mg, 76%); ^{1}H nmr: δ 1.20 (6H, t, J = 6.9 Hz, CH_3), 1.8-1.9 (2H, m, CH_2), 2.31 (3H, s, CH_3), 2.68 (2H, t, J = 7.9 Hz, CH_2), 3.49 (4H, qABq, J = 9.5, 6.9 Hz, CH_2), 4.47 (1H, t, J = 5.4 Hz, CH), 7.4-7.5 (3H, m, ArH), 7.72 (2H, dd, J = 8.3, 1.3 Hz, ArH); ^{13}C nmr: δ 10.3, 15.2, 15.3, 17.8, 33.4, 61.3, 61.6, 102.1, 113.5, 126.7, 128.6, 128.8, 129.4, 160.7, 164.5.

Anal. Calcd. for $C_{17}H_{23}O_3N$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.35; H, 8.12; N, 4.71.

Reaction of 4-(3,3-Diethoxypropyl)-3-methyl-5-phenylisoxazole **6a** with 1 Equivalent of Hydroxylamine Hydrochloride.

Compound **6a** (120 mg, 0.42 mmole) was treated with hydroxylamine hydrochloride (30 mg, 0.43 mmole) as the same way as for **2Aa** to afford **3a** (77 mg, 88%).

Reaction of 2-(2,2-Dimethoxyethyl)cyclohex-2-en-1-one **10** with 1 Equivalent of Hydroxylamine Hydrochloride.

A mixture of **10** (622 mg) and hydroxylamine hydrochloride (235 mg) in ethanol (15 ml) was refluxed for 5 hours and worked up in the usual manner. The resulting residue was subjected to column chromatography and preparative tlc to give an oily 2-(cyclohex-2-en-1-on-2-yl)acetaldehyde **11** (72 mg, 16%); ^{1}H nmr: δ 2.05 (2H, quintet, J = 6.5 Hz, 5-H), 2.45-2.53 (4H, m, 4-H and 6-H), 3.32 (2H, br s, CH_2), 7.20 (1H, t, J = 4.2 Hz, 3-H); ir (neat): ν 2250, 1675; ms: m/z 135 (M^+, 77), 107 (100), 94 (19), 79 (66), 55 (22), 52 (45).

Anal. Calcd. for C_8H_9ON: C, 71.09; H, 6.71; N, 11.84. Found: C, 71.25; H, 6.83; N, 11.72.

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