Synthesis of 3-Ethoxyisoxazole Derivatives and 3-Ethoxy-1*H*-pyrazole Derivatives from β-Oxo Thionoesters

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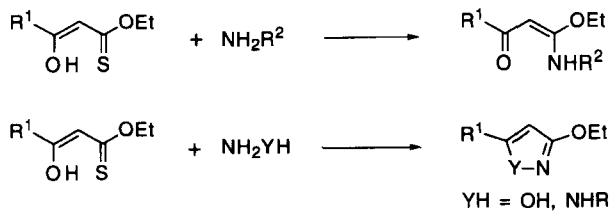
3-Ethoxyisoxazoles and 3-ethoxy-1*H*-pyrazoles were obtained in high yields from β-oxo thionoesters. The reaction of the ethyl β-oxo thionoesters with hydroxylamine hydrochloride in the presence of triethylamine at room temperature for 2 h gave the ethyl 3-oxopropiohydroximates and their hemiacetals, which were easily converted to the 3-ethoxyisoxazoles by refluxing for 3 h at pH 3—5. On the other hand, the reaction of the ethyl β-oxo thionoesters with hydrazine derivatives in the presence of triethylamine for 3—8 h at room temperature directly yielded the 3-ethoxy-1*H*-pyrazoles.

Ibotenic acid is a naturally occurring excitatory amino acid, and its derivatives have been discussed as potential bioisosteres of the excitatory amino acid antagonist.[1] They have usually been prepared from 3-isoxazolols.[1,2] 3-Isoxazolols mainly obtained from the reaction of β-oxo esters,[3] ketene,[3] or 2-alkynoate esters[4] with hydroxylamine have been converted to the 3-ethoxyisozaxoles in order to protect the hydroxy group in the synthetic pathway to the ibotenic acid derivatives, but this protection often gave a mixture of *N*-protected and *O*-protected products.

We have already reported that the ethyl β-oxo thionoesters **1** react with amines in the presence of triethylamine affording α-oxo ketene *O*,*N*-acetals under mild conditions (Scheme 1).[5] In this reaction, the ethoxy group in the substrate is preserved to the products. Therefore, if bifunctional amines are allowed to react with β-oxo thionoesters, bifunctional **1** could be converted to ethoxy-substituted heterocycles (Scheme 1).

There have been no examples of the direct preparation of 3-alkoxyisoxazole from linear starting materials. On the other hand, 3-ethoxy-5-phenyl-1*H*-pyrazole has been reported to be prepared by the reaction of ethyl 3-oxopropanethioate and hydrazine.[6] This reaction encouraged us to study the reaction of β-oxo thionoesters and bifunctional amines, and we found that hydroxylamine reacted with the β-oxo thionoesters **1** to give the 3-ethoxyisoxazole derivatives via oximes. We describe the details of this reaction and the reaction of the β-oxo thionoesters with the hydrazines.



Scheme 1.

Experimental

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra were measured on a JEOL JNM A-400 (400 MHz) spectrometer using tetramethylsilane as the internal standard. IR spectra were measured on a Shimadzu IR-408 spectrometer. Mass spectral (GC-MS) data were recorded on a Shimadzu GP2000A instrument and high-resolution mass spectra (FAB+) were measured on a JEOL M-700 using *m*-nitrobenzyl alcohol as an matrix. Elemental analyses were performed at the Microanalytical Center of Kyoto University. Melting points were measured on a Yanako Model MP and were not corrected.

All solvents were dried by standard methods.[7] Commercially available compounds were used without purification. The β-oxo thionoesters (**1**) were prepared according to a literature method.[5]

Preparation of 3-Ethoxy-5-hydroxy-5-methyl-4,5-dihydroisoxazole and Ethyl 3-Oxobutyrohydroximate (3a). In a 25-mL flask were placed ethyl 3-oxobutanethioate (0.292 g, 2.0 mmol), hydroxylamine hydrochloride (0.139 g, 2.0 mmol), triethylamine (0.404 g, 4.0 mmol), and acetonitrile (10 mL). The mixture was stirred for 2 h at room temperature. The resulting mixture was concentrated, subjected to column chromatography (silica gel 60, ethyl acetate), and then recrystallized to give a white solid. 3-Ethoxy-5-hydroxy-5-methyl-4,5-dihydroisoxazole and ethyl 3-oxobutyrohydroximate (**3a**): 197 mg, 1.36 mmol, 68% yield; the ratio of two isomers = 22 : 1 (^{1}H NMR); ^{1}H NMR ($CDCl_3$) major isomer (3-ethoxy-5-hydroxy-5-methyl-4,5-dihydroisoxazole): δ = 1.35 (3H, t, J = 7.4 Hz, CH_2CH_3), 1.68 (3H, s, C(=O)CH_3), 2.87 (1H, d, J = 16.4 Hz, C(=O)C*H*H), 3.01 (1H, d, J = 16.4 Hz, C(=O)-CH*H*), 3.42 (1H, s, O*H*), 4.14—4.26 (2H, m, CH_2CH_3); minor isomer (ethyl 3-oxobutyrohydroximate): δ = 1.30 (3H, t, J = 7.0 Hz, CH_2CH_3), 2.23 (3H, s, C(=O)CH_3), 3.50 (2H, s, C(=O)CH_2), 4.05 (2H, q, J = 7.0 Hz, CH_2CH_3), 6.74 (1H, s, O*H*); IR (KBr) 1612 cm^{-1} ($\nu_{C=N}$); MS *m/z* 145.

Preparation of 3-Ethoxy-5-hydroxy-5-phenyl-4,5-dihydroisoxazole and Ethyl 2-Benzoylacetohydroximate (3b). Same procedure as described for **3a**. 3-Ethoxy-5-hydroxy-5-phenyl-4,5-dihydroisoxazole and ethyl 2-benzoylacetohydroximate (**3b**):

340 mg, 1.64 mmol, 82% yield; the ratio of two isomers = 9 : 8 (^{1}H NMR); ^{1}H NMR ($CDCl_3$) major isomer (3-ethoxy-5-hydroxy-5-phenyl-4,5-dihydroisoxazole): δ = 1.38 (3H, t, J = 7.2 Hz, CH_2CH_3), 3.16 (1H, d, J = 16.8 Hz, C(=O)CHH), 3.22 (1H, d, J = 16.8 Hz, C(=O)CHH), 3.47 (1H, s, OH), 4.22—4.31 (2H, m, CH_2CH_3), 7.36—7.99 (5H, m, Ar); minor isomer (ethyl 2-benzoylacetohydroximate): δ = 1.25 (3H, t, J = 7.0 Hz, CH_2CH_3), 4.05 (2H, q, J = 7.0 Hz, CH_2CH_3), 4.07 (2H, s, C(=O)CH_2), 6.61 (1H, s, OH), 7.36—7.99 (5H, m, Ar); IR (KBr) 1617 cm^{-1} ($\nu_{C=N}$); MS *m/z* 207.

Preparation of 3-Ethoxy-5-methylisoxazole (4a). To a 25-mL flask were added above product mixture **3a**, (73 mg, 0.50 mmol), methanol (5.0 mL), and distilled H_2O (5.0 mL). After the acidity of the solution was adjusted with acetic acid to pH 3—5, the solution was heated at reflux for 3 h. The solvent was removed by an evaporator, and the resulting materials were purified by column chromatography to give product **4a** as a colorless liquid (60 mg, 0.47 mmol, 94% yield). The product was identified by a comparison of their ^{1}H NMR with those in the literature.[1]

Preparation of 3-Ethoxy-5-phenylisoxazole (4b). The same procedure for the preparation of **4a** was used. Product **4b** was obtained as a white solid (77 mg, 0.41 mmol, 81% yield); mp 34.0—35.5 °C (lit,[8] mp 35 °C, lit,[9] mp 38—40 °C). ^{1}H NMR ($CDCl_3$) δ = 1.44 (3H, t, J = 7.2 Hz, CH_2CH_3), 4.35 (2H, q, J = 7.2 Hz, CH_2CH_3), 6.12 (1H, s, CH), 7.26—7.47 (3H, m, Ar), 7.70—7.73 (2H, m, Ar).

Preparation of 3-Ethoxy-5-methyl-1*H*-pyrazole (6a). In a 25-mL flask, a mixture of ethyl 3-oxobutanethioate (0.292 g, 2.0 mmol), hydrazine hydrate (0.101 g, 2.0 mmol), triethylamine (0.404 g, 4.0 mmol), and acetonitrile (10 mL) was stirred at room temperature for 3 h. After removal of the solvent, the residue was purified by column chromatography and recrystallization to give the product as a pale-yellow solid. **6a**: 156 mg, 1.24 mmol, 62% yield; mp 67.0—68.2 °C. Analytical data are shown in Table 1. Elemental analysis: Calcd for $C_6H_{10}N_2O$: C, 57.12; H, 7.99; N, 22.21%. Found: C, 56.86; H, 8.10; N, 22.25%.

Preparation of 5-*t*-Butyl-3-ethoxy-1*H*-pyrazole (6b). The same procedure as in the preparation of **6a** was applied. **6b**: 273 mg, 1.62 mmol, 81% yield; mp 126.0—126.4 °C. The analytical data are given in Table 1. Elemental analysis, Calcd for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65%. Found: C, 64.39; H, 9.37; N, 16.78%.

Preparation of 3-Ethoxy-5-phenyl-1*H*-pyrazole (6c). The same procedure as in the preparation of **6a** was applied. **6c**: 373 mg, 1.98 mmol, 99% yield; mp 126.1—128.0 °C (lit,[6] mp 124.5—125.5 °C). The analytical data are given in Table 1.

Preparation of 3-Ethoxy-1,5-dimethyl-1*H*-pyrazole (6d). The same procedure as in the preparation of **6a** was applied, and the reaction time was 8 h. **6d**: 191 mg, 1.36 mmol, 68% yield; Pale yellow oil. The analytical data are given in Table 1. HRMS (FAB) Calcd for $C_7H_{13}N_2O$: (M^+ + H), 141.1027. Found: *m/z* 141.1035.

Preparation of 5-*t*-Butyl-3-ethoxy-1-methyl-1*H*-pyrazole (6e). The same procedure as in the preparation of **6a** was applied, and the reaction time was 8 h. **6e**: 266 mg, 1.46 mmol, 73% yield; Pale yellow oil. The analytical data are given in Table 1. HRMS (FAB), Calcd for $C_{10}H_{18}N_2O$: (M^+), 182.1418. Found: *m/z* 182.1390.

Preparation of 3-Ethoxy-1-methyl-5-phenyl-1*H*-pyrazole (6f). The same procedure as in the preparation of **6a** was applied, and the reaction time was 8 h. **6f**: 340 mg, 1.68 mmol, 84% yield; Pale yellow oil. The analytical data are given in Table 1. Elemental analysis, Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85%. Found: C, 71.02; H, 6.99; N, 13.99%.

Preparation of 3-Ethoxy-5-methyl-1-phenyl-1*H*-pyrazole (6g). The same procedure as in the preparation of **6a** was ap-

Table 1. Analytical Data of 3-Ethoxy-1*H*-pyrazole Derivatives

	IR (cm^{-1})	MS (*m/z*)	^{1}H NMR ($CDCl_3$) δ
6a	1493, 1575	126	1.38 (3H, t, J = 7.0 Hz, CH_2CH_3), 2.24 (3H, s, CH_3), 4.16 (2H, q, J = 6.8 Hz, CH_2CH_3), 5.47 (1H, s, –CH=)
6b	1498, 1568	168	1.29 (9H, s, $C(CH_3)_3$), 1.38 (3H, t, J = 7.0 Hz, CH_2CH_3), 4.18 (2H, q, J = 7.0 Hz, CH_2CH_3), 5.50 (1H, s, –CH=), 9.31 (1H, br, NH)
6c	1507, 1567	188	1.39 (3H, t, J = 7.2 Hz, CH_2CH_3), 4.22 (2H, q, J = 7.2 Hz, CH_2CH_3), 5.95 (1H, s, –CH=), 7.32—7.56 (5H, m, Ar), 10.19 (1H, br, NH)
6d	1485, 1550	140	1.38 (3H, t, J = 7.0 Hz, CH_2CH_3), 2.18 (3H, S, CCH_3), 3.61 (3H, S, NCH_3), 4.13 (2H, q, J = 7.0 Hz, CH_2CH_3), 5.41 (1H, s, –CH=)
6e	1465, 1540	182	1.33 (9H, S, $C(CH_3)_3$), 1.36 (3H, t, J = 7.0 Hz, CH_2CH_3), 3.80 (3H, S, NCH_3), 4.13 (2H, q, J = 7.0 Hz, CH_2CH_3), 5.43 (1H, s, –CH=)
6f	1505, 1542	202	1.41 (3H, t, J = 7.2 Hz, CH_2CH_3), 3.72 (3H, S, NCH_3), 4.21 (2H, q, J = 7.2 Hz, CH_2CH_3), 5.71 (1H, s, –CH=), 7.38—7.43 (5H, m, Ar)
6g	1495, 1500, 1555	202	1.40 (3H, t, J = 7.2 Hz, CH_2), 2.29 (3H, s, CH_3), 4.24 (2H, q, J = 7.2 Hz, CH_2CH_3), 5.65 (1H, s, –CH=), 7.27—7.43 (5H, m, Ar)
6h	1485, 1495, 1540	244	1.37 (3H, t, J = 7.2 Hz, CH_2), 1.41 (9H, S, $C(CH_3)_3$), 4.19 (2H, q, J = 7.2 Hz, CH_2CH_3), 5.63 (1H, s, –CH=), 7.36—7.44 (5H, m, Ar)
6i	1480, 1505, 1568	264	1.44 (3H, t, J = 7.2 Hz, CH_2), 4.31 (2H, q, J = 7.2 Hz, CH_2CH_3), 5.95 (1H, s, –CH=), 7.20—7.30 (10H, m, Ar)

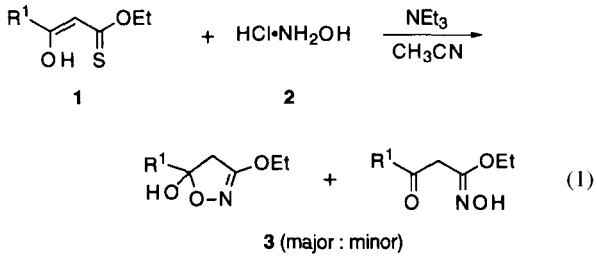
plied, and the reaction time was 8 h. **6g**: 238 mg, 1.18 mmol, 59% yield; mp 62.8—63.4 °C. The analytical data are given in Table 1. Elemental analysis, Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85%. Found: C, 71.36; H, 7.00; N, 13.84%.

Preparation of 5-*t*-Butyl-3-ethoxy-1-phenyl-1*H*-pyrazole (6h). The same procedure as in the preparation of **6a** was applied, and the reaction time was 8 h. **6h**: 342 mg, 1.40 mmol, 70% yield; mp 76.1—77.0 °C. The analytical data are given in Table 1. Elemental analysis, Calcd for $C_{15}H_{20}N_2O$: C, 73.74; H, 8.25; N, 11.47%. Found: C, 73.72; H, 8.39; N, 11.41%.

Preparation of 3-Ethoxy-1,5-diphenyl-1*H*-pyrazole (6i). The same procedure as in the preparation of **6a** was applied, and the reaction time was 8 h. **6i**: 460 mg, 1.74 mmol, 87% yield; Pale yellow oil. The analytical data are given in Table 1. HRMS (FAB), Calcd for $C_{17}H_{17}N_2O$: (M^+ + H), 265.1340. Found: *m/z* 265.1338.

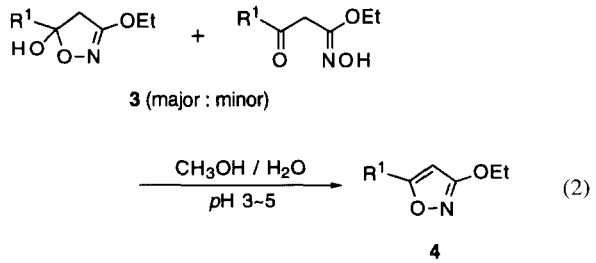
Results and Discussion

3-Ethoxyisoxazoles.



(1)

The reaction of **1** and primary amines has been previously reported by ourselves to give α-oxo ketene *O,N*-acetals in high yield. On the other hand, a mixture of two isomers was obtained from the reaction of **1** and **2** in the presence of triethylamine in acetonitrile at room temperature for 2 h (Eq. 1). These isomers could not be isolated by column chromatography, and the ratios of the two isomers from the reaction of **1a** and **1b** with **2** were 22 : 1 and 9 : 8, respectively. Their structures were identified as **3** (major: hemiacetals; minor: oximes) (Table 2). In the case of major isomers, methylene protons of the C2 carbon were shown as an AB qualtet pattern, which showed that the stereogenic carbon center was close. Furthermore, the major product **3a** does not have an acetyl group because the methyl signal appeared at 1.68 ppm, which is too high a field shift for the acetyl group in these kinds of compounds. On the other hand, the signals of minor products exhibited the singlet of methylene signals at 3.50 (for **3a**) and 4.07 (for **3b**) ppms and typical chemical shift for acetyl group at 2.33 ppm for **3a**. Similar intermediates were proposed for the reaction of enaminoketone with hydroxyamine.[10]



(2)

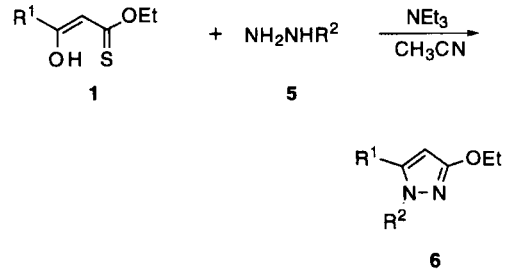
Table 2. Preparation of Oximes (**3**) and 3-Ethoxyisoxazoles (**4**)[a]

	β-Oxo thionoester **1**		Oxime **3**		Isoxazole **4**	
Entry		R^1		Yield[b]		Yield[c]
1	**1a**	CH_3	**3a**	68	**4a**	94
2	**1b**	C_6H_5	**3b**	82	**4b**	81

a) Reaction conditions: see experimental section. b) Isolated yield based on β-oxothiono ester **1**. c) Isolated yield based on oxime **3**.

These intermediate **3** was easily converted to 3-ethoxyisoxazole in high yield during reflux under acidic conditions (pH 3—5) using acetic acid (Eq. 2). The products were identified by a comparison with authentic data from the literature (see Experimental section).

3-Ethoxypyrazoles.



(3)

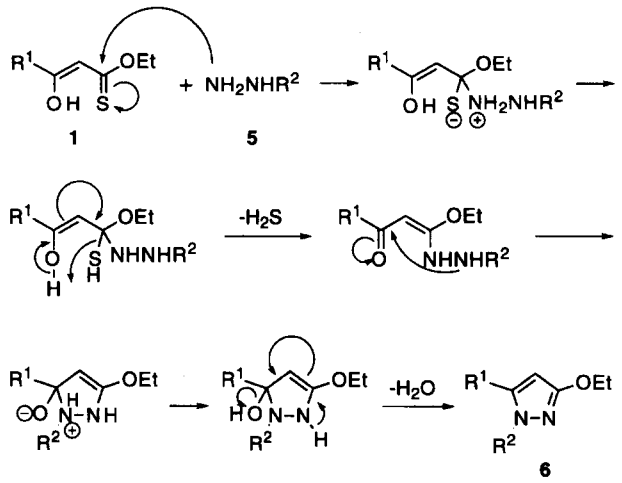
The β-oxo thionoesters **1** were easily converted to the 3-ethoxy-1*H*-pyrazole derivatives by a reaction with hydrazines at room temperature in the presence of triethylamine (Eq. 3). The reaction occurred by only mixing the substrates; also, the plausible intermediate, the enehydrazine or hydrazone derivatives, could not be isolated. This may be explained by the stronger nucleophilicity of the nitrogen atom of the enehydrazine or hydrazone intermediate compared to the oxygen atom of the oxime intermediate (Table 3). In the case of acylhydrazines, no cyclic product was formed at all.

Barnikow and Strickmann reported on the reaction of thiono ester derivatives and ethylenediamine or hydrazine in 1966.[6] Their report showed only one example of a similar

Table 3. Synthesis of 3-Ethoxypyrazoles (**6**) from β-Oxo Thionoesters with Hydrazines[a]

				Product	
Entry	R^1	R^2	Time/h		Yield[b]/%
1	Me	H	3	**6a**	62
2	*t*-Bu	H	3	**6b**	81
3	Ph	H	3	**6c**	99
4	Me	Me	8	**6d**	68
5	*t*-Bu	Me	8	**6e**	73
6	Ph	Me	8	**6f**	84
7	Me	Ph	8	**6g**	59
8	*t*-Bu	Ph	8	**6h**	70
9	Ph	Ph	8	**6i**	87

a) Reaction conditions: **1** (4.0 mmol), **2** (4.0 mmol), NEt_3 (8.0 mmol), CH_3CN (20 mL), room temperature. b) Isolated yield.



Scheme 2.

reaction of the β-oxothiono ester **1c** with hydrazine hydrate (**5**, R^2 = H) in ethanol; the yield of **6c** was 69%. In our reaction, the yield of **6c** reached 99%. In these reactions, hydrogen sulfide was formed; this acidic by-product tended to form a salt with the amine. Barnikow et al. have used an equimolar amount of the β-oxothiono ester **1c** with hydrazine hydrate (**5**, R^2 = H); therefore, hydrogen sulfide seemed to prevent a smooth reaction. On the other hand, adding triethylamine trapped the hydrogen sulfide in our system, and the reaction proceeded smoothly.

The reaction mechanism was considered to be as follows (Scheme 2). A nucleophilic attack of hydrazine at the thiocarbonyl carbon atom of **1** gave the ketene acetal (or hydrazone intermediates). A second nucleophillic attack by the nitrogen atom on the carbonyl carbon intramolecularly then occurred to yield the desired products.

β-Oxo esters were reported to be converted to 3-hydroxyheterocyclic compounds by their reaction with hydroxylamine or hydrazine. On the other hand, in the case of the β-oxo thionoesters, the ethoxy group in the substrate is preserved to the products described above. This is thought to be a result of the mercapto group being a better leaving group than the ethoxy moiety.

When using acylketene *X,Y*-acetals, pyrazole derivatives substituted at the 3-position with oxygen,[11,12] nitrogen,[9] or sulfur substituents[12–14] or isoxazole derivatives with an alkylthio-[14] or dialkylamino-substituent[15] on the heterocyclic ring were formed. These were also good methods for preparing pyrazoles and isoxazoles having heterofunctionalities; however, 3-ethoxyisoxazole as a versatile intermediate for the synthesis of ibotenic acid was not reported in these studies. Our starting materials, the β-oxo thionoesters, were conveniently prepared by the reaction of CS_2 and ketones in the presence of sodium amide, then with ethyl halide.

Conclusion. An easy method for the preparation of the 3-ethoxyisoxazole derivatives and 3-ethoxy-1*H*-pyrazole derivatives from β-oxo thionoesters was demonstrated. The starting β-oxo thionoesters can be easily obtained from CS_2, and the products are the protected forms of the 3-isoxazolols and 3-hydroxy-1*H*-pyrazoles, which are convenient for the next transformations.

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