Generation and Reactions of the Dianion of 3-Hydroxy-5-methylisoxazole, a Convenient β-Keto Amide Synthon. Total Synthesis of Muscimol

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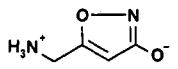
The title compound (4) has been prepared by treatment of diketene with *N,O*-bis(trimethylsilyl)hydroxylamine (2) to give *N*-(trimethylsiloxy)-*N*-(trimethylsilyl)acetoacetamide (3) as a stable liquid. Treatment of 3 with methanolic HCl removed the Me_3Si protective groups and cyclized the resulting hydroxamic acid to isoxazole 4 in good yield. The dianion of 4 was generated with lithium diisopropylamide and was found to react exclusively at the 5-methyl group when treated with electrophiles. The reactions of the dianion which were accomplished included carboxylation with CO_2, alkylation with benzyl chloride, condensation with benzophenone, and acylations with dimethyl carbonate, methyl acetate, *N,N*-dimethylacetamide, *N*-methoxy-*N*-methylacetamide, ethyl benzoate, and ethyl benzoylacetate. Hydrogenation of the condensation products (10, 11, 13, 14, and 15) using optimum conditions of the catalyst and solvent gave the corresponding β-keto amides (16, 17, 18, 19, and 20, respectively) in excellent yields. Treatment of the dianion with isoamyl nitrite gave 3-hydroxy-5-isoxazolecarboxaldehyde oxime (21) in good yield. Acetylation of 21 to the diacetate 22 followed by reduction with BH_3–THF gave muscimol (1), a constituent of the mushroom *Amanita muscaria*.

The chemistry of isoxazoles has been studied extensively, because of the many unique reactions that the heterocyclic ring undergoes and because a number of isoxazole derivatives have been found to be useful in agriculture and medicine.[1] Several isoxazoles have been found in nature,[2] the most notable being muscimol (1) produced by *Amanita*



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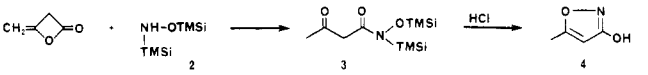
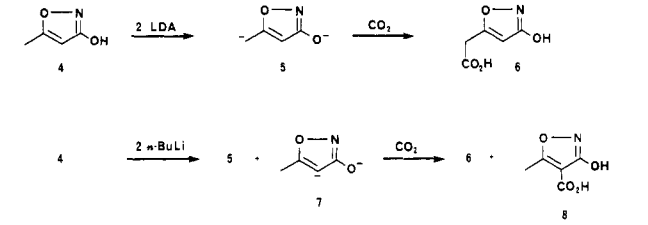
muscaria.[2d,e] This compound is an agonist of γ-aminobutyric acid and is responsible for the well-known hallucinogenic properties of this mushroom.[3]

In an examination of the chemistry of the isoxazole system, we were attracted to the possibility that the dianion of 3-hydroxy-5-methylisoxazole, if it could be formed, would react with electrophiles on the methyl group to give access not only to the resulting complex isoxazoles but also, by hydrogenolysis of the N–O bond, to the corresponding 4-substituted β-keto amides. The latter might be particularly useful; no method has yet been found for direct substitution at that position on acetoacetamide because the appropriate multiple anion is not accessible.[4]

Scheme I



Scheme II



The first problem which had to be faced with this project was the availability of 3-hydroxy-5-methylisoxazole. It cannot be prepared by direct condensation of hydroxylamine with acetoacetic esters[2d,5] or with diketene[6] because the reactions give the isomeric 3-methyl-5-isoxazolone, but it has been synthesized by processes employing condensations of hydroxylamine with methyl tetrolate and with the ethylene ketal of methyl acetoacetate.[7,8] The compound has attracted considerable attention as a fungicidal and plant growth-promoting agent.[7] We have developed yet another route, one that involves condensation of the *N,O*-bis(trimethylsilyl) derivative of hydroxylamine with diketene (Scheme I). The bis(silylated) hydroxylamine (2) is readily prepared by treatment of hydroxylamine with 1,1,1,3,3,3-hexamethyldisilazane.[9] The condensation with diketene was exothermic and was carried out at ambient temperature with external cooling. The resulting *N,O*-bis(trimethylsilyl) derivative of acetoacetylhydroxamic acid (3) was deprotected and cyclized to give isoxazole 4 in an

(1) (a) Wakefield, B. J.; Wright, D. J. In "Advances in Heterocyclic Chemistry"; Katritzky, A. R.; Boulton, A. J., Eds.; Academic Press: New York, 1979; Vol. 25, p 147. (b) Kochetkov, N. K.; Sokolov, S. D. In "Advances in Heterocyclic Chemistry"; Katritzky, A. R., Boulton, A. J., Lagowski, J. M., Eds.; Academic Press: New York, 1963; Vol. 2, p 365. (c) Quilico, A.; Speroni, G. In "Five- and Six-Membered Compounds with Nitrogen and Oxygen"; Wiley, R. H., Ed.; Wiley (Interscience): New York, 1962; Part I. (d) Barnes, R. P. In "Heterocyclic Compounds"; Elderfield, R. C., Ed.; Wiley: New York, 1952; Vol. 5, Chapter 7. (e) Barber, G. N.; Olofson, R. A. *J. Org. Chem.* **1978**, *43*, 3015.

(2) (a) Trumferol (seed germination inhibitor): Kusumi, T.; Chang, C. C.; Wheeler, M.; Kubo, I.; Nakanishi, K.; Naoki, H. *Tetrahedron Lett.* **1981**, 3451. (b) Antitumor agent AT-135 (U-42,126): Martin, D. G.; Duchamp, D. J.; Chidester, C. G. *Tetrahedron Lett.* **1973**, 2549. (c) Cycloserine (antituberculosis antibiotic): Kuehl, F. A., Jr.; Wolf, F. J.; Trenner, N. R.; Peck, N. R.; Buhs, R. H.; Putter, I.; Ormond, R.; Lyons, J. E.; Chaiet, L.; Howe, E.; Hunnewell, B. D.; Downing, G.; Newstead, E.; Folkers, K. *J. Am. Chem. Soc.* **1955**, *77*, 2344. (d) Muscimol (GABA agonist): Bowden, K.; Crank, G.; Ross, W. J. *J. Chem. Soc. C* **1968**, 172. (e) Syntheses: Jager, V.; Frey, M. *Liebigs Ann. Chem.* **1982**, 817 and references cited therein. (f) Ibotenic acid (CNS activity): Eugster, C. H.; Muller, G. F. R.; Good, R. *Tetrahedron Lett.* **1965**, 1813.

(3) (a) Lincoff, G.; Mitchel, D. H. In "Toxic and Hallucinogenic Mushroom Poisoning"; Williams, W. K., Ed.; Van Nostrand Reinhold Company: New York, 1977; p 77–99. (b) Krogsgaard-Larsen, P.; Brehm, L.; Schaumburg, K. *Acta Chem. Scand., Ser. B* **1981**, *35*, 311.

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(5) Schulz, H.; Wakil, S. J. *Anal. Biochem.* **1970**, *37*, 457.

(6) (a) Kato, T.; Katagiri, N.; Minami, N. *Chem. Pharm. Bull.* **1972**, *20*, 1368. (b) Fujimoto, M.; Sakai, M. *Chem. Pharm. Bull.* **1965**, *13*, 248; *Chem. Abstr.* **1974**, *80*, 108121f.

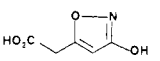
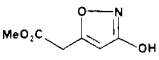
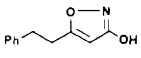
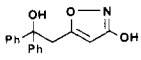
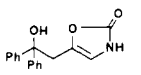
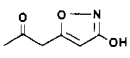
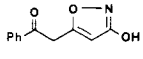
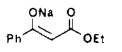
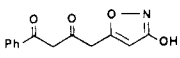
(7) The compound has been investigated in Japan by Sankyo Co., Ltd, which has given it the trade name Tachigaren, but the compound is not commerically available in the U.S. See: (a) Masago, H.; Yoshikawa, M.; Fukada, M.; Nakanishi, N. *Phytopathology* **1977**, *67*, 425. (b) Taso, P. H.; Guy, S. O. *Phytopathology* **1977**, *67*, 796. (c) Nakamura, T.; Yamaoka, K.; Kotakemori, M. In "Analytical Methods for Pesticides and Plant Growth Regulators"; Zweig, G.; Sherma, J., Eds.; Academic Press: New York, 1978; Vol. 10, p 215.

(8) (a) Jacquier, R.; Petrus, C.; Petrus, F.; Verducci, J. *Bull. Soc. Chim. Fr.* **1970**, *5*, 1978. (b) Tomita, K. (Sankyo Co. Ltd.) Japanese Patent 7 038 327, Dec. 4, 1970; *Chem. Abstr.* **1971**, *74*, 87946n.

(9) West, R.; Boudjouk, P. *J. Am. Chem. Soc.* **1973**, *95*, 3987. The compound is also available from Fluka Chemical Corp. (Tridom Chemical, Inc.)

0022-3263/83/1948-4307$01.50/0

Table I. Reactions of Dianion 5 with Electrophiles

electrophile	ratio electrophile:5	conditions	product	yield, %
CO_2	excess CO_2	−78 °C → room temp. 4 h	 6	51
$MeOCO_2Me$	1:2	−78 °C → room temp. 4 h	 9	24
$PhCH_2Cl$	3:1	−78 °C → room temp. 2 h	 10	72
PhCOPh	1:1	−78 °C 2 h	 11	53
			 12	15
CH_3CO_2Me	1:2	0 °C → room temp. 40 min	 13	35
CH_3CONMe_2	1:1	0 °C → room temp. 2 h		19
$CH_3CON(OMe)Me$	1:1	−10 °C → room temp. 3 h		45
$PhCO_2Et$	1:2	−78 °C → room temp. 1 h	 14	82
	1:1	−10 °C → room temp. 1 h		42
	1:2	−78 °C 3 h	 15	68

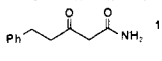
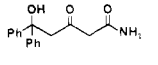
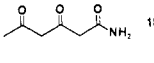
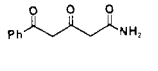
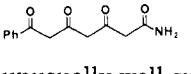
overall yield of 71% by treatment with methanolic HCl. [**Caution**: See Experimental Section concerning explosion hazard with compound **3**.]

The dianion (**5**) of isoxazole **4** was readily formed by treatment with 2 equiv of lithium diisopropylamide (LDA) in THF at −10 °C; the pale yellow dilithium salt was soluble in THF. Treatment with carbon dioxide at −78 °C gave exclusively (51% yield) the methyl carboxylated product **6** (Scheme II). In contrast, treatment of **4** with 2 equiv of *n*-butyllithium at −10 °C followed by carbon dioxide at −78 °C gave a 7:3 mixture of **6** and a compound tentatively identified as the isomeric acid **8** resulting from carboxylation at position 4 on the ring of **7**. Apparently with *n*-butyllithium lithiation at C-4 competed with reaction at the methyl group. Bowden and co-workers have reported a similar finding with respect to lithiation of 3-methoxy-5-methylisoxazole with 1 equiv of *n*-butyllithium but did not investigate the use of LDA.[2d]

Alkylation of dianion **5** with benzyl chloride proceeded smoothly giving the 5-phenethyl isoxazole **10** in good yield (72%) (Table I). Aldol condensation with benzophenone gave the adduct (**11**) at the 5-methyl position. A second product, which was formed in low yield, was separated from **11** by chromatography and identified as the isomeric oxazolinone (**12**) on spectroscopic grounds. Oxazolinones may also have been formed in the condensation of **5** with other electrophiles but they were not detected. Rearrangements of isoxazoles are well-documented and can be effected in high yield thermally and photochemically.[1]

Acetylation of dianion **5** with methyl acetate gave only a 35% yield of keto isoxazole **13** with a 2:1 ratio of dianion to ester; undoubtedly ionization of the ester by the dianion competed with the acylation reaction. Use of *N,N*-dimethylacetamide as the acylating agent also gave poor results; only a 19% yield of **13** was obtained when a 1:1 ratio of reagents was used. The yield of **13** was improved by the use of *N*-methoxy-*N*-methylacetamide as the acylating agent;[10] a 1:1 ratio of reagents gave **13** in 45% yield.

Table II. Hydrogenations of 5-Substituted-3-hydroxyisoxazoles

isoxazole	conditions	product	yield, %
10	Pd/C, EtOH, 30 min	 16	91
11	PtO_2, EtOAc, 30 min	 17	98
13	PtO_2, EtOH, 20 min	 18	87
14	PtO_2, EtOAc, 12 h	 19	98
15	PtO_2, EtOAc, 30 min	 20	97

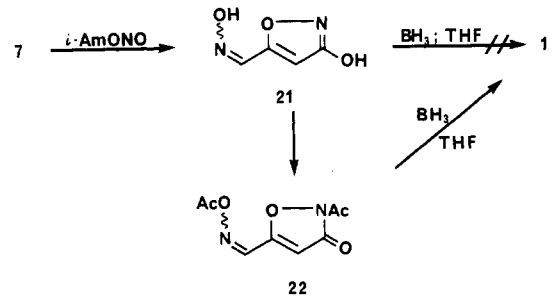
This last reagent appears to be unusually well-suited for effecting acetylation of very strongly basic anions and has the additional advantage that only a single equivalent of the anion is required whereas 2 equiv are required when esters are used. Acylations of dianion **5** with ethyl benzoate and with the monosodium salt of ethyl benzoylacetate were accomplished in good yields to provide keto isoxazoles **14** and **15** in yields of 82 and 68%, respectively, with 2:1 stoichiometry. An attempt was made to improve the synthesis of **14** by using a 1:1 ratio of dianion and ester along with 1 equiv of LDA, but the method gave only a 42% yield. Both the reaction of **5** with *N*-methoxy-*N*-methylacetamide and that with the salt of ethyl benzoylacetate serve to demonstrate the high nucleophilicity of dianion **5** since well stabilized anions such as that of acetophenone fail to react with these electrophiles.[10,11] The high reactivity of **5** offers a clear-cut advantage over the less reactive monoanion of 3-methoxy-5-methylisoxazole.[2d]

The isoxazole ring is readily cleaved by catalytic hydrogenation. The hydrogenolysis of 3,5-dialkyl isoxazoles

(10) Oster, T. A.; Harris, T. M. *Tetrahedron Lett.* **1983**, *24*, 1851.

(11) (a) Murray, T. P.; Harris, T. M. *J. Am. Chem. Soc.* **1972**, *94*, 8253. (b) Harris, T. M.; Murray, T. P.; Harris, C. M.; Gumulka, M. *J. Chem. Soc., Chem. Commun.* **1974**, 362.

Scheme III



has often been used for the preparation of β-diketones.[1,12] Similarly, 3-hydroxy-5-alkylisoxazoles give β-keto amides on hydrogenolysis.[13] The five isoxazoles, **10**, **11**, **13**, **14**, and **15**, were reduced in high yield, as shown in Table II, although to obtain these yields it was necessary in each case to optimize the reaction conditions. The reduction of **13** was readily accomplished by the use of PtO_2 in ethanol. However, PtO_2 was unsatisfactory for the reduction of **10**; overreduction occurred to give the 3-hydroxy analogue of **16**. A good yield of **16** could be obtained by using Pd/C. For the other three reductions, PtO_2 was used with ethyl acetate as the solvent since when the reduction was carried out in ethanol the terminal keto or hydroxy group was apparently reduced. In all cases the reductions were monitored by TLC to establish the optimum reaction period, since overreduction would probably have occurred if the reaction had been allowed to go too long.

A synthesis of muscimol (**1**) was undertaken as a final demonstration of the value of dianion **5**. Treatment of dianion **5** with isoamyl nitrite (2:1 stoichiometry) gave 3-hydroxyisoxazole-5-carboxaldehyde oxime as a mixture of geometrical isomers in 68% yield (Scheme III).[14] This oxime had previously been prepared by a more circuitous route involving eight steps.[15] Efforts to reduce this oxime to the amine by a previously described procedure involving BH_3–THF[15] were without success with the reduction stopping at the hydroxylamine stage, but complete reduction occurred after conversion of **21** to diacetate **22** by treatment with acetic anhydride.[16] Muscimol was obtained from the reduction in 38% yield.

In conclusion the dianion of 3-hydroxy-5-methylisoxazole has been found to be an excellent β-keto amide synthon. The reaction of **5** with various electrophiles proceeded in good to excellent yields. The resulting isoxazoles could be converted to keto amides in excellent yield. The dianion has also been used to synthesize the naturally occurring isoxazole muscimol. We are presently studying applications of the dianion to the synthesis of polycyclic compounds related to the tetracycline antibiotics.

Experimental Section

All glassware employed in anion reactions was oven dried at 150 °C for at least 3 h and assembled while hot under a stream of N_2. Tetrahydrofuran (THF) was used immediately after distillation from a sodium–potassium alloy–benzophenone ketyl. Diisopropylamine, distilled from Na and stored over 4 Å molecular sieves, was converted to lithium diisopropylamide (LDA) by treatment with a stoichiometric quantity of *n*-butyllithium at −10 °C in THF under N_2. In all cases a 10% excess of LDA (2.2 equiv) was employed for generation of dianion **5** to ensure complete reaction. Flash chromatography was carried out with silica gel 60 (E. Merck 9285, 230–400 mesh) or with the same silica gel which had been deactivated by treatment with 6 N HCl, followed by washing with H_2O to pH 5 and air-drying to a water content of approx 25%. All hydrogenations were performed at room temperature and atmospheric pressure, and the reductions were followed by TLC on precoated plates (0.25 mm) of silica gel 60F-254 (E. Merck 5765) and were visualized under UV light. ^1H NMR spectra were recorded on JEOL MH-100 and FX-90Q spectrometers; the latter was also used for ^{13}C spectra. IR spectra were taken on a Perkin-Elmer 727 spectrophotometer, mass spectra were taken on an LKB-9000 mass spectrometer (EI, 70 eV). Melting points (uncorrected) were taken in open capillaries. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN.

Dimethyl carbonate, methyl acetate, *N*,*N*-dimethylacetamide, ethyl benzoate, ethyl benzoylacetate, benzyl chloride, and isoamyl nitrite were distilled before use. *n*-Butyllithium (hexane solution) was obtained from Aldrich and was titrated before use. *N*,*O*-Bis(trimethylsilyl)hydroxylamine[9] and *N*-methoxy-*N*-methylacetamide[10] were prepared by known procedures.

***N*-(Trimethylsiloxy)-*N*-(trimethylsilyl)acetoacetamide (3).** Diketene (14.5 g, 0.172 mol) was added with stirring to *N*,*O*-bis(trimethylsilyl)hydroxylamine (**2**, 27.81 g, 0.157 mol). A cooling bath was applied during the initial stages of the reaction. After 6 h, the resulting orange solution was distilled by the use of a kugelrohr apparatus to provide 35.00 g (85% yield) of **3** as a colorless liquid: bp 66–70 °C (0.05 mm); ^1H NMR ($CDCl_3$) a mixture of rotational isomers δ 0.17, 0.21, 0.25, and 0.28 (4 s, 18 H total), 2.16 and 2.18 (2 s, 3 H total), 3.20 and 3.44 (2 s, 2 H total); ^{13}C NMR ($CDCl_3$) a mixture of rotational isomers δ −0.93, −0.79, −0.14, 1.51, 29.06, 29.25, 43.09, 47.80, 152.17, 160.75, 201.63, 202.82; IR (neat) 2954, 2895 (w), 1730, 1634, 1400, 1331, 1246 cm^{-1}; MS, *m*/*z* (relative intensity) 261 (M^+·, 7), 245 (12), 229 (22), 147 (100), 133 (23), 128 (19), 75 (23), 73 (86), 59 (16), 45 (37), 43 (55). Anal. Calcd for $C_{10}H_{23}NO_3Si_2$: C, 45.94; H, 8.87. Found: C, 46.14; H, 8.66.

Caution: *Care should be exercised during the distillation of* **3** *because of the potential for explosive decomposition if too high a pot temperature is reached. In one instance using a microdistillation apparatus spontaneous decomposition occurred with release of* NO_2*, leaving a crisp black solid in the distillation flask.*

3-Hydroxy-5-methylisoxazole (4). Hydrogen chloride gas was bubbled into a solution of keto amide **3** (14.03 g, 0.0537 mol) in MeOH (50 mL) for 5 min at room temperature. The mixture was allowed to stand for 45 min. Evaporation of the solvent in vacuo provided a light yellow solid which was sublimed (75–80 °C, 0.05 mm) to give 4.43 g (83% yield) of isoxazole **4** as a colorless crystalline solid: mp 84–85 °C (lit[5] mp 84–85 °C); ^1H NMR ($CDCl_3$) δ 2.32 (d, 3 H, *J* = 0.9 Hz), 5.66 (q, 1 H, *J* = 0.9 Hz), 11.75 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 12.70, 93.85, 170.34, 171.32; IR (KBr) 2986 (br), 2630 (br), 1631, 1516, 1334, 1241, 1021, 921 cm^{-1}; MS, *m*/*z* (relative intensity) 99 (M^+·, 73), 67 (7), 56 (20), 44 (7), 43 (100), 39 (20).

Preparation of Dianion 5, Lithium Salt. 3-Hydroxy-5-methylisoxazole (**4**, 0.495 g, 0.005 mol) in THF (15 mL) was added dropwise to LDA (0.011–0.012 mol) in THF (50–75 mL) at −10 °C. The resulting light yellow solution was stirred for 0.25–1.0 h to form dianion **5**. The dianion was held below 0 °C during treatment with electrophiles.

3-Hydroxy-5-isoxazoleacetic Acid (6). Crushed solid CO_2 (excess) was added to dianion **5** (0.005 mol) at −78 °C; the suspension was allowed to warm to room temperature over a 4 h period. After evaporation of the solvent, the residue was taken up in Et_2O (30 mL) at 0 °C and acidified with 6 N HCl to pH 1.0. The layers were separated and the aqueous layer was extracted further with Et_2O. The combined organic extracts were dried ($MgSO_4$) and evaporated to leave a light yellow solid. The NMR spectrum indicated only product **6** and starting material (**4**) were present, with no trace of ring-carboxylated material **9**. Starting material was removed by sublimation (75–80 °C, 0.05 mm) to leave 0.362 g (51%) of **6**, which gave pale yellow crystals upon recrystallization from EtOAc: mp 161–162 °C; ^1H NMR (acetone-d_6) δ 3.80 (s, 2 H), 6.00 (s, 1 H), 7.72 (br s, 2 H); ^{13}C NMR

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(acetone-d_6) δ 33.38, 95.62, 167.84, 169.30, 171.30; IR (KBr) 3050 (br), 1700, 1635, 1525, 1415, 1340, 1215 cm^{-1}; MS, *m/z* (relative intensity) 143 ($M^{+\cdot}$, 25), 99 (18), 98 (21), 56 (11), 55 (14), 54 (25), 45 (21), 44 (72), 43 (100), 42 (32). Anal. Calcd for $C_5H_5NO_4$: C, 41.97; H, 3.52. Found: C, 42.29; H, 3.72.

A similar reaction in which dianion **5** had been generated by treatment of **4** with 2 equiv of *n*-butyllithium gave a product mixture which contained 13% of **4**, 60% of **6**, and 27% of a compound tentatively identified as **8** based on the following spectra, in which carboxylation had occurred at C-4 of the ring: ^1H NMR (acetone-d_6) as a mixture with **6** δ 2.64 (s, CH_3); ^{13}C NMR (acetone-d_6) as a mixture with **6** δ 13.71, 100.01, 164.48, 170.06, 176.61.

Methyl 3-Hydroxy-5-isoxazoleacetate (9). Dimethyl carbonate (1.39 g, 0.0154 mol) was slowly added to dianion **5** (0.03 mol) in THF (150 mL) at −78 °C. The resulting bright orange suspension was stirred at room temperature for 4 h. A workup procedure similar to that employed for **6** gave an orange oil. Flash chromatography (3:2, EtOAc–hexane) followed by trituration with Et_2O gave 0.58 g of **9** (24% yield), which was recrystallized from Et_2O: mp 84–86 °C; ^1H NMR (acetone-d_6) δ 3.71 (s, 3 H), 3.81 (s, 2 H), 5.55 (br s, 1 H), 5.98 (s, 1 H); ^{13}C NMR (acetone-d_6) δ 33.43, 52.55, 95.68, 167.35, 168.76, 171.30; IR (KBr) 3010 (br), 2680 (br), 1730, 1640, 1530, 1435, 1400, 1360, 1340, 1265, 1210 cm^{-1}; MS, *m/z* (relative intensity) 157 ($M^{+\cdot}$, 61), 98 (100), 68 (35), 67 (17), 59 (87), 56 (13), 55 (22), 54 (13), 44 (17), 43 (26), 42 (30), 40 (26), 39 (30). Anal. Calcd for $C_6H_7NO_4$: C, 45.87; H, 4.49. Found: C, 45.85; H, 4.71.

5-(2-Oxopropyl)-3-hydroxyisoxazole (13). Methyl acetate (0.37 g, 0.005 mol) was added slowly to dianion **5** (0.01 mol) in THF (100 mL) at 0 °C and the mixture was stirred for 40 min to give a thick yellow suspension. Workup by the procedure employed for **6** except that EtOAc was used for extraction gave a crude product which was purified by flash chromatography (1:1, EtOAc–hexane) to give 0.250 g (35% yield) of **13** as a white solid which was recrystallized from EtOH to give colorless needles: mp 134–135 °C; ^1H NMR (acetone-d_6) δ 2.21 (s, 3 H), 3.91 (s, 2 H), 4.33 (br s, 1 H), 5.93 (s, 1 H); ^{13}C NMR (acetone-d_6) δ 29.53, 42.04, 95.62, 168.00, 171.25, 201.53; IR (KBr) 2980 (br), 2600 (br), 1720, 1640, 1530, 1355, 1315, 1260, 1160, 1020, 945, 820, 790, 775 cm^{-1}; MS, *m/z* (relative intensity) 141 ($M^{+\cdot}$, trace), 105 (10), 99 (24), 77 (12), 55 (10), 44 (10), 43 (100), 42 (19), 41 (10), 39 (24). Anal. Calcd for $C_6H_7NO_3$: C, 51.07; H, 5.00. Found: C, 51.17; H, 5.13.

A second approach to isoxazole **13** involved acylation of dianion **5** (0.01 mol) with *N,N*-dimethylacetamide (0.87 g, 0.01 mol) in THF (100 mL) at 0 °C for 0.5 h. Workup gave 0.27 g (19% yield) of **13**. The most satisfactory method for the preparation of **13** involved acylation of dianion **5** (0.05 mol) in THF (50 mL) with *N*-methoxy-*N*-methylacetamide (0.531 g, 0.0052 mol) at −10 °C for 45 min. The thick yellow suspension was evaporated in vacuo, taken up in Et_2O at 0 °C and acidified to pH 1 with 6 N HCl. The layers were separated and the aqueous layer was further extracted with Et_2O and CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and evaporated in vacuo. The residue was triturated with 1:1 EtOAc–hexane (7 mL) and filtered to give 0.261 g (37%) of **13**. Flash chromatography (7:3, EtOAc–hexane) of the filtrate provided an additional 0.054 g (8%) of **13** to give a total yield of 45%.

5-(2-Oxo-2-phenylethyl)-3-hydroxyisoxazole (14). Ethyl benzoate (0.375 g, 0.0025 mol) was added dropwise to dianion **5** (0.005 mol) in THF (50 mL) at −10 °C and the mixture was allowed to stir for 1 h to give an orange solution. Workup as with **6** except for the use of CH_2Cl_2 and EtOAc for extraction gave a yellow solid which was purified by flash chromatography (1:1, EtOAc–hexane) to give 0.42 g (82% yield) of **14**: mp 169–169.5 °C after recrystallization from EtOH; ^1H NMR ($CDCl_3$) δ 4.34 (d, 2 H, *J* = 0.7 Hz), 5.16 (br s, 1 H) 5.98 (t, 1 H, *J* = 0.7 Hz), 7.57 (m, 3 H), 7.98 (m, 2 H); ^{13}C NMR (acetone-d_6) δ 37.93, 95.89, 129.21, 129.59, 139.36, 137.06, 168.16, 171.30, 193.84; IR (KBr) 2926 (br), 2766 (br), 2566 (br), 1686, 1626, 1594, 1576, 1510, 1444, 1356, 1324, 1261, 1206 cm^{-1}; MS, *m/z* (relative intensity) 203 ($M^{+\cdot}$, 2), 105 (100), 77 (90), 69 (10), 51 (46), 50 (19), 39 (14). Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46. Found: C, 64.81; H, 4.59.

The reaction was also carried out with a 1:1 ratio of ester and dianion with addition of an extra equivalent of LDA. Ethyl benzoate (0.75 g, 0.005 mol) was added to dianion **5** (0.005 mol) and LDA (0.005 mol) in THF (50 mL) at −10 °C. After 1 h, the reaction mixture was worked up as above to give 0.43 g (42% yield) of **14**.

5-(2,4-Dioxo-4-phenylbutyl)-3-hydroxyisoxazole (15). Ethyl benzoylacetate (0.52 g, 0.0027 mol) was added to NaH (0.2 g of a 50% oil dispersion which was washed with pentane, 0.0042 mol) in THF (50 mL) at 0 °C. The mixture was allowed to stir until evolution of H_2 had ceased (0.25 h). The resulting yellow solution was added slowly to a THF solution of dianion **5** (0.005 mol) at −78 °C. After 3 h, the light orange solution was worked up as with **6** but CH_2Cl_2 and EtOAc were used for extraction to give a yellow solid. Recrystallization from EtOH gave 0.27 g of **15** and flash chromatography of the mother liquor (deactivated silica gel, 1:1, EtOAc–hexane) gave an additional 0.18 g (68% total yield). Analytically pure material was prepared by a second recrystallization from EtOH: mp 139–140 °C; ^1H NMR (acetone-d_6) mixture of tautomers, enol form δ 3.95 (s, 2 H), 4.20 (br s, 2 H), 6.03 (s, 1 H), 6.54 (s, 1 H), 7.59 (m, 3 H), 7.96 (m, 2 H); ^{13}C NMR (acetone-d_6) mixture of tautomers δ 38.31, 41.99, 95.73, 96.08, 97.03, 127.80, 129.21, 129.64, 133.54, 134.41, 134.84, 168.11, 171.36, 182.57, 192.65; IR (KBr) 3000 (br), 2580 (br), 1615, 1510, 1335, 1290, 1250, 950, 935, 792, 748, 648 cm^{-1}; MS, *m/z* (relative intensity) 245 ($M^{+\cdot}$, 7), 148 (26), 147 (100), 105 (98), 77 (11), 69 (24). Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52. Found: C, 63.73; H, 4.67.

5-(2-Phenylethyl)-3-hydroxyisoxazole (10). Benzyl chloride (1.90 g, 0.015 mol) was added rapidly to dianion **5** (0.005 mol) in THF (50 mL) at −10 °C and the solution was stirred for 2 h while warming to room temperature. The resulting yellow solution was worked up as with compound **6** to give a colorless solid. Flash chromatography (2:3, EtOAc–hexane) gave 0.68 g (72% yield) of **10** which was recrystallized from EtOAc/hexane: mp 104–105 °C; ^1H NMR (acetone-d_6) δ 2.97 (s, 4 H), 3.31 (br s, 1 H), 5.72 (s, 1 H), 7.26 (s, 5 H); ^{13}C NMR (acetone-d_6) δ 29.42, 33.81, 93.51, 127.04, 129.16 (br), 141.29, 171.30, 174.28; IR (KBr) 2960 (br), 2560 (br), 1625, 1520, 1445, 1430, 1350, 1280, 1255, 1015, 985, 940, 790, 760, 700, 680 cm^{-1}; MS, *m/e* (relative intensity) 189 ($M^{+\cdot}$, 20), 91 (100), 77 (11), 65 (17), 51 (12), 39 (16). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86. Found: C, 69.95; H, 5.86.

5-(2-Hydroxy-2,2-diphenylethyl)-3-hydroxyisoxazole (11) and 5-(2-Hydroxy-2,2-diphenylethyl)-3*H*-2-oxazolinone (12). Benzophenone (1.00 g, 0.0055 mol) in THF (10 mL) was added slowly to dianion **5** (0.005 mol) in THF (50 mL) at −78 °C. The mixture was stirred for 2 h to give an orange solution. Workup as with **6** except for the use of CH_2Cl_2 for extraction gave an orange solid which was purified by flash chromatography (45:55, EtOAc–hexane) to give 0.75 g (53% yield) of isoxazole **11** as a light yellow solid and 0.21 g (15% yield) of oxazole **12** as a white solid. Recrystallization of **11** from EtOH gave colorless crystals of the hemihydrate: mp 172–172.5 °C; ^1H NMR ($CDCl_3$) δ 3.62 (s, 2 H), 5.40 (s, 1 H), 5.96 (br s, 2 H), 7.36 (m, 10 H); ^{13}C NMR (acetone-d_6) δ 40.74, 77.42, 95.46, 126.88, 127.53, 128.78, 147.79, 170.92, 171.41; IR (KBr) 3210 (br), 2750 (br), 1610, 1490, 1440, 1380, 1200, 1050, 1005, 960, 895, 850, 810, 770, 740, 710, 680, 610 cm^{-1}; MS, *m/z* (relative intensity) 281 ($M^{+\cdot}$, 1), 184 (25), 183 (100), 182 (11), 105 (61), 91 (8). Anal. Calcd for $C_{17}H_{15}NO_3 \cdot {}^1/_2H_2O$: C, 70.33; H, 5.56. Found: C, 70.74; H, 5.75.

Oxazole **12** was recrystallized from EtOH: mp 197–198 °C; ^1H NMR (acetone-d_6) δ 2.97 (s, 2 H), 3.49 (d, 2 H, *J* = 1.2 Hz), 6.20 (t, 1 H, *J* = 1.2 Hz), 7.22–7.61 (m, 10 H); ^{13}C NMR (acetone-d_6) δ 39.39, 77.53, 111.22, 126.88, 127.42, 128.72, 138.47, 148.06;[17] IR (KBr) 3406, 3150, 3066, 1716, 1666, 1486, 1446, 1396, 1352, 1206, 1176, 1136, 1046, 960, 856, 770, 744, 686, 624 cm^{-1}; MS, *m/z* (relative intensity) 281 ($M^{+\cdot}$, 3), 184 (29), 183 (100), 182 (16), 105 (87), 91 (9). Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.38. Found: C, 72.68; H, 5.45.

3-Oxo-5-phenylpentanamide (16). Isoxazole **10** (0.200 g) was combined with 10% Pd/C (0.20 g) and 95% EtOH (10 mL) and treated with H_2 for 25 min at room temperature and atmospheric pressure during which time 183 mL of H_2 was absorbed. After filtration through Celite, the solvent was evaporated in vacuo to leave 0.185 g (91% yield) of keto amide **16** as a white solid, which was recrystallized from EtOAc: mp 105–106.5 °C; ^1H NMR ($CDCl_3$) δ 2.00 (br s, 1 H), 2.90 (s, 4 H), 3.39 (s, 2 H), 6.00 (br s,

(17) Signal-to-noise ratio was insufficient to observe the carbonyl signal(s) in the ^{13}C spectra.

1 H), 7.23 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 29.38, 45.20, 48.88, 126.35, 128.25, 128.57, 140.22, 167.80, 205.29; IR (KBr) 3377, 3152 (br), 2912, 1717, 1657, 1492, 1427, 1402, 1362, 1052, 812, 752, 702, 662 cm^{-1}; MS, m/z (relative intensity) 191 ($M^{+\cdot}$, 27), 174 (17), 131 (10), 105 (44), 104 (78), 103 (24), 91 (100), 86 (22), 79 (22), 78 (27), 77 (47), 65 (32), 63 (17), 59 (82), 51 (40), 50 (18), 44 (56), 43 (38), 42 (20), 41 (10), 39 (31). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85. Found: C, 68.84; H, 6.83.

3,5-Dioxo-5-phenylpentanamide (19). Keto isoxazole **14** (0.106 g) ws combined with PtO_2 (0.004 g) and EtOAc (20 mL) and treated with H_2 at room temperature and atmospheric pressure until TLC indicated the isoxazole was fully reduced (11.0 mL). After filtration through Celite, the solution was evaporated in vacuo to give **19** (0.105 g, 98% yield) as an off-white solid, which was recrystallized from EtOH: mp 121–122 °C; ^1H NMR ($CDCl_3$) mixture of enol–keto tautomers but mainly in the enol form δ 3.44 (s, 2 H, enol form), 3.61 (s, keto form), 4.26 (s, keto form), 5.65 (br s, 1 H), 6.28 (s, 1 H, enol form), 6.68 (br s, 1 H), 7.52 (m, 3 H), 7.90 (m, 2 H), 15.91 (br s, 1 H, enol form); ^{13}C NMR ($CDCl_3$) mixture of enol–keto tautomers δ 47.10, 97.21, 127.17, 128.74, 132.85, 133.67, 168.28, 182.21, 191.85, 192.77, 205.45; IR (KBr) 3400, 3140 (br), 1670, 1600 (br), 1540 (br), 1450 (br), 1365 cm^{-1}; MS, m/z (relative intensity) 205 ($M^{+\cdot}$, 13), 188 (40), 161 (23), 160 (83), 147 (30), 128 (10), 105 (100), 77 (10), 69 (27), 59 (18). Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40. Found: 64.16; H, 5.49.

3,5,7-Trioxo-7-phenylheptanamide (20). Diketoisoxazole **15** (0.0519 g) was reduced by the procedure used for compound **14** to give triketo amide **20** (0.0507 g, 97% yield) as a light yellow solid, which was recrystallized from EtOAc–hexane: mp 109–110 °C; ^1H NMR ($CDCl_3$) mixture of enol–keto tautomers δ 1.61 (br s), 3.23 (s), 3.30 (s), 3.61 (s), 3.70 (s), 3.99 (s), 5.07 (s), 5.40 (br s) 5.49 (s), 5.77 (s), 5.90 (s), 6.23 (s), 6.32 (s), 6.50 (br s), 7.50 (m), 7.85 (m), 14.59 (br s); IR (KBr) 3363, 3178, 1660, 1600, 1573, 1398, 1278 cm^{-1}; MS, m/z (relative intensity) 247 ($M^{+\cdot}$, 1), 230 (12), 229 (10), 212 (20), 184 (20), 147 (14), 128 (24), 105 (100), 78 (10), 77 (71), 69 (50), 59 (12), 55 (14), 51 (37), 50 (15), 44 (30), 43 (26), 42 (16), 39 (16). Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30. Found: C, 63.04; H, 5.21.

5-Hydroxy-3-oxo-5,5-diphenylpentanamide (17). Hydroxy isoxazole **11** (0.132 g) was reduced by the procedure used for compound **14** to give amide **17** as a white solid (0.131 g, 98% yield), which was recrystallized from EtOH: mp 154–155 °C; ^1H NMR (acetone-d_6) mixture of tautomers δ 2.93 (br s), 3.21 (s), 3.46 (s), 3.70 (s), 5.22 (s), 7.22–7.55 (m); ^{13}C NMR (acetone-d_6) mixture of tautomers δ 52.07, 53.85, 77.47, 126.56, 126.83, 127.42, 128.61, 128.83, 148.17;[17] IR (KBr) 3380, 3240 (br), 3150, 1704, 1665 cm^{-1}; MS, m/z (relative intensity) 283 ($M^{+\cdot}$, not observed), 183 (11), 182 (50), 105 (100), 77 (93), 51 (61), 50 (29), 44 (14), 43 (29). Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05. Found: C, 71.93; H, 6.09.

3,5-Dioxohexanamide (18). Ketoisoxazole **13** (0.206 g) was combined with PtO_2 (0.016 g) and 95% EtOH (20 mL) and treated with H_2 at atmospheric pressure for 20 min. Workup by filtration, evaporation of the solvent in vacuo, and crystallization from CH_2Cl_2 gave **18** (0.176 g, 87% yield) as a white solid, which was recrystallized from EtOAc–hexane: mp 63–64 °C; ^1H NMR ($CDCl_3$) 9:1 enol–keto mixture involving C-4 δ 2.08 (s, 3 H, enol), 2.27 (s, keto), 3.29 (s, 2 H, enol), 3.51 and 3.75 (2 s, keto), 5.63 (s, 1 H, enol), 5.68 and 6.62 (2 br s, 1 H, $-NH_2$), 15.29 (br s, 1 H, enol); ^{13}C NMR ($CDCl_3$) enol form δ 23.86, 46.23, 100.84, 168.66, 189.47, 189.90; IR (KBr) 3360, 3170, 1660 (br) cm^{-1}; MS, m/z (relative intensity) 143 ($M^{+\cdot}$, 7), 126 (37), 101 (12), 98 (14), 96 (12), 95 (47), 69 (65), 59 (36), 44 (39), 43 (100), 42 (30), 41 (14), 39 (14). Anal. Calcd for $C_6H_9NO_3$: C, 50.34; H, 6.34. Found: C, 50.20; H, 6.54.

3-Hydroxy-5-isoxazolecarboxaldehyde Oxime (21). Isoamyl nitrite (1.22 g, 0.0104 mol) was added slowly to dianion **5** (0.02 mol) in THF (150 mL) at −10 °C. The mixture was warmed to room temperature; after 2 h the orange suspension was worked up as with compound **6** to give 2.12 g crude product as a dark yellow solid. Unaltered isoxazole **4** was removed by sublimation (60–70 °C, 0.1 mm); the residue was triturated with Et_2O to give oxime **21** (0.91 g, 68% yield). The analytical sample was prepared by flash chromatography (EtOAc) followed by washing the crystalline product with acetone and CH_2Cl_2 and drying in vacuo: mp 176–179 °C; ^1H NMR (acetone-d_6) δ 4.66 (br s, 2 H), 6.71 (s, 1 H), 7.54 (s, 1 H); ^{13}C NMR (acetone-d_6) δ 100.66, 134,84, 160.74, 171.47; IR KBr) 2990 (br), 1600, 1500, 1330, 1300, 940 cm^{-1}; MS, m/z (relative intensity) 128 ($M^{+\cdot}$, 100), 85 (77), 68 (11), 67 (14), 56 (45), 55 (18), 52 (14), 44 (64), 43 (32), 42 (55), 41 (23), 40 (18), 39 (32). Anal. Calcd for $C_4H_4N_2O_3$: C, 37.51; H, 3.15. Found: C, 37.73; H, 3.36.

Diacetyl Oxime 22. Acetic anhydride (7 mL) was added to oxime **21** (0.3745 g, 2.93 mmol) at room temperature under N_2 and the suspension was stirred 3 h. The solid dissolved after 1 h followed by the formation of a white precipitate after 1.5 h. The Ac_2O and AcOH were evaporated in vacuo, the resulting solid was suspended in EtOAc (2 mL), and the mixture was filtered to give 0.374 g (60% yield) of pure **22** as a light tan solid. The filtrate contained isomeric and partially acetylated materials. The diacetyl oxime **22** was stored below 0 °C because it was observed to decompose over several days at room temperature: mp 101–104 °C; ^1H NMR ($CDCl_3$) δ 2.33 (s, 3 H), 2.63 (s, 3 H), 6.57 (s, 1 H), 7.70 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.03, 22.91, 107.39, 138.03, 156.72, 161.92, 162.03, 166.25; IR (KBr) 3120, 3028, 1785, 1745, 1705, 1610, 1378, 1340, 1270, 1220, 1160, 960, 930 cm^{-1}; MS, m/e (relative intensity) 212 ($M^{+\cdot}$ not observed), 170 (5), 128 (8), 60 (5), 45 (7), 43 (100).

5-Aminomethyl-3-isoxazolone (1, Muscimol). Borane (7.06 mL, 7.06 mmol, as a 1 M THF complex) was slowly added to diacetyl oxime **22** (0.3744 g, 1.77 mmol) in THF (10 mL) at room temperature. The solution was stirred 21.5 h, quenched with H_2O (5 mL) at 0 °C, and evaporated in vacuo. The salts were refluxed in methanolic HCl (30 mL) for 1 h. The solution was evaporated in vacuo and the residue was taken up in 10 mL of MeOH/HCl and evaporated again in vacuo. The resulting salt was purified on an ion exchange resin (5 mL, Bio Rad 50 W-X8 resin, H^+ form) and eluted with 2 N NH_4OH to give 0.185 g of crude product. Recrystallization (EtOH–H_2O) gave 0.0770 g (38% yield) of essentially pure muscimol. ^1H NMR of the filtrate indicated both under- and overreduction products. Recrystallization from methanol gave pure muscimol: mp 170.5–173 °C (lit.[2d] 172–174 °C); ^1H NMR (D_2O) δ 4.08 (s, 2 H), 5.75 (s, 1 H); ^{13}C NMR (D_2O) δ 35.89, 99.98, 164.56, 177.94; IR (KBr) 3400, 3200–2400 (br), 2200, 1640, 1470 cm^{-1}; MS, m/s (relative intensity) 114 ($M^{+\cdot}$, 57), 113 (33), 98 (24), 97 (43), 86 (19), 83 (45), 71 (78), 70 (45), 69 (26), 59 (11), 57 (13), 56 (13), 55 (20), 54 (23), 44 (40), 43 (67), 42 (100), 41 (32), 40 (19), 39 (20).

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Registry No. **1**, 2763-96-4; **2**, 22737-37-7; **3**, 87318-59-0; **4**, 10004-44-1; **5**, 87318-60-3; **6**, 54489-27-9; **7**, 87318-61-4; **8**, 16880-48-1; **9**, 87318-62-5; **10**, 87318-63-6; **11**, 87318-64-7; **12**, 87336-00-3; **13**, 87318-65-8; **14**, 87318-66-9; **15**, 87318-67-0; **16**, 87336-01-4; **17**, 87318-68-1; **18**, 87318-69-2; **19**, 87318-70-5; **20**, 87318-71-6; **21**, 87318-72-7; **22**, 87318-73-8; CO_2, 124-38-9; $MeOCO_2Me$, 616-38-6; $PhCH_2Cl$, 100-44-7; PhCOPh, 119-61-9; CH_3CO_2Me, 79-20-9; CH_3CONMe_2, 127-19-5; $CH_3CON(OMe)Me$, 78191-00-1; $PhCO_2Et$, 93-89-0; ethyl benzoylacetate, 94-02-0; diketene, 674-82-8.