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STUDIES ON DIHYDROPYRIDINE DERIVATIVES—I

4,7-DIHYDROISOXAZOLO[5,4-b]PYRIDINES

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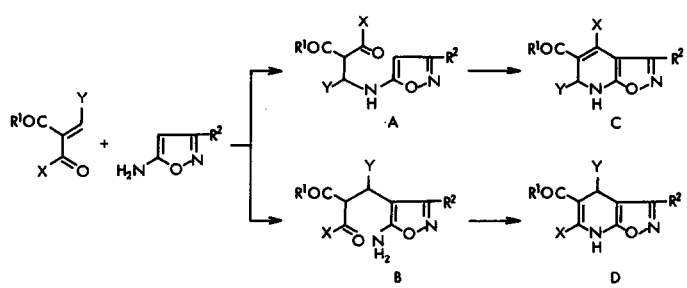
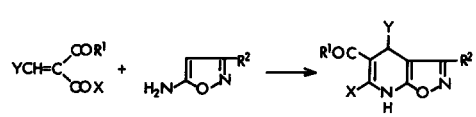
Abstract—Reactions of 5-aminoisoxazoles with α,β-unsaturated ketones in t-butanol on heating afforded 4,7-dihydroisoxazolo[5,4-b]pyridines. However, when the reactions were carried out at 20° using ethylene glycol as the solvent, the kinetically controlled amino adducts were obtained in excellent yields. The amino adducts were converted into the thermodynamically controlled 4,7-dihydroisoxazolo[5,4-b]pyridines by heating. Tentative mechanisms for the reactions are also presented.

In our continuing studies on the chemistry and utilisation of isoxazoles, we tried to synthesise a series of 4,7-dihydroisoxazolo[5,4-b]pyridine derivatives in order to examine their biological activities. Although a number of studies[1] have been conducted on the preparation of isoxazolo[5,4-b]pyridines, they have neglected the 4,7-dihydro derivatives. The most suitable method for synthesising the 4,7-dihydroisoxazolo[5,4-b]pyridine system is that using the reaction of 5-aminoisoxazoles with α,β-unsaturated ketones. However, complications were expected because 5-aminoisoxazoles have the properties of an ambient nucleophile:[2] the Michael addition reaction can give the amino adduct A and C_4 adduct B, which may cyclise to form the corresponding dihydroisoxazolo[5,4-b]pyridines, form C and form D, respectively. The present paper reports on the results of our detailed research on the reactions of 5-aminoisoxazoles with α,β-unsaturated ketones, such as benzylidene-acetoacetate and ethylidene-acetoacetate derivatives, ethyl ethylidene-benzoylacetate and 3-nitrobenzylideneacetylacetone.

Heating a mixture of ethyl 3-nitrobenzylideneacetoacetate (**1a**)[3] with 3-phenyl-5-aminoisoxazole (**2a**)[4] in t-butanol afforded a yellow crystalline product **3a**, $C_{22}H_{19}N_3O_5$, in excellent yield. The product **3a** was deduced to have the structure of ethyl 4,7-dihydro-6-methyl-4-(3-nitrophenyl)-3-phenylisoxazolo[5,4-b]pyridine-5-carboxylate from its IR and ^{1}H-NMR spectra. Similar reactions of some α,β-unsaturated ketones **1a–e**, with 5-aminoisoxazoles **2a–d** in t-butanol gave the corresponding 4,7-dihydroisoxazolo[5,4-b]pyridine derivatives **3b–g**, shown in Table 1. Although products **3a–g** were characterised as having the structure of the 1,4-dihydropyridine of form D on the basis of their ^{1}H-NMR spectra showing a singlet (5.0–6.0 ppm) assignable to the proton at the 4-position, the evidence did not rigorously exclude another structure, the 1,2-dihydropyridine of form C. Conformation of the form D came when oxidation of **3g**



Scheme 1.

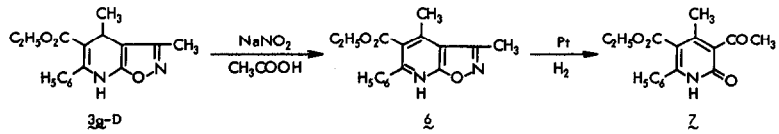


1 2 3

1a: Y = 3-$NO_2C_6H_4$, X = CH_3, R^1 = C_2H_5O 2a: R^2 = C_6H_5
b: Y = C_6H_5, X = CH_3, R^1 = C_2H_5O b: R^2 = 4-$CH_3OC_6H_4$
c: Y = CH_3, X = C_6H_5, R^1 = C_2H_5O c: R^2 = 3-$C_2H_5O_2CC_6H_4$
d: Y = CH_3, X = CH_3, R^1 = C_2H_5O d: R^2 = CH_3
e: Y = 3-$NO_2C_6H_4$, X = CH_3, R^1 = CH_3

Table 1. Reactions of 1 with 2 in tert-butanol

Compound No.	Y	X	R^1	R^2	Yield (%)
3a	3-$NO_2C_6H_4$	CH_3	C_2H_5O	C_6H_5	83.7
3b	3-$NO_2C_6H_4$	CH_3	CH_3	C_6H_5	86.7
3c	CH_3	CH_3	C_2H_5O	C_6H_5	93.9
3d	C_6H_5	CH_3	C_2H_5O	4-$CH_3OC_6H_4$	81.2
3e	3-$NO_2C_6H_4$	CH_3	C_2H_5O	3-$C_2H_5O_2CC_6H_4$	83.8
3f	C_6H_5	CH_3	C_2H_5O	CH_3	80.5
3g	CH_3	C_6H_5	C_2H_5O	CH_3	70.4



Scheme 2.

Table 2. Solvent effects on the reaction of 1a with 2a

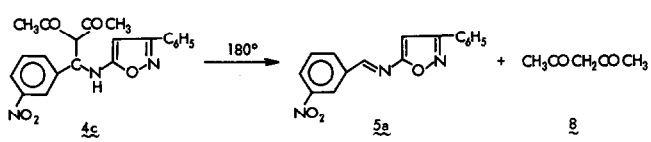
Solvent	React. temp. (°C)	Yield % of 3a	5a*
C_6H_6	Reflux	7.4	-
CH_3CN	Reflux	8.6	-
tert-C_4H_9OH	Reflux	83.7	-
iso-C_3H_7OH	Reflux	74.0	-
C_2H_5OH	Reflux	49.4	-
CH_3OH	Reflux	38.3	1.7
EG**	60	-	68.0
CH_3COOH	20	-	34.1

* 5a: 5-(3-Nitrobenzylideneamino)-3-phenylisoxazole

** EG: Ethylene glycol

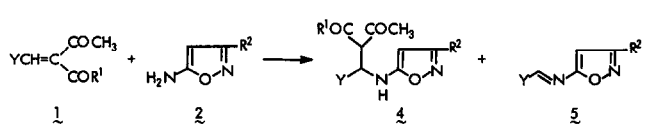
followed by isoxazole-ring cleavage on hydrogenolysis gave the known ethyl 3-acetyl-4-methyl-6-phenyl-2-pyridone-5-carboxylate (**7**).[5] Our results suggested that Michael addition of 5-aminoisoxazoles **2** to α,β-unsaturated ketones **1** occurred mainly at the C_4-position of **2**. The polarity of the solvents used in the reaction affected the reactivity as well as the reaction course. Table 2 summarises the dependence of the yield of **3a** on the solvents used in the reaction of **1a** with **2a** under heating. Aprotic solvents such as benzene and acetonitrile gave a markedly low yield of **3a**. t-Butanol gave a preferable result, with isopropanol, ethanol and methanol giving lower yields. Methanol also caused the formation of a small amount of 5 - (3 - nitrobenzyl - ideneamino) - 3 - phenylisoxazole (**5a**, Schiff base).[6] When a more polar solvent, ethylene glycol, was used, no **3a** was produced but **5a** was obtained in good yield. Compound **5a** was probably formed *via* the amino adduct, form A, arising from Michael addition of the amino group of **2a** to **1a**.[7] Thus, we tried conducting the reaction in ethylene glycol under controlled temperature, using ethyl benzylidene-acetoacetate (**1b**) and 3-nitrobenzylideneacetylacetone (**1e**). The results are summarised in Table 3.

Treatments of **1b** and **1e** with **2a** and **2d** in ethylene glycol at 20 to 40° afforded the crystalline products **4a–c** in good yields. Similar reaction of **1b** with **2b** afforded **4d** and the Schiff base **5b** in 54.8 and 29.5% yields, respectively. Products **4a–d** were assigned the structures of the corresponding amino adducts, form A, from their spectral data and elementary analysis, and these assignments were supported by the thermal decomposition of **4c** by heating at melting point to give **5a** together with acetylacetone (**8**) (Scheme 3).



Scheme 3.

Next, we tried to convert these amino adducts **4** into the dihydropyridine derivatives. Heating the amino adduct **4b** in ethylene glycol did not give the form C, which would have resulted from direct dehydration, but gave **3f** having the form D structure. When t-butanol was used as the solvent in the thermal treatment of **4b**, the result was similar, with an excellent



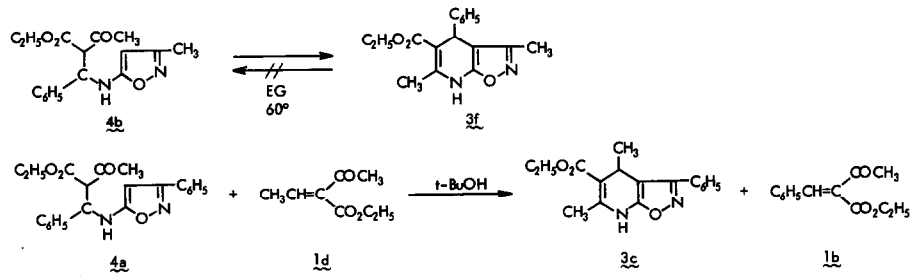
1b: Y = C_6H_5, R^1 = OC_2H_5 2a: R^2 = C_6H_5

1e Y = 3-$NO_2C_6H_4$, R^1 = CH_3 b: R^2 = 4-$CH_3OC_6H_4$

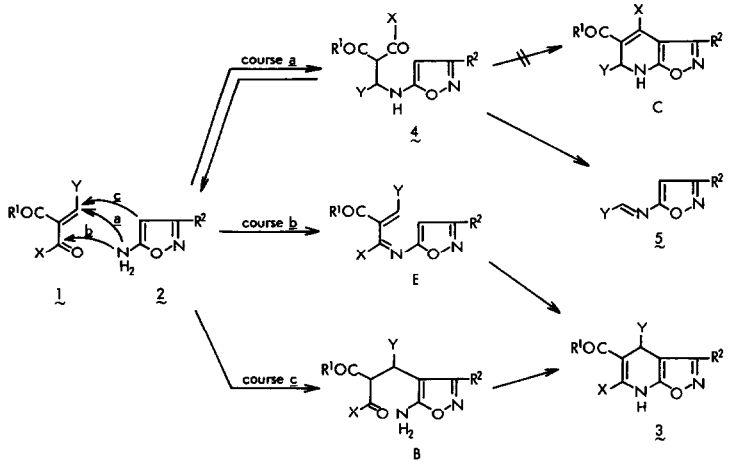
d: R^2 = CH_3

Table 3. Reactions of 1 with 2 in ethylene glycol

Compound No.	Y	R^1	R^2	React. temp. (°C)	Yield (%) of 4	5
a	C_6H_5	OC_2H_5	C_6H_5	20	94.4	-
b	C_6H_5	OC_2H_5	CH_3	20	85.4	-
c	3-$NO_2C_6H_4$	CH_3	C_6H_5	40	76.3	-
d	C_6H_5	OC_2H_5	4-$CH_3OC_6H_4$	40	54.8	29.5



Scheme 4.



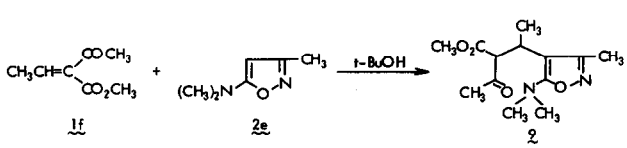
Scheme 5.

yield of **3f**. Therefore, heating the amino adduct **4a** in the presence of ethyl ethylideneacetoacetate (**1d**) in t-butanol caused the cross reaction giving **3c** and ethyl benzylideneacetoacetate (**1b**) in high yields. No transformation of **3f** into the amino adduct **4b** occurred.

These results suggest that the amino adducts **4** and 4,7-dihydroisoxazolo[5,4-b]pyridine derivatives **3** that we obtained are kinetically and thermodynamically controlled products,[8] respectively. The retro-Michael reaction of the amino adduct **4** may mainly proceed to give the reversible starting materials, **1** and **2**, which ultimately form the thermodynamically stable product **3** *via* Michael addition at the C_4-position of **2**. In some cases, the cleavage reaction of **4** partly occurs to form the irreversible Schiff base **5**.

Tentative mechanisms for the reactions of **1** with **2** are presented in Scheme 5. 5-Aminoisoxazoles **2** act as both amine and enamine, toward the electrophiles **1**.[9] Michael addition of **2** to **1** *via* course *a* results in the formation of amino adducts **4**, thermal reaction of which does not afford Skraup-type cyclising products C,[10] but give the starting materials, **1** and **2** by the retro-reaction, and Schiff bases **5** by the cleavage. Course *c* involves the addition at the C_4 of **2**. Formation of the 4,7-dihydroisoxazolo[5,4-b]pyridines **3** occur *via* either course *b* or *c*. As for the mode of the amino function attack to the α,β-unsaturated ketones, the 1,2-addition *via* course *b* to give E seems to be less likely than the 1,4-addition[1,12] *via* course *c* to give **3**. Although the reaction courses have not yet been clarified in detail, course *c* seems to be the mechanism for the formation of **3**. To verify the proposed mechanism, we tried to isolate intermediate **B**, the C_4-adduct, but were not successful because of the rapid cyclisation into **3**. However, in another reaction of methyl ethylideneacetoacetate (**1f**) with 5-dimethylamino-3-methylisoxazole (**2e**), we obtained the C_4-adduct **9** in good yield.

The reaction presented here is convenient for the preparation of dihydroisoxazolo[5,4-b]pyridine de-



Scheme 6.

rivatives. Its scope and application to the synthesis of other dihydroazolopyridine systems are under investigation.

EXPERIMENTAL

All m.ps are uncorrected. IR spectra were recorded on a JASCO IRA-I spectrometer taken in Nujol. NMR spectra were recorded on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a RMU-6 mass spectrometer.

General method for the preparation of 4,7-dihydroisoxazolo[5,4-b]pyridines (3)

The results are summarised in Table 1. A mixture of α,β-unsaturated ketone **1a–e** (10 mmol) and **2a–d** (10 mmol) in t-BuOH (10 ml) was refluxed for 3 days under N_2. The mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2–$CH_3CO_2C_2H_5$ (10:1) and gave a solid which was recrystallised from the appropriate solvents to afford **3a–g** in the yields shown in Table 1.

Ethyl 6-methyl-4-(3-nitrophenyl)-3-phenyl-4,7-dihydroisoxazolo[5,4-b]pyridine-5-carboxylate (**3a**). M.p. 210–211° (from $CH_3CO_2C_2H_5$). IR 1350 (NO_2), 1678 (CO), 3300 (NH) cm^{-1}. NMR (DMSO-d_6) δ 1.1 (3H, t, J = 7 Hz), 2.42 (3H, s), 4.03 (2H, q, J = 7 Hz), 5.58 (1H, s), 7.3–8.1 (9H, m). (Found: C, 65.13; H, 4.47; N, 10.47. Calc for $C_{22}H_{19}N_3O_5$: C, 65.18; H, 4.72; N, 10.37%.) MS: 405 (M^+).

5-Acetyl-6-methyl-4-(3-nitrophenyl)-3-phenyl-4,7-dihydroisoxazolo[5,4-b]pyridine (**3b**). M.p. 244–247° (dec) (from $CH_3CO_2C_2H_5$). IR 1380 (NO_2), 1670 (CO), 3205 (NH) cm^{-1}. NMR (DMSO-d_6) δ 2.17 (3H, s), 2.37 (3H, s), 4.0 (1H, bs), 5.67 (1H, s), 7.23–8.03 (9H, m). (Found: C, 67.28; H, 4.43; N, 11.14. Calc for $C_{21}H_{17}N_3O_4$: C, 67.19; H, 4.57; N, 11.20%.)

Ethyl 4,6-dimethyl-3-phenyl-4,7-dihydroisoxazolo[5,4-b]pyridine-5-carboxylate (**3c**). M.p. 177–178° (from $CH_3CO_2C_2H_5$). IR 1668 (CO), 3255 (NH) cm^{-1}. NMR ($CDCl_3$) δ 1.15 (3H, d, J = 7 Hz), 4.17–4.50 (1H, m), 7.07 (1H, bs), 7.27–7.83 (5H, m). (Found: C, 68.17; H, 5.99; N, 9.32. Calc for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39%.)

Ethyl 6-methyl-3-(4-methoxyphenyl)-4-phenyl-4,7-dihydroisoxazolo[5,4-b]pyridine-5-carboxylate (**3d**). M.p. 199–200° (from $CH_3CO_2C_2H_5$). IR 1662 (CO), 3265 (NH) cm^{-1}. NMR ($CDCl_3$) δ 1.2 (3H, t, J = 7 Hz), 2.33 (3H, s), 3.77 (3H, s), 4.08 (2H, q, J = 7 Hz), 5.27 (1H, s), 6.7–7.53 (9H, m). (Found: C, 70.78; H, 5.76; N, 7.29. Calc for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.18%.)

Ethyl 3-(3-ethoxycarbonylphenyl)-6-methyl-4-(3-nitrophenyl)-4,7-dihydroisoxazolo[5,4-b]pyridine-5-carboxylate (**3e**). M.p. 194° (from $CH_3CO_2C_2H_5$). IR 1380 (NO_2), 1670, 1722 (CO), 3270 (NH) cm^{-1}. NMR ($CDCl_3$) δ 1.18 (3H, t, J = 7 Hz), 1.4 (3H, t, J = 7 Hz), 2.45 (3H, s), 4.05 (2H, q, J = 7 Hz), 5.48 (1H, s), 7.07–8.5 (8H, m). (Found: C, 62.96; H, 4.90; N, 8.83. Calc for $C_{25}H_{23}N_3O_7$: C, 62.88; H, 4.86; N, 8.80%.)

Ethyl 3,6-dimethyl-4-phenyl-4,7-dihydroisoxazolo[5,4-b]pyridine-5-carboxylate (**3f**). M.p. 205–206° (from $CH_3CO_2C_2H_5$). IR 1690 (CO), 3200 (NH) cm^{-1}. NMR ($CDCl_3$) δ 0.97 (3H, t, J = 7 Hz), 1.82 (3H, s), 2.3 (3H, s), 3.87 (2H, q, J = 7 Hz), 5.0 (1H, s), 7.2 (5H, s). (Found: C, 68.53; H, 5.98; N, 9.26. Calc for $C_{17}H_{18}N_2O_3$: C, 68.44, H, 6.08; N, 9.39%.)

Ethyl 3,4-dimethyl-6-phenyl-4,7-dihydroisoxazolo[5,4-b]pyridine-5-carboxylate (**3g**). M.p. 155–156° (from isopropyl ether). IR 1675 (CO), 3250 (NH) cm^{-1}. NMR ($CDCl_3$) δ 0.83 (3H, t, J = 7 Hz), 1.27 (3H, d, J = 7 Hz), 2.07 (3H, s), 3.63–4.23 (3H, m), 7.3 (5H, s). (Found: C, 68.42; H, 6.01; N, 9.42. Calc for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39%.)

Ethyl 3,4-dimethyl-6-phenylisoxazolo[5,4-b]pyridine-5-carboxylate (**6**). To a stirred soln of **3g** (0.596 g) in CH_3COOH (30 ml) was added $NaNO_2$ (0.69 g) in portions, and the mixture was stirred for 1 day. After removal of the solvent, the residue was extracted with CH_2Cl_2 and the extract was chromatographed over silica gel with CH_2Cl_2, giving **6** (0.59 g, 9.99%). M.p. 109–110° (from isopropyl ether). IR 1720 cm^{-1}. NMR ($CDCl_3$) δ 0.98 (3H, t), 2.68 (6H, s), 4.1 (2H, q), 7.23–7.73 (5H, m). (Found: C, 68.90; H, 5.43; N, 9.44. Calc. for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45%.)

Ethyl 3-acetyl-4-methyl-2-oxo-6-phenylpyridine-5-carboxylate (**7**). A mixture of **6** (0.59 g) in EtOH–AcOH (10–0.5 ml) was hydrogenated over Pt (0.1 g). After uptake of H_2 (50 ml), the soln was filtered and evaporated. The residue was extracted with CH_2Cl_2, and the extract was chromatographed on silica gel. A CH_2Cl_2–$CH_3CO_2C_2H_5$ (1:1) eluate afforded **7** (0.45 g, 75.3%). M.p. 186–187° (from $CH_3CO_2C_2H_5$). IR 1683, 1690, 1715 (CO), 2600–3050 (NH) cm^{-1}. NMR ($CDCl_3$) δ 0.94 (3H, t, J = 7 Hz), 2.26 (3H, s), 2.36 (3H, s), 4.0 (2H, q, J = 7 Hz), 7.44 (5H, s). (Found: C, 67.84; H, 5.53; N, 4.68. Calc for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68%.)

Solvent effects on the reaction of **1a** *with* **2a** (Table 2)

(i) A mixture of **1a** and **2a** was treated for 3 days in C_6H_6 (in CH_3CN, iPrOH and EtOH) generally following the method described above, and the results are shown in Table 2. (ii) A mixture of **1a** (2.63 g) and **2a** (1.61 g) in MeOH (10 ml) was refluxed for 3 days under N_2. The reaction mixture was concentrated, and the residue was chromatographed on silica gel. The fraction eluted with CH_2Cl_2 gave **5a** (49.8 mg, 1.7%). The second fraction eluted with CH_2Cl_2–$CH_3CO_2C_2H_5$ (10:1) gave **3a** (1.5 g, 38.3%). (iii) A mixture of **1a** (2.63 g) and **2a** (1.61 g) in ethylene glycol (10 ml) at 60° (in CH_3COOH at 20°) was stirred for 3 days. The mixture was extracted with CH_2Cl_2 and the extract was chromatographed on silica gel with CH_2Cl_2, giving **5a** (1.99 g, 68%). M.p. 181–182° (from $CH_3CO_2C_2H_5$). IR 1360 (NO_2) cm^{-1}. NMR ($CDCl_3$) δ 6.6 (1H, s), 6.67–8.5 (8H, m), 8.73–8.87 (1H, s), 8.95 (1H, s). (Found: C, 65.79; H, 3.69; N, 14.55. Calc for $C_{16}H_{11}N_3O_3$: C, 65.52; H, 3.98; N, 14.33%.)

General method for preparation of amino-adducts (**4**) (Table 3).

A mixture of **1b, e** (10 mmol) and **2a, b, d** (10 mmol) in ethylene glycol (10 ml) was stirred for 3 days at 20–40°. The mixture was extracted with CH_2Cl_2 and the extract was chromatographed on silica gel. The fraction eluted with CH_2Cl_2 gave **5b**, and the second fraction eluted with $CH_3COOC_2H_5$ gave **4a–d** in the yields shown in Table 3.

5-(2-Ethoxycarbonyl-3-oxo-1-phenyl)butylamino-3-phenylisoxazole (**4a**). M.p. 146–147° (from $CH_3CO_2C_2H_5$). IR 1720, 1740, 1745 (CO), 3340 (NH) cm^{-1}. NMR ($CDCl_3$) δ (epimeric mixture of 1:1) 1.13, 1.15 (3H, t, J = 7 Hz), 2.17, 2.22 (3H, s), 3.91–4.31 (3H, m), 5.07–5.32 (1H, m), 5.22 (1H, s), 6.11, 6.21 (1H, s) 7.16–7.8 (10H, m). (Found: C, 69.88; H, 5.80; N, 7.43. Calc for $C_{22}H_{22}N_2O_4$: C, 69.82; H, 5.86; N, 7.40%.)

5-(2-Ethoxycarbonyl-3-oxo-1-phenyl)butylamino-3-methylisoxazole (**4b**). M.p. 136–137° (from isopropyl ether). IR 1718, 1741 (CO), 3250 (NH) cm^{-1}. NMR ($CDCl_3$) δ (epimeric mixture of 1:1) 1.13 (3H, t, J = 7 Hz), 2.07 (3H, s), 2.17, 2.22 (3H, s), 3.83–4.35 (3H, m), 4.77 (1H, s), 4.92–5.25 (1H, m), 5.93 (1H, bs), 7.17–7.45 (5H, m). (Found: C, 64.55, H, 6.32; N, 8.96. Calc for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86%.)

5-[2-Acetyl-3-oxo-1-(3-nitrophenyl)]butylamino-3-phenylisoxazole (**4c**). M.p. 150–151° (from $CH_3CO_2C_2H_5$). IR 1360 (NO_2), 1705, 1730 (CO), 3320 (NH) cm^{-1}. NMR ($CDCl_3$) δ 2.17 (3H, s), 2.2 (3H, s), 4.27 (1H, d), 5.3 (1H, s), 5.17–5.53 (1H, m), 6.1 (1H, bs), 7.27–8.3 (9H, m). (Found: C, 64.36; H, 4.97; N, 10.68. Calc for $C_{21}H_{19}N_3O_5$: C, 64.11; H, 4.87; N, 10.68%.)

5-(2-Ethoxycarbonyl-3-oxo-1-phenyl)butylamino-3-(4-methoxyphenyl)isoxazole (**4d**). M.p. 138–140° (from isopropyl ether). IR 1715, 1745 (CO), 3180 (NH) cm^{-1}. NMR ($CDCl_3$) δ (epimeric mixture of 1:1) 1.17 (3H, t, J = 7 Hz), 2.17, 2.23 (3H, s), 3.8 (3H, s), 3.87–4.37 (3H, m), 5.0–5.33 (1H, m), 5.17 (1H, s), 6.08 (1H, bs), 6.82–7.72 (9H, m). (Found: C, 67.33; H, 5.95; N, 6.89. Calc for $C_{23}H_{24}N_2O_5$: C, 67.63; H, 5.92; N, 6.86%.)

5-(Benzylideneamino)-3-(4-methoxyphenyl)isoxazole (**5b**). M.p. 138–139° (from isopropyl ether). IR 1610 cm^{-1}. NMR ($CDCl_3$) δ 3.85 (3H, s), 6.42 (1H, s), 6.85–8.07 (9H, m), 8.88 (1H,

s). (Found: C, 73.38; H, 5.13; N, 10.04. Calc for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07%.)

Pyrolysis of **4c**. **4c** (1.18 g) was heated at 180° for 1 hr under reduced pressure. Degradation products were dissolved in CH_2Cl_2. The solution was chromatographed on silica gel with CH_2Cl_2 and afforded acetylacetone (**8**) (0.23 g, 78.7%) and **5a** (0.35 g, 40.2%).

Conversion of **4b** *to* **3f**. A soln of **4b** (0.316 g) in ethylene glycol (5 ml) was heated at 60° for 3 days under N_2. The solution was extracted with CH_2Cl_2 and the extract was chromatographed on silica gel with CH_2Cl_2–$CH_3CO_2C_2H_5$ (10:1), giving **3f** (0.246 g, 82.4%). A soln of **4b** (0.316 g) in t-BuOH (5 ml) was refluxed for 3 days under N_2 and gave **3f** (0.244 g, 81.7%).

Cross reaction of **1d** *with* **4a**. A mixture of **1d** (1.2 g) and **4a** (1.9 g) in t-BuOH (30 ml) was refluxed for 3 days under N_2. After evaporation of the solvent, the residue was chromatographed on silica gel with CH_2Cl_2 and afforded **1b** (1.0 g, 91.7%). Subsequent elution with $CH_3CO_2C_2H_5$ gave **3c** (1.18 g, 79.1%.)

5 - *Dimethylamino* - 4 - (2 - *methoxycarbonyl* - 1 - *methyl* - 3 - *oxo*)*butyl* - 3 - *methylisoxazole* (**9**). A mixture of **1f** (0.284 g) and **2e** (0.252 g) in t-BuOH (2 ml) was refluxed for 3 days. After evaporation of the solvent, the residue was chromatographed on silica gel. A CH_2Cl_2–$CH_3CO_2C_2H_5$ (1:1) eluate afforded an oily product **9** (0.477 g, 88.9%). IR 1720, 1742 (CO) cm^{-1}. NMR ($CDCl_3$) δ (epimeric mixture of 1:1) 1.19 (3H, t, J = 7 Hz), 2.06, 2.27 (3H, s), 2.23 (3H, s), 3.94, 3.95 (3H, s), 3.96 (3H, s), 3.54, 3.76 (3H, s), 3.46–4.05 (2H, m). (Found: C, 58.19; H, 7.50; N, 10.21. Calc for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44%.) MS: 268 (M^+).

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[6] The structure of **5a** was assigned from its elementary analysis and spectral data and confirmed by unambiguous synthesis essentially according to the procedure of Kano and Makisumi.[2a]

[7] Compound **5a** may also originate from 3-nitrobenzaldehyde. However, hydrolysis of **2a** into the aldehyde did not occur in ethylene glycol at 60°.

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